Movement Disorders and Inherited Metabolic Disorders

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Recognition, Understanding, Improving Outcomes

Edited by
Darius Ebrahimi-Fakhari
Harvard Medical School
Phillip L. Pearl
Harvard Medical School

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With thanks to our contributors, who made this book possible.

With commitment to our colleagues and patients, who give our lives purpose.

With love to our families, who we need most of all.

Contents

Contributors

Jan O. Aasly, MD
Department of Neurology, St. Olavs Hospital and Norwegian University of Science and Technology, Trondheim, Norway

Mohammed Almuqbil, MD, FRCPC
Institute of Genetic Medicine, Johns Hopkins Hospital, Baltimore, MD, USA
Division of Pediatric Neurology, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Erika F. Augustine, MD, MS
Departments of Neurology and Pediatrics, University of Rochester Medical Center, Rochester, NY, USA

Nenad Blau, PhD
Dietmar-Hopp Metabolic Centre, University Children's Hospital, University of Heidelberg, Heidelberg, Germany
Division of Metabolism, University Children's Hospital, University of Zürich, Zürich, Switzerland

Thomas Bourinaris, MD, MSc
Department of Neuromuscular Disorders, Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK

Heiko Brennenstuhl, MD
Department of General Pediatrics, Division of Neuropediatrics and Metabolic Medicine, University Children's Hospital Heidelberg, Heidelberg, Germany

Peter T. Clayton, MD, FRCP, FRCPCH
UCL Great Ormond Street Institute of Child Health, University College London, and Great Ormond Street Hospital for Children NHS Trust, London, UK

Claudio Melo de Gusmao, MD
Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Tom J. de Koning, MD, PhD, MBA
Expertise Center Movement Disorders Groningen, Department of Neurology and Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
Pediatrics, Department of Clinical Sciences, Lund University, Lund, Sweden

Darryl C. De Vivo, MD
Division of Pediatric Neurology, Departments of Neurology and Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

Philippe De Vloo, MD, PhD
Division of Neurosurgery, Toronto Western Hospital, Toronto, ON, Canada
Department of Neurosurgery, Great Ormond Street Hospital for Children NHS Trust, London, UK

Melissa DiBacco, MD
Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Darius Ebrahimi-Fakhari, MD, PhD
Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Florian S. Eichler, MD
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Hendriekje Eggink, MD, PhD
Expertise Center Movement Disorders Groningen, Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Carmen Espinós, PhD
Unit of Genetics and Genomics of Neuromuscular and Neurodegenerative Disorders, Centro de

Investigación Príncipe Felipe (CIPF), Valencia, Spain

Ali Fatemi, MD, MBA
The Kennedy Krieger Institute, Johns Hopkins Medical Institutions, Baltimore, MD, USA

Carlos R. Ferreira, MD
Division of Genetics and Metabolism, Children's National Health System, Washington, DC, USA
National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

Angeles García-Cazorla, MD, PhD
Neurometabolic Unit and Synaptic Metabolism Laboratory, Hospital Sant Joan de Déu Barcelona, Barcelona, Spain

K. Michael Gibson, PhD
Washington State University College of Pharmacy, Spokane, WA, USA

Georg F. Hoffmann, MD
Dietmar-Hopp Metabolic Center and Centre for Pediatrics and Adolescent Medicine, University Children's Hospital, University of Heidelberg, Heidelberg, Germany

Gabriella A. Horvath, MD, PhD
Division of Biochemical Genetics, Department of Pediatrics, University of British Columbia, BC Children's Hospital, Vancouver, BC, Canada

Henry Houlden, MD, PhD
Department of Neuromuscular Disorders, UCL Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK

George M. Ibrahim, MD, PhD, FRCSC
Division of Neurosurgery, the Hospital for Sick Children, Toronto, ON, Canada

Fatima Y. Ismail, MBBS
Kennedy Krieger Institute, The John Hopkins Hospital, Baltimore, MD, USA

Hyder A. Jinnah, MD, PhD
Departments of Neurology, Human Genetics, and Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Krisztina K. Johansen, MD, PhD
Department of Neurology, St. Olavs Hospital and Norwegian University of Science and Technology, Trondheim, Norway

Suneil K. Kalia, MD, PhD, FRCSC
Division of Neurosurgery, Toronto Western Hospital, and Krembil Brain Institute, University of Toronto, Toronto, ON, Canada

Christine Klein, MD
Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

Lisette H. Koens, MD
Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Stefan Kölker, MD
Division of Child Neurology and Metabolic Medicine, Centre for Child and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany

Anouk Kuiper, MD
Expertise Center Movement Disorders Groningen, Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Anthony E. Lang, MD
Edmond J Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital and Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada

Saadet Mercimek-Andrews, MD, PhD
Division of Clinical and Metabolic Genetics, Department of Pediatrics, University of Toronto and Genetics and Genome Biology Program, The Hospital for Sick Children, Toronto, ON, Canada

Jonathan W. Mink, MD, PhD
Division of Child Neurology, Department of Neurology, University of Rochester Medical Centre, Rochester, NY, USA

Albert L. Misko, MD, PhD
Massachusetts General Hospital, Department of Neurology, Harvard Medical School, Boston, MA, USA

Fanny Mochel, MD, PhD
Department of Genetics and Reference Center for Neurometabolic Diseases in Adults, and Faculty of Medicine, Sorbonne University, and Institute of Brain and Spine (ICM), AP-HP, Pitié-Salpêtrière Hospital, Paris, France

Eva Morava, MD, PhD
Department of Clinical Genomics, Mayo Clinic College of Medicine, Rochester, MN, USA

Thomas Opladen, MD
Department of General Pediatrics, Division of Neuropediatrics and Metabolic Medicine, University Children's Hospital Heidelberg, Heidelberg, Germany

Marc C. Patterson, MD, FRACP
Departments of Neurology, Pediatrics and Medical Genetics, Mayo Clinic College of Medicine, Rochester, MN, USA

Phillip L. Pearl, MD
Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Toni S. Pearson, MBBS
Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA

Belén Pérez-Dueñas, MD, PhD
Department of Pediatric Neurology, Hospital Vall d'Hebrón, Universitat Autònoma de Barcelona, Barcelona, Spain

Roser Pons, MD
First Department of Pediatrics, National and Kapodistrian University of Athens, Aghia Sofia Hospital, Athens, Greece

Lance Rodan, MD
Division of Genetics and Genomics, Department of Medicine and Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Jean-Baptiste Roullet, PhD
Washington State University College of Pharmacy, Spokane, WA, USA

Emmanuel Roze, MD, PhD
Department of Neurology, AP-HP Pitié-Salpêtrière Hospital, Paris, France

Afshin Saffari, MD
Division of Child Neurology and Metabolic Medicine, Center for Paediatrics and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany

Manuel Schiff, MD, PhD
Reference Center for Inborn Errors of Metabolism, AP-HP Necker University Hospital and Imagine Institute, Paris University, Paris, France

Susanne A. Schneider, MD, PhD
Department of Neurology, Ludwig-Maximilians-University of Munich, Munich, Germany

Laura Silveira-Moriyama, MD, PhD
Reta Lila Weston Institute of Neurological Studies, Fundação Espírita Américo Bairral, Itapira, Brazil

Bianca M. L. Stelten, MD
Department of Neurology, Catharina Hospital, Eindhoven, The Netherlands

Scellig S. Stone, MD, PhD, FRCSC
Department of Neurosurgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Marina A. J. Tijssen, MD, PhD
Expertise Center Movement Disorders Groningen, Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Laura Tochen, MD
Division of Neurology, Children's National Health System, Washington, DC, USA

Karin Tuschl, MD
Department of Developmental Neurobiology, Kings College London, Guy's Campus, London, UK

Martje E. van Egmond, MD, PhD
Expertise Center Movement Disorders Groningen, Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
Department of Neurology, Ommelander Hospital Groningen, Scheemda, The Netherlands

Bart P. C. van de Warrenburg, MD, PhD
Department of Neurology, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

Clara D. van Karnebeek, MD, PhD
Department of Pediatrics, Institute for Life Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands
Department of Pediatrics, Amsterdam University Medical Centres, Amsterdam, The Netherlands

Jennifer Vermilion, MD
Department of Neurology, Division of Child Neurology, University of Rochester Medical Center, Rochester, NY, USA

Jasper E. Visser, MD, PhD
Department of Neurology, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands
Department of Neurology, Amphia Hospital, Breda, The Netherlands

Ana Westenberger, PhD
Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

Sarah Wiethoff, MD, PhD
Department of Neuromuscular Disorders, UCL Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK
Centre for Neurology and Hertie-Institute for Clinical Brain Research, Tübingen, Germany

Colin Wilbur, MD
Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada

Edward Yang, MD, PhD
Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Rodi Zutt, MD, PhD
Department of Neurology, Haga Hospital, The Hague, The Netherlands

Preface

Inherited metabolic movement disorders are an important and evolving group of disorders that bridge two subspecialty areas, "childhood-onset movement disorders" and "inborn errors of metabolism." The impetus for this book came from the simple recognition that there is a gap in communication between experts in both fields. In this book we strive to combine the time-honored approach of clinical phenomenology with modern molecular understanding of movement disorders. The emphasis is on treatable conditions – disorders that should never be missed. Awareness of these disorders can have significant therapeutic implications and has the potential to improve outcomes dramatically. Conceptually, this book is divided into three parts that serve the triad: recognition–understanding–improving outcomes. We begin with a **phenomenology-based approach** – an approach that we as neurologists take in the clinic. In the second part, we change our perspective and provide a detailed clinical, molecular, and biochemical discussion of individual diseases or groups of disorders – a **metabolism-based approach**. Finally, the third part of the book takes on the challenge of discussing new molecular techniques and treatments that are beginning to enter our field. This includes a review of new methods for genetic testing and new treatments – so the focus is on **improving outcomes**.

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Neurology and neuroscience have always been and will always be communal disciplines. This book has greatly benefitted from being written by a community of movement disorder neurologists and specialists in inborn errors of metabolism. We are deeply grateful to our diverse team of authors whose contributions have made this book an outstanding and unique resource.

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Chapter 1

Treatable Metabolic Movement Disorders: The Top 10

Darius Ebrahimi-Fakhari and Phillip L. Pearl

Introduction

Inherited metabolic movement disorders are an important and evolving group of disorders that bridge two subspecialty areas: **childhood-onset movement disorders** and **inborn errors of metabolism**. Individually, many of these disorders are rare but in aggregate they represent a substantial clinical burden. It is in their complex nature that they require a multidisciplinary approach that includes pediatricians, neurologists, and geneticists among others. The amount of information and the pace at which new genetic techniques and therapeutic advances are evolving and shaping the definition of new and older disorders represent a significant challenge for physicians and investigators. Clinicians seeing patients with inherited metabolic movement disorders need to synthesize key concepts in neurology as well as biochemical and clinical genetics, and as we are approaching a molecular reclassification of many diseases, they need to have an increasing understanding of next-generation sequencing techniques in addition to traditional biochemical testing. The treatment of many of these disorders is evolving, too, and now bridges dietary approaches with pharmacotherapy and increasingly invasive treatments such as deep brain stimulation. This book intends to cover all these aspects in a clear, concise, and practical way by bringing the expertise in the various inherited metabolic movement disorders under one roof, from a clinical, biochemical, and genetic perspective.

Treatable Metabolic Movement Disorders

Since the description of alkaptonuria (or "black urine disease") by Garrod in 1902 [1] and subsequently the first emergence of the term inborn error of metabolism (IEM) in 1908 [2], we have learned of several hundred single gene disorders that we classify as IEM today [3]. The classic IEMs stem from defects in enzymes that mediate the metabolism of amino acids, carbohydrates, and fatty acids, or mitochondrial and lysosomal function. The recent introduction of next-generation sequencing and other "omics" approaches has significantly expanded the spectrum of IEMs beyond traditional "enzymopathies" [4] and a broader definition is that of a deficiency in a metabolic pathway that results in an accumulation of a substrate or intermediate and/or a reduced ability to produce an essential compound [5]. It is the nature of IEMs that they are highly heterogeneous and often rare or even extraordinarily rare. In addition, most IEMs are multisystem diseases with neurological and non-neurological manifestations and initial clinical manifestations are often relatively non-specific. Therefore, IEMs call for an interdisciplinary approach requiring close collaboration of pediatric neurologists, neurologists, geneticists, and experts in metabolism.

Over the last decades, new treatment approaches have changed the scope of IEMs from a group of rare, untreatable, and often fatal disorders to an important cause of potentially treatable diseases. The recognition that early detection can improve outcomes for some IEMs has led to the development of advanced newborn screening efforts. In many cases, the diagnosis relies on clinical pattern recognition and biochemical testing but also, increasingly, next-generation sequencing. Here we present an approach to identifying the "top 10" treatable IEMs that present with movement disorders – diagnoses that should not be missed. Although the choice of our top 10 is certainly arbitrary, they illustrate important principles and herald the following chapters.

The Top 10 Treatable Metabolic Movement Disorders

The clinician is challenged with two tasks when evaluating a movement disorder of potential metabolic

etiology: (1) identifying the correct movement disorder phenomenology; and (2) developing a differential diagnosis and rational approach to counseling and testing. The first task is similar to the general approach to any patient with a movement disorder but, in addition, is guided by the principles listed in the "key points" at the end of the chapter. The second task is challenged by the need to identify treatable conditions quickly in order to prevent irreversible complications and to reduce long-term morbidity and mortality. The following short presentation of the top 10 treatable metabolic movement disorders may help with this task.

Number 10: Niemann–Pick Disease Type C

Niemann–Pick disease type C (NPC, OMIM 257220 and 601015) is an autosomal-recessive lysosomal storage disease with significant clinical heterogeneity ranging from severe forms with neonatal onset to delayed presentations in adulthood [6, 7]. The disorder is caused by bi-allelic variants in *NPC1* (~95%) [8] or *NPC2* (~5%) [9] leading to the accumulation of unesterified cholesterol in lysosomes in several tissues including the central nervous system. Broadly speaking, there are two neurological presentations: (1) an early-onset and often rapidly progressive form with significant developmental delay starting in early childhood, followed by cerebellar dysfunction with ataxia and dysarthria, spasticity, dystonia, vertical supranuclear gaze palsy, gelastic cataplexy, seizures, and cognitive decline; and (2) a delayed form with onset in adolescence or adulthood with intellectual disability, ataxia, vertical supranuclear gaze palsy, and psychiatric symptoms. Movement disorders are common across the spectrum of NPC and sometimes a presenting symptom [10, 11], particularly in adult patients [12]. The most prevalent movement disorder in NPC is cerebellar ataxia with prominent involvement of the trunk and limbs, which is present in over 70% of patients [6, 7, 12, 13]. Hence, NPC should be evaluated for in all patients with onset of ataxia before the age of 40 years. The diagnostic yield is high particularly when ataxia is present in combination with abnormal vertical saccades, cognitive decline, or neuropsychiatric symptoms [14–16]. Dystonia is a second important movement disorder in NPC, occurring in up to 40% of patients [12], and can present initially as dystonic tremor of the head and neck and often progresses to generalized dystonia [10, 11, 13]. Facial involvement, particularly of perioral muscles is common. Myoclonus has been reported in a few cases [10, 12, 13, 17], sometimes as the presenting symptom [13], and can be quite impairing. Chorea appears to be rare overall [10, 12]. Vertical supranuclear gaze or saccade palsy is an important diagnostic clue. Other manifestations are hepatosplenomegaly, hepatic dysfunction, dysphagia, dysarthria, seizures, gelastic cataplexy, acute psychosis, depression, obsessive-compulsive disorder, and other neuropsychiatric symptoms. Brain MRI findings are variable. Cerebral (particularly frontal lobe) and cerebellar atrophy, elevated T2 signals in the periventricular white matter, and deep grey matter and hippocampal atrophy have been described but are non-specific. Normal brain MRI does not exclude NPC [14]. Owing to the clinical heterogeneity, the diagnosis of NPC is often significantly delayed (on average by ~4 years); hence, there is a great need to improve recognition [18]. New biomarker profiling (i.e. with oxysterols and bile acids) and genetic analysis technologies are now recommended as first-line diagnostic tests for NPC [14]. Miglustat is currently the only approved therapy for patients with neurological manifestations (approved by the European Medicines Agency) [19]. Several promising therapies are being investigated in clinical trials, i.e. 2-hydroxypropyl-beta-cyclodextrin, which has shown positive results in open-label phase I/II trials (see Table 1.1, which provides a summary of all treatable IEMs, at the end of the chapter) [20]. The development of these treatments has a high chance of turning NPC into a treatable disorder and it is anticipated that early diagnosis and treatment will lead to superior outcomes. The approach to NPC in the context of ataxia is discussed in Chapter 7 by Stelten and van de Warrenburg.

Number 9: Manganese Transporter Defects

Inborn errors of manganese transport are important treatable disorders that present with prominent movement disorders (see Table 1.1). Bi-allelic mutations in *SLC30A10* [21, 22] lead to a syndrome of dystonia and parkinsonism, hepatic cirrhosis, polycythemia, and hypermanganesemia (OMIM 613280) [23–25]. Symptoms start in early childhood with truncal hypotonia, impaired gait, dystonia, and impaired fine motor skills [21, 26]. Early-onset limb dystonia is almost universal and in most cases progresses to generalized

dystonia. Adult-onset, akinetic–rigid parkinsonism has been reported in older individuals [22] and is usually poorly responsive to levodopa therapy. Intellectual development and cognitive function are relatively preserved. Variable expressivity has been noted within families [27]. Blood and urine manganese levels are markedly elevated, iron stores are usually depleted, transaminases and unconjugated bilirubin are elevated, and there is polycythemia [21, 26]. Brain MRI can facilitate a diagnosis as it shows a pattern of bilateral, symmetrical T1 signal hyperintensity of the globus pallidus, putamen, caudate, subthalamic and dentate nuclei, consistent with manganese deposition [21]. Abdominal imaging often reveals hepatomegaly and cirrhotic changes. Bi-allelic mutations in another manganese transporter gene, *SLC39A14* [28] were more recently described in a syndrome of childhood-onset dystonia with hypermanganesemia (OMIM 617013) [28–31]. Onset is in infancy or early childhood with developmental delay, dystonia, and bulbar dysfunction [28, 32]. The course is progressive and most children develop generalized dystonia, spasticity, contractures, and severe scoliosis within the first 10 years of life [28]. Akinetic–rigid parkinsonism may develop as well. Just like with *SLC3A10*-associated hypermanganesemia, intellect and cognition seem to remain relatively preserved. Interestingly, while manganese blood levels are high and T1 hyperintensity in the basal ganglia is seen, similar to patients with *SLC3A10* mutations, polycythemia is typically not present and liver involvement has not been reported [28]. Chelation therapy with disodium calcium ethylenediaminetetraacetic acid (EDTA) combined with iron supplementation can lower blood manganese levels in both *SLC3A10*- and *SLC39A14*-related hypermanganesemia, halt disease progression, and improve the movement disorder [21–23, 28, 32–36]. Penicillamine and DMSA have been suggested as alternative chelating agents (see Table 1.1) [27, 37]. A detailed review by the disorders of manganese metabolism and their movement disorders is provided in Chapter 17 by Tuschl and Clayton, who discovered these fascinating disorders.

Number 8: Cerebrotendinous Xanthomatosis

An important metabolic movement disorder, often diagnosed late, is cerebrotendinous xanthomatosis (CTX, OMIM 213700), an autosomal-recessive lipid storage disease caused by defective bile acid synthesis due to mutations in the cytochrome P450 gene *CYP27A1* [38]. The onset of symptoms is mostly in young adulthood and the disease is progressive. Spasticity is the leading movement disorder; signs of corticospinal tract dysfunction are the predominant neurological features [39, 40]. Cognitive decline, seizures, psychiatric symptoms, peripheral neuropathy, and atypical parkinsonism are seen later in the disease course [39]. In addition to ataxia that is present in the majority of patients, dystonia and myoclonus [41] have been reported in a subset of patients. Parkinsonism in older patients (average age ~40 years) is often asymmetrical and most patients will present with walking difficulties and balance impairment including early falls [42]. The response to levodopa is often limited [42]. Non-neurological manifestations are often key to a diagnosis. A history of neonatal cholestatic jaundice, bilateral childhood-onset cataracts, or chronic diarrhea may represent the earliest clinical manifestation of CTX and should raise suspicion for this disorder. Xanthomas are pathognomonic but often only appear in the second or third decade of life. The average diagnostic delay for CTX is estimated to 15–20 years, highlighting the need to improve clinical recognition [34]. Brain MRI shows cortical and cerebellar atrophy, white matter signal alterations, and symmetrical hyperintensities in the dentate nuclei [43]. Plasma cholestanol levels are elevated and together with low levels of bile alcohols in plasma or urine are usually diagnostic. Confirmation is obtained by sequencing of *CYP27A1*. While treatment with chenodeoxycholic acid can lower cholestanol levels and can prevent progression, the effect on existing symptoms is variable (see Table 1.1) [42, 44]. In Chapter 10, Tochen and Pearson discuss CTX in the differential diagnosis of metabolic movement disorders that present with spasticity and Chapter 26 by Mochel and Roze reviews all aspects of CTX in detail.

Number 7: Glutaric Aciduria Type 1

The most common among the organic acidurias, glutaric aciduria type 1 (GA-1, OMIM 231670), is an important metabolic movement disorder (see Table 1.1). GA-1 is caused by bi-allelic variants in the glutaryl-coenzyme A dehydrogenase (*GCDH*) gene [45] leading to accumulation of neurotoxic metabolites, 3-hydroxyglutaric and glutaric acids [46]. The classic presentation of GA-1 is that of early progressive macrocephaly, hypotonia, and developmental delay

followed by acute encephalopathic crises in the setting of an intercurrent illness or other catabolic state [47]. These metabolic crises often occur early with a sepsis-like clinical picture during infancy, and irreversibly damage the basal ganglia (putamen and caudate nuclei), leading to a sudden onset of movement disorders, usually in early childhood [47, 48]. A combination of axial hypotonia and dystonia with movement is typical and as the disease progresses, a fixed, generalized dystonia with intermittent tonic posturing develops [48]. Early orofacial involvement, with dystonia and dyskinesias, has been described and can lead to swallowing dysfunction and dysphagia [48]. Dystonia occurs most often after at least one metabolic crisis but a subset of patients shows a more insidious-onset dystonia [47]. Akinetic–rigid parkinsonism or choreoathetoid movements are also common, leading to a mixed movement disorder in the majority of patients [48]. A late-onset form in a small subset of patients can present with non-specific neurological signs such as polyneuropathy, headaches, early-onset cognitive decline, or tremor [49]. Non-neurological manifestations are rare but an increased risk for adult-onset renal impairment has been reported [50]. Brain imaging classically shows a widened operculum with dilatation of the subarachnoid spaces surrounding underdeveloped frontotemporal lobes, subdural fluid collections, diffuse white matter changes, and abnormal signal intensity of the caudate and putamen. Encephalopathic crises lead to major changes in the putamen, globus pallidus, and caudate nucleus [51]. Given its treatable nature, GA-1 has been included in routine mass-spectrometry-based newborn screening in many countries. Metabolic crises carry a high morbidity and can be life-threatening. Immediate and adequate emergency treatment is imperative [52–54]. Early diagnosis and consequent metabolic treatment (low lysine diet, carnitine supplementation, and intensified emergency treatment during periods of catabolism) can prevent metabolic crises and subsequent dystonia (see Table 1.1). The movement disorders associated with GA-1 are discussed by Kölker in Chapter 12.

Number 6: Cerebral Creatine Deficiency

A group of three disorders, cerebral creatine deficiencies are important treatable IEMs. Movement disorders are relatively common in guanidinoacetate N-methyltransferase (GAMT) deficiency (OMIM 612736), which is an autosomal-recessive condition, and creatine transporter (CRTR) deficiency (OMIM 300352), which is X-linked [55, 56]. Dystonia and ataxia are the most common movement disorders in GAMT deficiency and are found in about a third of patients [55, 57]. Often, the movement disorder is a mixed picture of ataxia, dystonia, tremors, and choreoathetosis, superimposed on developmental delay, intellectual disability, seizures, and behavioral problems. While the onset of symptoms, including movement disorders, is usually during childhood, delayed presentations are possible [58]. In the largest cohort of males with CRTR deficiency published to date, motor dysfunction was reported in about two-thirds of patients [59]. Hypotonia was most common, followed by spasticity in about 30% and dystonia or athetosis in about 10% of cases. The latter included athetoid hand movements, intermittent dystonic posturing of the hands or wrists, choreoathetoid movements, or facial dystonia [59]. Early recognition and testing for creatine deficiency syndromes is crucial as disease-specific treatments can improve neurodevelopmental outcomes and can ameliorate movement disorders. A diagnosis can be achieved through a combination of biochemical tests (plasma or urine guanidinoacetate level, urine creatine to creatinine ratio) and magnetic reonance spectroscopy (see Table 1.1). Molecular testing can further support a diagnosis. GAMT deficiency is treated with a combination of creatine and ornithine supplementation as well as a protein- or arginine-restricted diet, while CRTR deficiency is treated with creatine, arginine, and glycine supplementation. *Mercimek-Andrews* discusses the latest knowledge about cerebral creatine deficiency in Chapter 28.

Number 5: Biotin–Thiamine-Responsive Basal Ganglia Disease

In 1998, Ozand and colleagues described a peculiar biotin-responsive basal ganglia disease in ten patients from consanguineous families [60]. Seven years later, bi-allelic mutations in *SLC19A3* [61], encoding the human thiamine transporter-2, were discovered as the cause of what is now referred to as biotin–thiamine-responsive basal ganglia disease (BTBGD, OMIM 607483). Mutations in *SLC19A3* leading to thiamine transporter-2 deficiency cause a spectrum of disease manifestations including at least two allelic diseases: BTBGD and Wernicke's-like encephalopathy [62]. Although thiamine transporter-2 deficiency is rare, a correct diagnosis is important

because of the therapeutic benefit resulting from high doses of biotin [60, 63] and/or thiamine [64, 65]. BTBGD usually presents acutely in childhood with encephalopathy, dysarthria, dysphagia, dystonia, external ophthalmoplegia, ataxia, and seizures; often in the setting of a minor febrile illness [66, 67]. Progression to severe cogwheel rigidity, dystonia, parkinsonism, quadriplegia, epilepsy, and, eventually, death is seen in individuals who are left untreated [66, 67]. Dystonia is the most common and important movement disorder occurring in nearly all patients [60, 63–66]. Like dystonia, ataxia is often part of the initial acute presentation [66]. Cogwheel rigidity is a classic feature and parkinsonism may develop in untreated individuals [66]. Brain imaging is often diagnostic and shows a "Leigh syndrome-like" pattern with central bilateral necrosis in the head of the caudate and putamen nuclei [66, 67]. Vasogenic edema is seen during the acute presentation while atrophy and gliosis in the affected regions are seen in chronic disease [67]. A dramatic response to thiamine or high-dose biotin corroborates the diagnosis and sequencing of *SLC19A3* confirms it (see Table 1.1). Misko and Eichler discuss their approach to BTBGD in Chapter 25.

Number 4: Ataxia with Vitamin E Deficiency

Ataxia with vitamin E deficiency (AVED, OMIM 277460) is a rare but important treatable condition caused by autosomal-recessive mutations in the alpha-tocopherol transfer protein (*TTPA*) gene [68]. AVED patients present in late childhood or adolescence with a slowly progressive spinocerebellar ataxia that often mimics Friedreich ataxia [69, 70]. Manifestations shared with the latter include a progressive ataxia, dysarthria, areflexia, loss of proprioception and sensory disturbance, as well as upper motor neuron signs. Cardiomyopathy, however, is usually not a prominent feature in AVED. Head titubation or tremor and dystonia seem more common to AVED and atypical presentations with dystonia preceding ataxia have been reported [71, 72]. The phenotype varies greatly between families and sometimes even within a given family. The mechanism of neurological dysfunction in AVED is unknown. Brain imaging shows cerebellar atrophy in the majority of patients [73]. Post-mortem studies show a loss of cerebellar Purkinje cells, posterior column degeneration, and lipofuscin accumulation [74]. The diagnosis is suspected when a very low plasma vitamin E concentration is detected (with a normal lipid and lipoprotein profile) and confirmed by a pathogenic biallelic *TTPA* variant. Early diagnosis is imperative as treatment with high doses of vitamin E [75] can halt disease progression or even reverse some manifestations (see Table 1.1) [70, 73, 76]. Primary prevention is possible and treatment should be continued lifelong. Plasma vitamin E levels should be monitored in regular intervals. Chapter 24 by Johansen and Aasly examines AVED in the context of the ataxias.

Number 3: GLUT1 Deficiency Syndrome

The phenotypic spectrum of glucose transporter type 1 (GLUT1) deficiency (OMIM 606777) forms a fascinating continuum from the classic syndrome of infantile-onset seizures, developmental delay, acquired microcephaly, and complex movement disorders [77] to several paroxysmal movement disorders including paroxysmal exercise-induced dyskinesia [78]. The underlying genetic defects are heterozygous variants in the glucose transporter gene, *SLC2A1* [79], leading to impaired glucose uptake through the blood–brain barrier. The majority of patients with GLUT1 deficiency have seizures that usually develop in infancy and are often resistant to treatment with conventional antiseizure drugs [80]. Motor symptoms in GLUT1 deficiency syndrome consist of both persistent (ataxia, dystonia, spasticity, chorea, myoclonus) and episodic paroxysmal dyskinesias of various forms [81]. The predominant movement disorders are ataxia (often as an ataxic-spastic gait), chorea (often mild and distal), and dystonia (more often limb then axial) in the classic form [81]. A peculiar paroxysmal eye–head movement disorder has recently been described in infants with GLUT1 deficiency syndrome and can be an important early manifestation [82]. Presentations with predominant ataxia and dystonia but without seizures have been reported [83]. Paroxysmal exercise (or exertion)-induced dyskinesia (PED, OMIM 612126) with or without epilepsy is a well-described phenotype in GLUT1 deficiency [79, 84]. PED is characterized by episodes of involuntary movements that typically last between 5 minutes and 30 minutes and are clearly triggered by sustained exercise. Other triggering or precipitating factors include stress, prolonged fasting, anxiety, and sleep deprivation. A classic presentation is that of lower limb dystonia brought on by running

or exercising for a few minutes, but other, often more complex, movement disorders involving chorea, dystonic movements, or myoclonus are also observed. First attacks typically occur in childhood or early adolescence. Most patients with PED have a normal interictal examination but learning disabilities or developmental delay is reported in some 30% of individuals. Other less common presentations of GLUT1 deficiency with a predominant movement disorder include cases presenting with choreoathetosis [85, 86], stereotypies [81], alternating hemiplegia of childhood [87], overlap syndromes between hemiplegic migraine and alternating hemiplegia [88], and writer's cramp [89]. In general, patients with GLUT1 deficiency syndrome show a variety of episodic symptoms [81]; hence, the presence of non-epileptic paroxysmal symptoms should raise suspicion for this disease. Recognizing the broad range of neurological phenotypes associated with GLUT1 deficiency is key to diagnosing this treatable IEM. A reduced cerebrospinal fluid (CSF) glucose concentration in the setting of a normal blood glucose level (often meeting a ratio of less than 0.4) is the classic laboratory abnormality. Brain imaging is usually normal [90]. Identification of a heterozygous pathogenic variant in *SLC2A1* confirms the diagnosis. Early and prompt treatment with a ketogenic [81] or related diet such as the modified Atkins diet [91] can mitigate symptoms, as nicely illustrated in the original description of the syndrome [77] and confirmed in many subsequent studies (see Table 1.1). Supplementation with L-carnitine and alpha-lipoic acid is often recommended. Several medications including phenobarbital, valproic acid, and carbonic anhydrase inhibitors should be avoided. Written by experts, Pons, Pearson, and De Vivo, Chapter 13 reviews the fascinating spectrum of movement disorders in GLUT1 deficiency syndrome.

Number 2: Wilson Disease

Perhaps the most classic example of a storage disease presenting with movement disorders, Wilson disease is an important cause of early-onset parkinsonism and dystonia (see Table 1.1). The onset of symptoms is generally in the first and second decade of life [92, 93] but onset at both a much younger and a much older age has been reported. Importantly, about half of Wilson disease patients initially present with neurological symptoms and the recognition of a movement disorder often leads to a diagnosis. Although the presence of the classic flapping tremor is strongly suggestive of Wilson disease (particularly in combination with dysarthria or psychiatric symptoms), the most common tremor is an irregular, jerky dystonic tremor. Dystonia is common, present in about two-thirds of patients, and can be focal, multifocal, or generalized as the disease progresses [94]. Focal forms of dystonia include blepharospasm, cervical dystonia, or risus sardonicus. With orofacial dystonia or oropharyngeal dyskinesia, patients may develop dysphonia, dysarthria, or dysphagia. Parkinsonism and ataxia are also found in Wilson disease although they are rarely an isolated clinical feature and are typically accompanied by other neurological deficits. Chorea is more common in children and adolescents with Wilson disease [95]. Kayser–Fleischer rings are present in nearly all Wilson disease patients with neurological involvement [93]. The diagnosis is suspected on clinical grounds with a slit-lamp examination and laboratory tests (serum ceruloplasmin and 24-hour urinary copper excretion) confirming the diagnosis. Brain imaging shows a variety of abnormalities, none of which are specific. Bi-allelic variants in the ATPase gene *ATP7B* corroborate the diagnosis. Treatment consists of chelation with penicillamine or trientine (see Table 1.1). The diagnosis of Wilson disease should be entertained in all young patients with unexplained movement disorders, particularly in patients with concomitant hepatic or psychiatric disease. Tuschl and Clayton cover Wilson disease in Chapter 17.

Number 1: Segawa Disease (Autosomal-Dominant GTPCH1 Deficiency)

The neurotransmitter disorders are perhaps the most classic metabolic movement disorders [96, 97], yet their diagnosis is often delayed [98]. This can have grave consequences as some of the monoamine transmitter diseases are amenable to treatment and early treatment can reduce morbidity. The most iconic neurotransmitter disease, in which a significant amelioration of motor symptoms can be achieved with appropriate treatment, is autosomal-dominant GTP cyclohydrolase 1 (GTPCH1) deficiency or Segawa disease (OMIM 128230) [99]. Segawa disease is the most common inherited dystonia in children and a form of dopa-responsive dystonia [100]. The mean age of onset in this disorder is typically between 5 years and 10 years of age and there is a well-established female preponderance [99, 101]. The classic presentation is that of postural dystonia of the extremities, most commonly of

the legs with inward rotation of the feet. This typically impairs walking and balance and leads to postural instability. Deep tendon reflexes can be brisk and pyramidal signs may be present, often leading to an apparent diagnosis of spastic diplegia [102]. If left untreated the dystonia progresses from focal to segmental and finally to generalized dystonia. Upon initial presentation, leg dystonia is most commonly followed by arm dystonia and cranio-cervical dystonia (including torticollis, blepharospasm, or oromandibular dystonia) [103]. Diurnal fluctuation with worsening in the evening is a recognized feature and a response to levodopa is usually evident quickly and remains sustained [99]. Atypical cases of action dystonia presenting as retrocollis or oculogyric crises, postural tremor, or features of parkinsonism (particularly in older individuals) have been reported and the clinician should be aware of these, as therapy with levodopa can have a profound effect. Adult-onset cases may present with writer's cramp or hand tremors only. Depression and anxiety seem more common in patients with dopa-responsive dystonia compared to the general population [101]. The diagnosis is made by a combination of clinical features, biochemical, and genetic tests and is supported by an L-dopa trial. Brain MRI is usually normal. The biochemical signature of GTPCH1 deficiency consists of a low CSF level of homovanillic acid (HVA), biopterin, and neopterin with a normal plasma level of phenylalanine. A phenylalanine challenge is sometimes employed to support the diagnosis. A therapeutic trial of levodopa/carbidopa is able to establish the cardinal feature of dopa-responsiveness. A gradual titration to a standard dose of 2–5mg/kg of levodopa daily is recommended (see Table 1.1). Genetic testing for variants in *GCH1* confirms the diagnosis. Levodopa/carbidopa has a sustained beneficial effect but a subset of patients may have residual symptoms [101]. Opladen and Brennenstuhl discuss the disorders of dopamine metabolism, including Segawa disease, in Chapter 21.

Conclusions and Future Directions

Metabolic movement disorders are an important and evolving group of disorders that bridge two subspecialty areas, "childhood-onset movement disorders" and "inborn errors of metabolism (IEMs)." Individually, many of these disorders are rare but in aggregate they represent a substantial clinical problem. Further, early-life onset is typical but not universal, and adult onset and phenotypic evolution with age occur. Clinical history and examination remain key for the selection and interpretation of biochemical, genetic, and imaging tests. Early detection of treatable metabolic movement disorders allows for referral to expert centers and timely intervention to prevent disease progression and irreversible central nervous system damage, and in some cases to improve neurological functioning. Detection of metabolic movement disorders for which no treatment currently exists beyond symptomatic management still allows for anticipatory guidance to affected families and improved management of comorbidities. Systematic studies that detail movement disorders in patients with IEMs are missing. Better phenotypic descriptions of movement disorders in IEMs are needed and depend on collaborative efforts between subspecialties and institutions. A summary of the top 10 treatable IEMs is given in Table 1.1.

Key Points and Clinical Pearls

- Most metabolic movement disorders are rare or even extraordinarily rare.
- Most metabolic movement disorders present in childhood but atypical cases may present in adulthood.
- Most metabolic movement disorders are multisystem diseases.
- Most metabolic movement disorders initially present with non-specific findings and movement disorders are rarely the presenting or only manifestation.
- Early recognition of movement disorders in inborn errors of metabolism (IEMs) can facilitate a diagnosis.
- Movement disorders cause significant morbidity in IEMs.
- Most metabolic movement disorders present with a mixed movement disorder phenomenology.
- Recognition of treatable IEMs that present with movement disorders is paramount as an early diagnosis can improve outcomes.
- Metabolic movement disorders require interdisciplinary care and collaboration between pediatric neurologists, neurologists, geneticists, and experts in metabolism.

Table 1.1 Top 10 treatable IEMs presenting with movement disorders

Number	Disease (related gene)	Age of onset	Movement disorder	Other manifestations	Diagnostic tests	Treatment[a]
10	Niemann–Pick disease type C (*NPC1*; *NPC2*)	Early childhood – adulthood	Ataxia, dystonia	Developmental delay, intellectual disability, dysarthria, supranuclear vertical gaze palsy, hepato-splenomegaly, dysphagia, dysarthria, seizures, gelastic cataplexy, acute psychosis, depression, obsessive-compulsive disorder and other neuropsychiatric symptoms	Biomarkers (oxysterols, lysosphingomyelin derivatives, bile acids) *NPC1/NPC2* sequencing	Miglustat Evidence level: 1b References: [104], [105]
9	Manganese transporter defects (*SLC30A10*; *SLC39A14*)	Childhood	Dystonia, parkinsonism, spasticity	Hypermanganesemia, hepatic cirrhosis (*SLC30A10*), polycythemia (*SLC30A10*), symmetric T1 signal hyperintensity in the basal ganglia consistent with manganese deposition	Blood manganese levels CBC, liver function tests, iron studies Brain MRI *SLC30A10* and *SLC39A14* sequencing	Chelation (disodium calcium EDTA) Evidence level: 4–5 Reference: [106]
8	Cerebrotendinous xanthomatosis (*CYP27A1*)	Young adulthood	Ataxia, spasticity, parkinsonism	Xanthomas, cognitive decline, seizures, psychiatric symptoms, peripheral neuropathy, neonatal cholestatic jaundice, bilateral childhood-onset cataracts, chronic diarrhea	Plasma cholestanol levels, bile alcohols in plasma and urine Brain MRI *CYP27A1* sequencing	Chenodeoxycholic acid Evidence level: 4 Reference: [107]
7	Glutaric aciduria type 1 (*GCDH*)	Abrupt onset in early childhood	Dystonia, parkinsonism, chorea	Acute encephalopathic crises during episodes of catabolism, macrocephaly, hypotonia, developmental delay, intellectual disability, seizures	Included in newborn screening in many countries Plasma and urine organic acids Plasma acylcarnitines Brain MRI *GCDH* sequencing GCDH enzyme analysis	Lysine and tryptophan restricted diet, carnitine supplementation, intensified emergency treatment during periods of catabolism Evidence level: 2c Reference: [53]
6	Cerebral creatine deficiencies (GAMT and CTRT deficiencies[b]) (*GAMT* *SLC6A8*)	Early childhood	Ataxia, dystonia, choreoathetosis	Developmental delay, intellectual disability, seizures, behavioral problems	GAMT deficiency: elevated GAA in urine, plasma and CSF; creatine deficiency on MRS; *GAMT* sequencing CTRT deficiency: elevated urine creatine to creatinine ratio; creatine deficiency on magnetic resonance spectroscopy; *SLC6A8* sequencing	GAMT: Creatine, ornithine, protein- or arginine-restricted diet CTRT: Creatine, arginine, glycine supplementation Evidence level: 4 Reference: [57]
5	Biotin and thiamine responsive basal ganglia disease (*SLC19A3*)	Abrupt onset in early childhood	Dystonia, parkinsonism, ataxia spasticity	Subacute encephalopathy, dysarthria, dysphagia, external ophthalmoplegia, seizures	Brain MRI *SLC19A3* sequencing	Treatment: Thiamine, biotin, trigger avoidance Evidence level: 4 Reference: [108]

4	Ataxia with vitamin E deficiency (*TTPA*)	Late childhood	Ataxia, dystonia	Dysarthria, areflexia, loss of proprioception and sensory disturbance, upper motor neuron signs	Plasma vitamin E level Brain MRI *TTPA* sequencing	Treatment: Oral vitamin E Evidence level: 4 Reference: [75]
3	GLUT1 deficiency syndrome (*SLC2A1*)	Early childhood – adulthood	Ataxia, dystonia, spasticity, chorea, myoclonus paroxysmal exertion-induced dyskinesia	Infantile-onset epileptic encephalopathy or other seizure disorder, acquired microcephaly, developmental delay, intellectual disability	CSF/plasma glucose ratio *SLC2A1* sequencing	Ketogenic (or related) diet Evidence level: 4 References: [83], [91]
2	Wilson disease (*ATP7B*)	Childhood – young adulthood	Dystonia including blepharospasm and risus sardonicus, parkinsonism, ataxia, chorea, tremor	Flapping tremor, Kayser–Fleischer rings, dysarthria, liver disease, psychiatric symptoms	Slit-lamp exam Serum ceruloplasmin and 24hr urinary copper excretion *ATP7B* sequencing	Penicillamine or trientine Evidence level: 1b Reference: [109]
1	Segawa disease (autosomal-dominant GTPCH1 deficiency) (*GCH1*)	Childhood	Dystonia, postural tremor, parkinsonism		CSF neurotransmitter levels Phenylalanine load test L-dopa trial *GCH1* sequencing	L-dopa/carbidopa Evidence level: 4 Reference: [110]

[a] Levels of evidence (source: www.cebm.net): Level 1a = systematic review of randomized controlled trials (RCT), 1b = individual RCT, 1c = 'all or none' (=[prolongation of] survival with therapy); Level 2a = systematic review of cohort studies, 2b = individual cohort study, 2c = 'outcomes research' (focused on end results of therapy for chronic conditions, including functioning and quality of life (www.ahrq.gov/prevention/clinician/index.html); Level 3 = systematic review of case–control studies; Level 4 = individual case–control study or case-series/report; Level 4–5 = single case report; Level 5 = expert opinion without critical appraisal. [b] Movement disorders do not seem to be prevalent in AGAT deficiency.

Directions for Future Research

- Clinical history and examination remain key for the selection and interpretation of biochemical, genetic, and imaging tests. Diagnostic pathways focused on the presenting movement disorder remain to be established.
- Improved methods for early detection of treatable metabolic movement disorders allow for referral to expert centers and timely intervention to prevent disease progression and irreversible central nervous system damage.
- Systematic studies that detail movement disorders in patients with IEMs are missing. Better phenotypic descriptions of movement disorders in IEMs are needed and depend on collaborative efforts between subspecialties and institutions.

References

1. Garrod AE. The incidence of alkaptonuria: A study in chemical individuality. Lancet. 1902;**2**:1616–20.
2. Garrod AE. The Croonian lectures on inborn errors of metabolism. Lancet. 1908;**2**:1–7.
3. Ferreira CR, van Karnebeek CDM, Vockley J, Blau N. A proposed nosology of inborn errors of metabolism. Genet Med. 2019;**21**(1):102–6.
4. Ebrahimi-Fakhari D, Saffari A, Wahlster L, et al. Congenital disorders of autophagy: An emerging novel class of inborn errors of neuro-metabolism. Brain. 2016;**139**(Pt 2):317–37.
5. Ebrahimi-Fakhari D, Van Karnebeek C, Munchau A. Movement disorders in treatable inborn errors of metabolism. Mov Disord. 2019;**34**:598–613.
6. Patterson MC, Mengel E, Wijburg FA, et al. Disease and patient characteristics in NP-C patients: Findings from an international disease registry. Orphanet J Rare Dis. 2013;**8**:12.
7. Stampfer M, Theiss S, Amraoui Y, et al. Niemann–Pick disease type C clinical database: Cognitive and coordination deficits are early disease indicators. Orphanet J Rare Dis. 2013;**8**:35.
8. Carstea ED, Morris JA, Coleman KG, et al. Niemann–Pick C1 disease gene: Homology to mediators of cholesterol homeostasis. Science. 1997;**277**(5323):228-31.
9. Naureckiene S, Sleat DE, Lackland H, et al. Identification of *HE1* as the second gene of Niemann–Pick C disease. Science. 2000;**290**(5500):2298–301.
10. Anheim M, Lagha-Boukbiza O, Fleury-Lesaunier MC, et al. Heterogeneity and frequency of movement disorders in juvenile and adult-onset Niemann–Pick C disease. J Neurol. 2014;**261**(1):174–9.
11. Ebrahimi-Fakhari D, Hildebrandt C, Davis PE, et al. The spectrum of movement disorders in childhood-onset lysosomal storage diseases. Mov Disord Clin Pract. 2018;**5**(2):149–55.
12. Sevin M, Lesca G, Baumann N, Millat G, Lyon-Caen O, Vanier MT, et al. The adult form of Niemann–Pick disease type C. Brain. 2007;**130**(Pt 1):120–33.
13. Koens LH, Kuiper A, Coenen MA, et al. Ataxia, dystonia and myoclonus in adult patients with Niemann–Pick type C. Orphanet J Rare Dis. 2016;**11**:121.
14. Patterson MC, Clayton P, Gissen P, et al. Recommendations for the detection and diagnosis of Niemann–Pick disease type C: An update. Neurol Clin Pract. 2017;**7**(6):499–511.
15. Synofzik M, Harmuth F, Stampfer M, et al. NPC1 is enriched in unexplained early onset ataxia: A targeted high-throughput screening. J Neurol. 2015;**262**(11):2557–63.
16. Synofzik M, Fleszar Z, Schols L, et al. Identifying Niemann-Pick type C in early-onset ataxia: two quick clinical screening tools. J Neurol. 2016;**263**(10):1911-8.
17. Canafoglia L, Bugiani M, Uziel G, et al. Rhythmic cortical myoclonus in Niemann–Pick disease type C. Mov Disord. 2006;**21**(9):1453–6.
18. Pineda M, Mengel E, Jahnova H, et al. A suspicion index to aid screening of early-onset Niemann–Pick disease type C (NP-C). BMC Pediatrics. 2016;**16**:107.
19. Patterson MC, Hendriksz CJ, Walterfang M, et al. Recommendations for the diagnosis and management of Niemann–Pick disease type C: An update. Mol Genet Metab. 2012;**106**(3):330–44.
20. Ory DS, Ottinger EA, Farhat NY, et al. Intrathecal 2-hydroxypropyl-beta-cyclodextrin decreases neurological disease progression in Niemann–Pick disease, type C1: A non-randomised, open-label, phase 1-2 trial. Lancet. 2017;**390**(10104):1758–68.
21. Tuschl K, Clayton PT, Gospe SM, Jr., et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. Am J Hum Genet. 2012;**90**(3):457–66.
22. Quadri M, Federico A, Zhao T, et al. Mutations in *SLC30A10* cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet. 2012;**90**(3):467–77.
23. Tuschl K, Mills PB, Parsons H, et al. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia:

A new metabolic disorder. J Inherit Metab Dis. 2008;**31**(2):151–63.

24. Gospe SM, Jr., Caruso RD, Clegg MS, et al. Paraparesis, hypermanganesaemia, and polycythaemia: A novel presentation of cirrhosis. Arch Dis Child. 2000;**83**(5):439–42.
25. Brna P, Gordon K, Dooley JM, Price V. Manganese toxicity in a child with iron deficiency and polycythemia. J Child Neurol. 2011;**26**(7):891–4.
26. Quadri M, Kamate M, Sharma S, et al. Manganese transport disorder: Novel SLC30A10 mutations and early phenotypes. Mov Disord. 2015;**30**(7):996–1001.
27. Zaki MS, Issa MY, Elbendary HM, et al. Hypermanganesemia with dystonia, polycythemia and cirrhosis in 10 patients: Six novel SLC30A10 mutations and further phenotype delineation. *Clin Genet*. 2018;**93**(4):905–12.
28. Tuschl K, Meyer E, Valdivia LE, et al. Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism–dystonia. Nature Commun. 2016;**7**:11601.
29. Aydemir TB, Kim MH, Kim J, et al. Metal Transporter Zip14 (SlC39A14) deletion in mice increases manganese deposition and produces neurotoxic signatures and diminished motor activity. J Neurosci. 2017;**37**(25):5996–6006.
30. Jenkitkasemwong S, Akinyode A, Paulus E, et al. SLC39A14 deficiency alters manganese homeostasis and excretion resulting in brain manganese accumulation and motor deficits in mice. Proc Natl Acad Sci USA. 2018;**115**(8):E1769–78.
31. Xin Y, Gao H, Wang J, et al. Manganese transporter SlC39A14 deficiency revealed its key role in maintaining manganese homeostasis in mice. Cell Discov. 2017;**3**:17025.
32. Rodan LH, Hauptman M, D'Gama AMet al. Novel founder intronic variant in SLC39A14 in two families causing manganism and potential treatment strategies. Mol Genet Metab. 2018;**124**(2):161–7.
33. Stamelou M, Tuschl K, Chong WK, et al. Dystonia with brain manganese accumulation resulting from SLC30A10 mutations: A new treatable disorder. Mov Disord. 2012;**27**(10):1317–22.
34. Di Toro Mammarella L, Mignarri A, Battisti C, et al. Two-year follow-up after chelating therapy in a patient with adult-onset parkinsonism and hypermanganesaemia due to SLC30A10 mutations. J Neurol. 2014;**261**(1):227–8.
35. Gulab S, Kayyali HR, Al-Said Y. Atypical neurologic phenotype and novel SLC30A10 mutation in two brothers with hereditary hypermanganesemia. Neuropediatrics. 2018;**49**(1):72–5.
36. Marti-Sanchez L, Ortigoza-Escobar JD, Darling A, et al. Hypermanganesemia due to mutations in SLC39A14: Further insights into Mn deposition in the central nervous system. Orphanet J Rare Dis. 2018;**13**:28.
37. Mukhtiar K, Ibrahim S, Tuschl K, Mills P. Hypermanganesemia with dystonia, polycythemia and cirrhosis (HMDPC) due to mutation in the *SLC30A10* gene. Brain Dev. 2016;**38**(9):862–5.
38. Cali JJ, Hsieh CL, Francke U, Russell DW. Mutations in the bile acid biosynthetic enzyme sterol 27-hydroxylase underlie cerebrotendinous xanthomatosis. J Biol Chem. 1991;**266**(12):7779–83.
39. Wong JC, Walsh K, Hayden D, Eichler FS. Natural history of neurological abnormalities in cerebrotendinous xanthomatosis. *J Inherit Metab Dis*. 2018;**41**(4):647–56.
40. Degos B, Nadjar Y, Amador Mdel M, et al. Natural history of cerebrotendinous xanthomatosis: A paediatric disease diagnosed in adulthood. Orphanet J Rare Dis.. 2016;**11**:41.
41. Lagarde J, Roze E, Apartis E, et al. Myoclonus and dystonia in cerebrotendinous xanthomatosis. Mov Disord. 2012;**27**(14):1805–10.
42. Rubio-Agusti I, Kojovic M, Edwards MJ, et al. Atypical parkinsonism and cerebrotendinous xanthomatosis: Report of a family with corticobasal syndrome and a literature review. Mov Disord. 2012;**27**(14):1769–74.
43. Mignarri A, Dotti MT, Federico A, et al. The spectrum of magnetic resonance findings in cerebrotendinous xanthomatosis: Redefinition and evidence of new markers of disease progression. J Neurol. 2017;**264**(5):862–74.
44. Berginer VM, Gross B, Morad K, et al. Chronic diarrhea and juvenile cataracts: Think cerebrotendinous xanthomatosis and treat. Pediatrics. 2009;**123**(1):143–7.
45. Biery BJ, Stein DE, Morton DH, Goodman SI. Gene structure and mutations of glutaryl-coenzyme A dehydrogenase: impaired association of enzyme subunits that is due to an A421V substitution causes glutaric acidemia type I in the Amish. Am J Hum Genet. 1996;**59**(5):1006–11.
46. Kolker S, Burgard P, Sauer SW, Okun JG. Current concepts in organic acidurias: Understanding intra- and extracerebral disease manifestation. J Inherit Metab Dis. 2013;**36**(4):635-44.
47. Kolker S, Garcia-Cazorla A, Valayannopoulos V, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: The initial presentation. J Inherit Metab Dis. 2015;**38**(6):1041–57.
48. Gitiaux C, Roze E, Kinugawa K, et al. Spectrum of movement disorders associated with glutaric aciduria

type 1: A study of 16 patients. Mov Disord. 2008;**23**(16):2392–7.

49. Kulkens S, Harting I, Sauer S, et al. Late-onset neurologic disease in glutaryl-CoA dehydrogenase deficiency. Neurology. 2005;**64**(12):2142–4.
50. Kolker S, Valayannopoulos V, Burlina AB, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: The evolving clinical phenotype. J Inherit Metab Dis. 2015;**38**(6):1059–74.
51. Harting I, Neumaier-Probst E, Seitz A, et al. Dynamic changes of striatal and extrastriatal abnormalities in glutaric aciduria type I. Brain. 2009;**132**(Pt 7):1764–82.
52. Heringer J, Boy SP, Ensenauer R, et al. Use of guidelines improves the neurological outcome in glutaric aciduria type I. Ann Neurol. 2010;**68**(5):743–52.
53. Boy N, Muhlhausen C, Maier EM, et al. Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: Second revision. J Inherit Metab Dis. 2017;40(1):75–101.
54. Strauss KA, Brumbaugh J, Duffy A, et al. Safety, efficacy and physiological actions of a lysine-free, arginine-rich formula to treat glutaryl-CoA dehydrogenase deficiency: Focus on cerebral amino acid influx. Mol Genet Metab. 2011;**104**(1-2):93–106.
55. Mercimek-Mahmutoglu S, Stoeckler-Ipsiroglu S, Adami A, et al. GAMT deficiency: Features, treatment, and outcome in an inborn error of creatine synthesis. Neurology. 2006;**67**(3):480–4.
56. Salomons GS, van Dooren SJ, Verhoeven NM, et al. X-linked creatine-transporter gene (SLC6A8) defect: A new creatine-deficiency syndrome. Am J Hum Genet. 2001;**68**(6):1497–500.
57. Khaikin Y, Sidky S, Abdenur J, et al. Treatment outcome of twenty-two patients with guanidinoacetate methyltransferase deficiency: An international retrospective cohort study. Eur J Paed Neurol. 2018;**22**(3):369–79.
58. O'Rourke DJ, Ryan S, Salomons G, et al. Guanidinoacetate methyltransferase (GAMT) deficiency: Late onset of movement disorder and preserved expressive language. Dev Med Child Neurol. 2009;**51**(5):404–7.
59. van de Kamp JM, Betsalel OT, Mercimek-Mahmutoglu S, et al. Phenotype and genotype in 101 males with X-linked creatine transporter deficiency. J Med Genet. 2013;**50**(7):463–72.
60. Ozand PT, Gascon GG, Al Essa M, et al. Biotin-responsive basal ganglia disease: A novel entity. *Brain*. 1998;**121**(Pt 7):1267–79.
61. Zeng WQ, Al-Yamani E, Acierno JS, Jr., et al. Biotin-responsive basal ganglia disease maps to 2q36.3 and is due to mutations in *SLC19A3*. Am J Hum Genet. 2005;**77**(1):16–26.
62. Kono S, Miyajima H, Yoshida K, et al. Mutations in a thiamine-transporter gene and Wernicke's-like encephalopathy. N Engl J Med. 2009;**360**(17):1792–4.
63. Debs R, Depienne C, Rastetter A, et al. Biotin-responsive basal ganglia disease in ethnic Europeans with novel *SLC19A3* mutations. Arch Neurol. 2010;**67**(1):126–30.
64. Serrano M, Rebollo M, Depienne C, et al. Reversible generalized dystonia and encephalopathy from thiamine transporter 2 deficiency. Mov Disord. 2012;**27**(10):1295–8.
65. Ortigoza-Escobar JD, Serrano M, Molero M, et al. Thiamine transporter-2 deficiency: Outcome and treatment monitoring. Orphanet J Rare Dis. 2014;**9**:92.
66. Alfadhel M, Almuntashri M, Jadah RH, et al. Biotin-responsive basal ganglia disease should be renamed biotin–thiamine-responsive basal ganglia disease: A retrospective review of the clinical, radiological and molecular findings of 18 new cases. Orphanet J Rare Dis. 2013;**8**:83.
67. Tabarki B, Al-Shafi S, Al-Shahwan S, et al. Biotin-responsive basal ganglia disease revisited: Clinical, radiologic, and genetic findings. Neurology. 2013;**80**(3):261–7.
68. Hentati A, Deng HX, Hung WY, et al. Human alpha-tocopherol transfer protein: Gene structure and mutations in familial vitamin E deficiency. Ann Neurol. 1996;**39**(3):295–300.
69. Harding AE, Matthews S, Jones S, et al. Spinocerebellar degeneration associated with a selective defect of vitamin E absorption. N Engl J Med. 1985;**313**(1):32–5.
70. El Euch-Fayache G, Bouhlal Y, Amouri R, Feki M, Hentati F. Molecular, clinical and peripheral neuropathy study of Tunisian patients with ataxia with vitamin E deficiency. *Brain*. 2014;**137**(Pt 2):402–10.
71. Becker AE, Vargas W, Pearson TS. Ataxia with vitamin e deficiency may present with cervical dystonia. Tremor Other Hyperkinet Mov (NY). 2016;**6**:374.
72. Angelini L, Erba A, Mariotti C, et al. Myoclonic dystonia as unique presentation of isolated vitamin E deficiency in a young patient. Mov Disord. 2002;**17**(3):612–4.
73. Mariotti C, Gellera C, Rimoldi M, Mineri R, Uziel G, Zorzi G, et al. Ataxia with isolated vitamin E deficiency: Neurological phenotype, clinical follow-up and novel mutations in *TTPA* gene in Italian families. Neurol Sci. 2004;**25**(3):130–7.
74. Yokota T, Uchihara T, Kumagai J, et al. Postmortem study of ataxia with retinitis pigmentosa by mutation

of the alpha-tocopherol transfer protein gene. J Neurol Neurosurg Psychiatry. 2000;**68**(4):521–5.

75. Schuelke M. Ataxia with vitamin E deficiency. GeneReviews®. 2005;May 20 (updated 16 Oct 2013).
76. Gabsi S, Gouider-Khouja N, Belal S, et al. Effect of vitamin E supplementation in patients with ataxia with vitamin E deficiency. Eur J Neurol. 2001;**8** (5):477–81.
77. De Vivo DC, Trifiletti RR, Jacobson RI, et al. Defective glucose transport across the blood–brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N Engl J Med. 1991;**325** (10):703–9.
78. Pearson TS, Akman C, Hinton VJ, Engelstad K, De Vivo DC. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep. 2013;**13**(4):342.
79. Suls A, Dedeken P, Goffin K, et al. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in *SLC2A1*, encoding the glucose transporter Glut1. Brain. 2008;**131**(Pt 7):1831–44.
80. Pong AW, Geary BR, Engelstad KM, et al. Glucose transporter type I deficiency syndrome: Epilepsy phenotypes and outcomes. Epilepsia. 2012;**53** (9):1503–10.
81. Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in Glut-1 deficiency. Mov Disord. 2010;**25**(3):275–81.
82. Pearson TS, Pons R, Engelstad K, et al. Paroxysmal eye–head movements in Glut1 deficiency syndrome. Neurology. 2017;**88**(17):1666–73.
83. Leen WG, Klepper J, Verbeek MM, et al. Glucose transporter-1 deficiency syndrome: The expanding clinical and genetic spectrum of a treatable disorder. Brain. 2010;**133**(Pt 3):655–70.
84. Weber YG, Storch A, Wuttke TV, et al. Glut1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak. J Clin Invest. 2008;**118**(6):2157–68.
85. Perez-Duenas B, Prior C, Ma Q, et al. Childhood chorea with cerebral hypotrophy: A treatable Glut1 energy failure syndrome. Arch Neurol. 2009;**66** (11):1410–4.
86. Friedman JR, Thiele EA, Wang D, et al. Atypical Glut1 deficiency with prominent movement disorder responsive to ketogenic diet. Mov Disord. 2006;**21** (2):241–5.
87. Rotstein M, Doran J, Yang H, et al. Glut1 deficiency and alternating hemiplegia of childhood. Neurology. 2009;**73**(23):2042-4.
88. Weller CM, Leen WG, Neville BG, et al. A novel *SLC2A1* mutation linking hemiplegic migraine with alternating hemiplegia of childhood. Cephalalgia. 2015;**35**(1):10–5.
89. Urbizu A, Cuenca-Leon E, Raspall-Chaure M, et al. Paroxysmal exercise-induced dyskinesia, writer's cramp, migraine with aura and absence epilepsy in twin brothers with a novel *SLC2A1* missense mutation. J Neurol Sci. 2010;**295**(1-2):110–3.
90. Pascual JM, Van Heertum RL, Wang D, Engelstad K, De Vivo DC. Imaging the metabolic footprint of Glut1 deficiency on the brain. Ann Neurol. 2002;**52** (4):458–64.
91. Leen WG, Mewasingh L, Verbeek MM, et al. Movement disorders in Glut1 deficiency syndrome respond to the modified Atkins diet. Mov Disord. 2013;**28**(10):1439–42.
92. Machado A, Chien HF, Deguti MM, et al. Neurological manifestations in Wilson's disease: Report of 119 cases. Mov Disord. 2006;**21**(12):2192–6.
93. Taly AB, Meenakshi-Sundaram S, Sinha S, Swamy HS, Arunodaya GR. Wilson disease: Description of 282 patients evaluated over 3 decades. Medicine. 2007;**86**(2):112–21.
94. Svetel M, Kozic D, Stefanova E, et al. Dystonia in Wilson's disease. Mov Disord 2001;**16**(4):719–23.
95. Walshe JM, Yealland M. Wilson's disease: The problem of delayed diagnosis. J Neurol Neurosurg Psychiatry. 1992;**55**(8):692–6.
96. Pearl PL. Monoamine neurotransmitter deficiencies. Handbook Clin Neurol. 2013;**113**:1819–25.
97. Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders: Clinical advances and future perspectives. Nature Rev Neurol. 2015;**11**(10):567–84.
98. Jan MM. Misdiagnoses in children with Dopa-responsive dystonia. Pediatr Neurol. 2004;**31** (4):298–303.
99. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol. 2003;**54** (Suppl 6):S32–45.
100. Assmann B, Surtees R, Hoffmann GF. Approach to the diagnosis of neurotransmitter diseases exemplified by the differential diagnosis of childhood-onset dystonia. Ann Neurol. 2003;**54** (Suppl 6):S18–24.
101. Tadic V, Kasten M, Bruggemann N, et al. Dopa-responsive dystonia revisited: Diagnostic delay, residual signs, and nonmotor signs. Arch Neurol. 2012;**69**(12):1558–62.
102. Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: Long-term treatment response and prognosis. Neurology. 1991;**41**(2 Pt 1)):174–81.

103. Trender-Gerhard I, Sweeney MG, Schwingenschuh P, et al. Autosomal-dominant GTPCH1-deficient DRD: Clinical characteristics and long-term outcome of 34 patients. J Neurol Neurosurg Psychiatry. 2009;**80** (8):839–45.

104. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann–Pick C disease: A randomised controlled study. Lancet Neurol. 2007;**6**(9):765–72.

105. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann–Pick disease type C. Orphanet J Rare Dis. 2018;**13**:50.

106. Tuschl K, Clayton PT, Gospe SM, Jr., Mills PB. Dystonia/parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease. GeneReviews. 2003 Jul 16 (updated Apr 14, 2016).

107. Federico A, Dotti MT, Gallus GN. Cerebrotendinous xanthomatosis. GeneReviews®. 2003;Jul 16 (updated Apr 14, 2016).

108. Tabarki B, Al-Hashem A, Alfadhel M. Biotin-thiamine-responsive basal ganglia disease. GeneReviews®. 2013;Nov 21 (initial posting).

109. Weiss KH. Wilson disease GeneReviews®. 1999; October 22 (updated Jul 29, 2016).

110. Furukawa Y. GTP Cyclohydrolase 1-deficient dopa-responsive dystonia. *GeneReviews®*. 2002; Feb 21 (updated Jan 24, 2019).

Chapter 2

The Importance of Movement Disorders in Inborn Errors of Metabolism

Angeles García-Cazorla

Introduction

The study of abnormal movements has been an important topic in neurology since over a century ago. In fact, movement disorders are a rapidly growing subspecialty that receives contributions from different disciplines including adult neurology, child neurology, neurosurgery, psychiatry, and physical medicine and rehabilitation. The main focus is on normal and abnormal functioning of the motor systems and on possibilities to treat motor dysfunction. The traditional approach to study and treat movement disorders has been largely based on the analysis of the clinical phenomenology that results from the interaction of a number of brain regions that provide motor control under different functional states. Therefore the development of anatomical and physiological studies of the neural circuitry of motor systems, together with the precise description of corresponding clinical signs, has encouraged the study of this broad topic during the last decades. Brain imaging, neurophysiology, and basic research studies in animal models have provided an increasing amount of knowledge. However, even though inborn errors of metabolism (IEMs) have more than 100 years of history [1], they have only become a relevant part of the movement disorders field in the last couple of decades. This is due to the fact that IEMs historically were considered a pediatric subspecialty and therefore have been the province predominantly of pediatricians. As neurological manifestations have been appreciated to be a major contributing factor, an increasing body of literature has highlighted the vulnerability of the nervous system in IEMs. Some of the first systematic approaches to well-defined neurological syndromes were reported in 2007 and 2009 [2–5]. From these first descriptions until now, both neurology and the field of IEMs have experienced a significant transformation driven by the advent of next-generation sequencing techniques.

The recent updated nosology of IEMs [6] includes more than 1,100 diseases and almost 80% of them exhibit neurological symptoms. In particular, during the last 5 years, more than 300 new IEMs have been described as emerging causes of neurological dysfunction. These new disorders have changed paradigms, transforming the concept and classification of IEMs and are contributing enormously to our understanding of mechanisms in neurological diseases. Therefore, there is a great need for both fields – neurology (and in particular the field of movement disorders) and metabolism – to converge and share perspectives. Crucial aspects such as clinical phenomenology, pathophysiological categories, and therapeutic approaches need to be redefined.

General Concepts

Prevalence and Types of Movement Disorders in IEMs

There are no detailed epidemiological studies that provide the exact prevalence of movement disorders in IEMs. However, if we consider that 80% of IEMs exhibit neurological symptoms and that movement disorders include a broad spectrum of manifestations appearing at any age, one would estimate that they are present in some 70% of IEMs. Movement disorders in IEMs include ataxia, athetosis, chorea, dystonia, myoclonus, stereotypies, tics, tremor, and parkinsonism. They may be accompanied by hypotonia, weakness, spasticity, apraxia, and other motor deficits [7]. Movement disorders have been traditionally divided into "hyperkinetic" disorders, in which there is excessive movement, and "hypokinetic" disorders, in which there is a paucity of voluntary movements. Hyperkinetic disorders include chorea, dystonia, athetosis, myoclonus, stereotypies, tics, and tremor. They consist of abnormal and often repetitive

involuntary movements. Hypokinetic movement disorders mainly present as akinetic–rigid syndromes.

All kinds of movement disorders are present in IEMs [8]. As a general rule, hyperkinetic and complex movement disorders (a combination of different types of movement disorders) are common in children. In fact, parkinsonism is very rare in the pediatric age group. In a case series of pediatric movement disorders including 673 individuals seen at a single center, Fernández-Álvarez and Aicardi found a prevalence of parkinsonism of 2%, and the average age at onset was 11.3 years [9]. In contrast, in adolescents and adults, hypokinetic movement disorders are more frequent, particularly in neurodegenerative diseases.

Special Characteristics of Movement Disorders in IEMs

The diagnosis of IEMs that primarily affect the nervous system is a major challenge. The same neurological symptoms and pattern of disease progression may be caused by non-metabolic disorders. Over the last years, this has become even more challenging because of the rapidly increasing number of new disease entities and novel pathophysiological categories. Early detection remains key, as outcomes tend to be better, particularly in treatable IEMs. Some characteristics of movement disorders that may lead to the suspicion of an IEM are highlighted (Box 2.1). The diagnostic challenge is even greater in early childhood, where many features of neurodevelopmental disorders can mimic a movement disorder. Similarly, patients with advanced neurodegenerative disease as a result of different IEMs may present with similar movement disorders.

Box 2.1 Special characteristics of movement disorders in IEMs

- Diffuse clinical picture with other neurological or systemic symptoms
- Atypical presentations, such as the coexistence of different neurological features, that do not localize to a distinct neuroanatomical region
- Acute, subacute, or recurrent presentations including severe presentation such as with status dystonicus
- Progressive movement disorders
- Focal movement disorders (such as unilateral dystonia) do not exclude an IEM, however as a rule, focal signs tend to generalize or be associated with other symptoms over time.
- Fluctuation of symptoms: For example, in neurotransmitter defects with dopaminergic dysfunction, dystonia and oculogyric crises may worsen over the day and improve with rest. In glucose transporter type 1 (GLUT1) deficiency syndrome, symptoms like ataxia, dysarthria, and dyskinesia may worsen with fasting and improve after eating or rest; in urea cycle disorders, altered mental status, hyperkinesia, and other symptoms may develop with intercurrent illnesses or fluctuate depending on protein intake.
- Symmetrical lesions on brain MRI
- Lack of response to symptomatic treatment
- Movement disorders that are not explained by classic etiologies (acquired brain injury, hypoxia, stroke, trauma, infection, inflammation, demyelinating disease)
- Positive family history, particularly if suggestive on an autosomal-recessive inheritance

Biochemical and Neurobiological Aspects of Movement Disorders in IEMs

Neurobiology of Movement Disorders

The complex neurobiology of movement disorders goes beyond the scope of this chapter. Nevertheless, it is interesting to summarize the main characteristics of brain circuitries involved in motor dysfunction, in order to better understand the reason why movement disorders are frequent in IEMs. Correlations of involuntary movements with pathological changes in the basal ganglia were established in the first half of the twentieth century. The classic teaching is that the basal ganglia and the cerebellum are the two major motor centers controlling voluntary movements [10].

Dystonia and parkinsonism have been explained based on the classic model of basal ganglia circuitry. Cortical input to the striatum is relayed to two main output nuclei: the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNpr), through indirect and direct pathways. The activity in the direct pathway facilitates movement by reducing the inhibitory output from the GPi. The activation of the indirect pathway increases inhibitory outputs and reduces movement. Dystonia is thought to result from an imbalance in the direct and indirect pathways, which leads to reducing the inhibition of the thalamus and increasing the excitability of the motor cortex. Conversely, parkinsonism results from the overactivity of GPi and SNpr output, which causes an increased

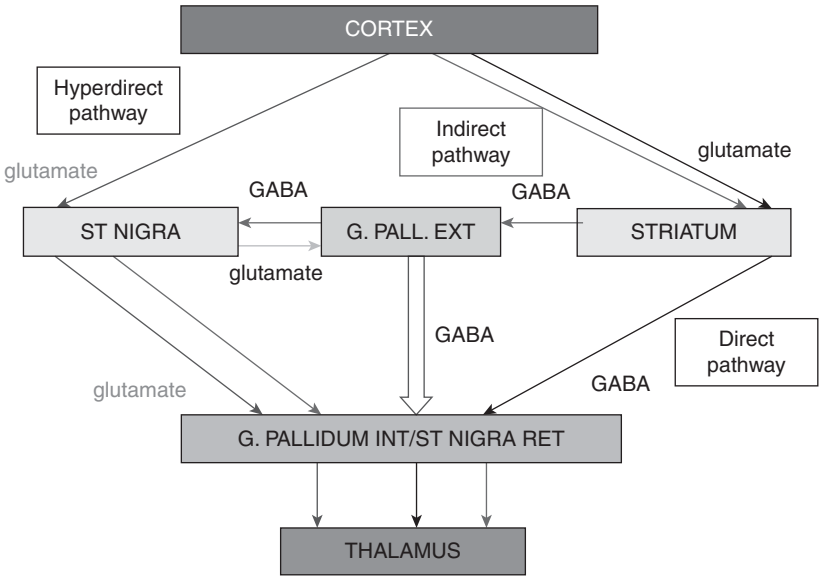

Figure 2.1 Dynamic model of basal ganglia function. The hyperdirect pathway, the cortical-subthalamo-pallidal circuit, regulates the execution of voluntary movement. This pathway inhibits all voluntary motor tasks. Glutamate and GABA are involved in the modulation of this circuit.
Abbreviations: G. PALL. globus pallidus; INT: interna; EXT: externa; RET: reticularis; ST: substantia.

inhibition of the thalamus and reduced motor cortex excitability [11].

Other hyperkinetic involuntary movement disorders such as chorea or ballismus are thought to result from a disinhibition of motor output caused by the disturbance of inhibitory mechanisms in the basal ganglia [10]. This dynamic model of basal ganglia function (Figure 2.1) is mediated by dopamine, acetylcholine, glutamate, and gamma-aminobutyric acid (GABA). Pathways that connect motor structures are myelinated axons organized in complex circuits. Glutamate and GABA are key molecules in both energy and intermediate metabolism. Excess glutamate can lead to excitotoxicity, a process that is common not only in intoxication-type IEMs but in many neurodegenerative diseases. Disorders of complex molecules such as peroxisomal and lysosomal disorders strongly affect white matter composition and integrity [12]. Moreover, axonal transport is a high-energy-consuming mechanism. Therefore, the proper function of the basal ganglia, together with other motor structures and the circuits between them, depends on a perfectly regulated metabolism, which explains the high prevalence of movement disorders in IEMs.

Biochemical Properties of Motor Structures and Circuitries

Although elementary concepts have been introduced in the paragraph above, we are far from having a detailed knowledge about the biochemical properties of the basal ganglia and other brain structures involved in motor function. Additionally, brain metabolism evolves over time, being markedly different across the diverse pre- and postnatal developmental stages, as well as throughout adulthood and with aging.

Recent neurochemical studies of the striatum reveal a heterogeneous pattern with separation into discrete compartments known as striosome and matrix compartments. These differ in their expression of neurochemical markers, and have also been suggested to have different involvements in a range of neurological diseases [13]. The striosome compartments form a three-dimensional labyrinth-like structure that interdigitates the matrix and expresses high levels of μ-opioid receptor, substance P, dopamine 1-receptor, met-enkephalin, calretinin, nuclear receptor subfamily 4 group A member 1 (Nr4a1), pro-dynorphin, generalized anxiety disorder 2-item (GAD-2), and growth response protein 1 (ERG-1). The extrastriosomal matrix, by contrast, is enriched with calbindin, somatostatin, enkephalin, DA2-receptor, and cholinergic markers including acetylcholine esterase and choline acetyltransferase [13–16]. Striosome and matrix compartments are thought to have distinct anatomical connections and developmental programs and may be separately involved in pathological processes [17].

A recent study investigating the longitudinal increase of brain metabolite levels in 5–10-year-old

children [18], reported increasing levels of glutamate (Glu) and glutamine, N-acetylaspartate (NAA), and NAA+NAAG (N-acetyl-aspartyl-glutamate). The increase of NAA+NAAG levels with age was about twice that of NAA, implying similar increases in NAAG levels. The age-related rise of both NAA and Glu levels are likely linked to the production of NAAG (NAA is combined with Glu to form NAAG). A possible explanation for increased NAAG levels in the basal ganglia is its role in regulating the release of glutamate and dopamine [19], indicating an age-related increased demand to modulate neurotransmitters during this developmental stage. The age-related rise in Glu could also be associated with an increase in intracellular Ca^{2+} that triggers biochemical events involved in both functional and structural plasticity of the synapses in childhood [20].

This complex metabolic regulation across different life stages may interact with the abnormal network of metabolites and cellular mechanisms that are characteristic of IEMs.

Pathophysiological Categories of IEMs That Cause Prominent Movement Disorders

The recently updated nosology of IEMs lists more than 1,100 IEMs, provisionally classified into 110 groups [6]. These groups are very diverse and may imply either one compound, one pathway, one cofactor common to many pathways, one system common to several compounds, and multiple pathophysiological mechanisms involving energy production, mitochondrial machinery, signaling and trafficking, various organelles, nucleic acid metabolism, or metabolite repair. An extensive list of conditions may be overwhelming to clinicians and has little in common with the clinical approach to IEMs. A simplified and updated classification of IEMs proposed by Professor Jean-Marie Saudubray mixes elements from the practical diagnostic approach with pathophysiological considerations into three large categories, based on the size of molecules ("small and simple" or "large and complex") and their implication in energy metabolism [21] (Box 2.2)

Box 2.2 Movement disorders according to the different pathophysiological categories of IEMs

- Movement disorders in intoxication-type disorders may present acutely at any age. They may be also one of the prominent neurological symptoms in the long-term evolution of the disease; i.e. generalized dyskinesias and chorea in glutaric aciduria type 1 (GA-1), tremor in phenylketonuria, diverse movement disorders in galactosemia.
- Movement disorders in small-molecule deficiencies are associated with early and severe global encephalopathies in the majority of cases. Spasticity is the most common sign in amino acid and fatty acid defects whereas dystonia and dyskinetic movements are common in metal storage diseases
- Movement disorders are frequent in defects of energy metabolism since the basal ganglia and cerebellum are particularly vulnerable. Movement disorders can appear abruptly in acute crises in "classic" energy defects such as Leigh syndrome. GLUT1 deficiency syndrome is an important disorder with a wide range and expanding phenotype of movement disorders including ataxia, dyspraxia, spasticity, abnormal ocular movements, chorea, and paroxysmal dyskinetic attacks.
- Movement disorders are common in complex molecule defects and tend to be chronic and progressive.

Disorders of Small and Simple Molecules

Almost all IEMs in this category have metabolic markers and their diagnosis relies on plasma, urine, and cerebrospinal fluid (CSF) investigations (amino acid, organic acid, and metals analyses, etc.) with a metabolic signature. There are two subcategories in small-molecule disorders, depending on whether the phenotype primarily results from an accumulation or a deficiency:

1. Diseases linked to an accumulation: "Intoxication" disorders. These IEMs result from the abnormal accumulation of compounds proximal to the block and potentially reverse as soon as the accumulation is removed. Disorders in this category share some characteristics: (i) They do not interfere with fetal development and present after a symptom-free interval (days to years) with clinical signs of intoxication (acute, intermittent, chronic, and even progressive) provoked by fasting, catabolism, fever, intercurrent illness, or food intake. (ii) Most of these disorders are treatable and require prompt removal of the "toxin or stressor." Treatments include special diets, scavengers, and cofactors. (iii) This group encompasses IEMs of amino acid

metabolism (phenylketonuria or maple syrup urine disease), urea cycle defects, organic acidurias (methylmalonic aciduria, propionic aciduria, or GA-1), disorders of carbohydrate metabolism, metal storage diseases (i.e Wilson disease), and the porphyrias. Some purines/pyrimidines and metabolite repair defects (D/L-2-OH-glutaric aciduria and others) could be also included in this group.

2. Diseases linked to a deficiency: Symptoms result primarily from the defective synthesis of compounds distal to a block or from the defective transport of an essential molecule. These are, at least in theory, treatable by providing a missing compound. Most of these defects interfere with fetal development, have a prenatal or neonatal presentation, present with congenital defects, and share many characteristics with disorders in the complex molecule group. This group encompasses amino acid and fatty acid synthesis and transport defects and cofactor deficiencies (e.g. zinc, manganese, and copper) [22, 23].

Energy-Metabolism-Related Defects

These consist of IEMs with symptoms due, at least in part, to a deficiency in energy production or utilization within one or more tissues.

1. Membrane carriers (glucose, fatty acids, ketone bodies, monocarboxylic acids). GLUT1 (the glucose cerebral transporter) deficiency is an example.
2. Mitochondrial defects encompass aerobic glucose oxidation defects, presenting with congenital lactic acidemia (pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase, and Krebs cycle defects), mitochondrial respiratory-chain disorders, mitochondrial transporters of energetic molecules, amino acids, ions, metals and vitamins, coenzyme Q biosynthesis, fatty acid oxidation, and ketone body defects. A large and growing group of already more than 110 disorders involves the mitochondrial machinery: Mitochondrial fusion, fission, replication, mitochondrial protein import and mitochondrial protein quality control, ribosomopathies, mitochondrial DNA depletion and intergenomic modification, mitochondrial transfer RNA (tRNA) synthetases and tRNA modification, phospholipid membrane metabolism, and other biological processes.
3. Cytoplasmic energy defects include disorders of glycolysis, glycogen metabolism, gluconeogenesis, hyperinsulinism, and GLUT1 deficiency syndrome (all treatable), creatine metabolism disorders (partially treatable), and, finally, inborn errors of the pentose phosphate pathways (untreatable).

Complex Molecules

This expanding group encompasses diseases that disturb the metabolism of complex molecules and involves metabolic processes in all organelles (mitochondria, lysosomes, peroxisomes, endoplasmic reticulum, Golgi apparatus, lipid droplets, and the synaptic vesicle). Cellular membranes are formed from a chemically diverse set of lipids. Lipids have several major functions in cells, including membrane structural components, energy and heat sources, signaling molecules, protein recruitment platforms, and substrates for post-translational protein–lipid modification [24]. In this complex molecule category there are two main subgroups:

1. Defects of catabolism, leading to storage of macromolecules (classic lysosomal defects, e.g. sphingolipidoses or mucopolysaccharidoses).
2. Synthesis, remodeling, processing, trafficking, and quality-control defects:
   This rapidly expanding group encompasses classic organelle disorders (lysosome and peroxisome defects), congenital disorders of glycosylation (CDG) syndromes, and glycosaminoglycan synthesis defects [25], inborn errors of cholesterol and bile acid synthesis, the vast new group of complex-lipid synthesis and remodeling defects (triglycerides, phospholipids, glycosphingolipids), fatty acid synthesis and transport (elongation of essential and non-essential fatty acids, branched-chain fatty acids, fatty alcohols, and eicosanoids like arachidonic acid derived compounds and leukotrienes) [12, 26]. These all share some characteristics. They may interfere with embryonal and fetal development and have a pre- or neonatal presentation. Symptoms are permanent, very often progressive, independent of intercurrent events, and unrelated to food intake. Furthermore, many other defects affecting intracellular vesiculation, trafficking, processing of complex molecules, and quality-control processes (like protein folding and autophagy) have been recently discovered using the next-generation sequencing (NGS) technique. Some examples include CEDNIK due to mutation of the *SNAP29* gene

implicated in intracellular vesiculation [27], hereditary spastic paraplegia due to *AP5Z1* mutations [28], Rabenosyn-5 mutations resulting in defective endocytic trafficking [29], synaptic vesicle cycle disorders [30], and congenital disorders of autophagy [31].

Main Types of Movement Disorders in IEMs

Age-Related Aspects

Movement disorders may have different characteristics according to the age at presentation, both in general but also within the spectrum of a given IEM [32]. Traditionally, clinical neurology relies on a collection of well-defined symptoms (i.e. epilepsy, intellectual disability, movement disorders, and others). While these are very useful categories, there isn't always a pathophysiological rationale linked to this approach. In children, a spectrum of abnormal movements is more common than an isolated movement disorder. In fact, the younger the patient, the higher the likelihood of a combination of different motor symptoms (dyskinetic movements, pyramidal signs, hypotonia, ataxia). For example, whereas children with hereditary spastic paraparesis may have additional neurological manifestations, e.g. intellectual disability or epilepsy, adults are more likely to present with pure spastic paraparesis. Hyperkinetic movements are frequent in children whereas hypokinetic ones are rare and tend to be complex. In children with IEMs, dystonia is often a prelude to parkinsonism in later childhood and adolescence. In adults with IEMs, dystonia tends to involve the orofacial region [33].

Considerations Based on Movement Disorder Phenomenology

Dystonia

Dystonia is related to lesions or dysfunction in the pallidus and striatum, although thalamic, cortical, and cerebellar involvement may also contribute. It is defined by the occurrence of sustained/intermittent muscle contractions, causing aberrant, repetitive twisting movements and abnormal postures [34]. Dystonia can be classified as focal (affecting a single body part), multifocal (affecting two or more non-contiguous regions), segmental (affecting two or more contiguous body parts), hemidystonia (affecting the arm and leg on one side of the body), and generalized [35]. Focal and slowly progressive isolated dystonia is most likely to be caused by primary neurotransmitter deficiencies (such as GTP cyclohydrolase type I, other tetrahydrobiopterin, and tyrosine hydroxylase deficiencies) but can be also the initial sign of complex molecule defects (neurodegeneration with brain iron accumulation [NBIA] syndromes such as pantothenate kinase-associated neurodegeneration [PKAN], or late-onset lysosomal disorders). If dystonia appears abruptly, settles rapidly, and is generalized and postural from the very first stages of the disease, a metabolic cause should be strongly considered (Table 2.1). Some of the most common IEMs in abrupt dystonia are organic acidurias (such as GA-1) and mitochondrial disorders [8]. GLUT1 deficiency syndrome can cause paroxysmal exercise-induced dyskinesia and also complex movement disorders even without epilepsy [8].

Chorea

The term "chorea" is a derived from the Greek word, *choreia*, for dancing. Chorea is related to dysfunction of the striatum and subthalamic nucleus and refers to involuntary, brief, random, rapid, spasmodic movements of the face, neck, and proximal limb muscles. These are neither rhythmic nor stereotypical. Chorea may extend to the oropharyngeal muscles, generating swallowing difficulties, and can migrate from one side of the body to the other [8]. It is a prominent feature of GA-1, GLUT1 deficiency syndrome, Lesch–Nyhan disease, PKAN and other NBIA syndromes, homocystinuria, and Niemann–Pick disease type C (NPC), among others (Table 2.1).

Parkinsonism (Hypokinetic–Rigid Syndrome)

Early-onset forms of parkinsonism have distinctive features as compared to parkinsonism in adults. In general, the descriptions of a "hypokinetic–rigid syndrome," "dystonia-parkinsonism," "parkinsonism-plus," or "parkinsonism-like" are more accurate in children. IEMs constitute an important group amongst the genetic causes of parkinsonism at any age. The main IEMs causing parkinsonism (Table 2.1) are: (1) Metal storage diseases such as Wilson disease, manganese transporter deficiency, or different forms of NBIA; (2) Neurotransmitter defects (initially present with dystonia and later develop into dystonia-parkinsonism); (3) Lysosomal and complex molecule disorders. In the latter group, special consideration should be given to the

Table 2.1 Predominant movement disorders and the associated clinical signs with recommended laboratory tests

Predominant movement disorder	Associated clinical features	Selected laboratory tests
Dystonia	**Pure, isolated dystonia** May be the initial presentation of homocysteine-related disorders, mitochondrial disorders, neurotransmitter defects, and metal-related disorders	Plasma amino acids and total homocysteine, lactate, pyruvate, metals and ceruloplasmin Biogenic amines and pterins (CSF) *DYT* genes, in particular: *DYT1*, *DYT6*, *DYT25*, *DYT4* Exome sequencing
	Parkinsonism Early forms are mainly linked to neurotransmitter defects and mitochondrial diseases	Biogenic amines and pterins (CSF) Metals and ceruloplasmin, lactate, pyruvate, plasma amino acids (consider respiratory chain activity and mitochondrial DNA study) Consider *PANK2* and other NBIA genes depending on MRI and other clinical findings Lysosomal disorders at late stages Gaucher disease and the neuronal ceroid lipofuscinoses may present with parkinsonism in early childhood Genes related to juvenile and hereditary forms of parkinsonism Exome sequencing
	Cerebellar ataxia Dystonia in combination with ataxia is a mixed movement disorder found in organic acidurias (in particular during metabolic crises) Mitochondrial diseases, and complex molecule disorders (storage and defects in synthesis, processing, trafficking, and autophagy)	Organic acids in urine, plasma and urine amino acids, plasma vitamin E with cholesterol and triglyceride studies Consider mitochondrial investigations, aprataxin gene (if oculomotor apraxia) and immunological studies (ataxia–telangiectasia) Depending on other data consider investigations for NPC and other lysosomal diseases Spinocerebellar ataxias, NBIA syndromes and other complex molecule defects (lipid synthesis and remodeling, autophagy, trafficking, and others) should be considered
	Myoclonus Dystonia–myoclonus is normally related to a genetic disease (DYT5) Mitochondrial disorders are the most common cause of this association in IEMs	Urine organic acids, *DYT5* gene, consider mitochondrial and lysosomal investigations
	Abrupt onset Organic acidurias and mitochondrial defects are among the most frequent	Organic acids (including glutaric and 3-hydroxyglutaric acids), lactate, pyruvate, plasma amino acids including total homocysteine Consider other mitochondrial and PDH studies, thiamine in the CSF (usually low in thiamine transporter deficiency). Consider DYT12 (*ATP1A3*)
	Treatable conditions should always be prioritized: • Biogenic amines, pterins, glucose, folate, and thiamine in CSF • CSF and plasma glucose • Plasma and urinary amino acids and total homocysteine in blood • Creatine and guanidinoacetate in urine • Copper (plasma and urine), ceruloplasmin (plasma) • Manganese (plasma) • Plasma biotinidase activity • Oxysterols in plasma	
Parkinsonism	**See Dystonia + Parkinsonism**	
Ataxia	**Acute/intermittent** Amino acid disorders Organic acidurias PDH Biotinidase deficiency Other mitochondrial disorders Hartnup disease GLUT1 deficiency (being more evident at fasting) Channelopathies	Basal laboratory investigations (including blood gases, lactate, ammonia, and albumin), erythrocyte morphology Plasma amino acids Urine organic acids CSF and plasma glucose CSF lactate (and pyruvate) Vitamin E Ceruloplasmin Cholesterol, lipid electrophoresis Coenzyme Q10 Sterols (including oxysterols) Phytanic acid Transferrin electrophoresis

Table 2.1 (cont.)

Predominant movement disorder	Associated clinical features	Selected laboratory tests
		Alpha-fetoprotein Consider lysosomal studies if regression Consider studies of lipidome (plasma/CSF) Consider genetic panel testing: genetic panels of inherited ataxias and other NGS techniques
	Chronic CDG, SSADH deficiency (both may improve over time) Ataxia with vitamin E deficiency Wilson disease Refsum disease Cerebrotendinous xanthomatosis Ataxia–telangiectasia Lysosomal storage diseases	
Chorea	**Chronic** GLUT1 deficiency Lesch–Nyhan disease Organic acidurias (i.e. GA-1) Non-ketotic hyperglycinemia Guanidinoacetate N-methyltransferase (GAMT) deficiency Galactosemia Homocystinuria Sulfite oxidase/molybdenum cofactor deficiency FOLR deficiency Dopaminergic deficiencies **With neurodegeneration** Ataxia–telangiectasia Dentato-rubro-pallido-luysian (DRPL) atrophy With oculomotor apraxia (aprataxin) Spinocerebellar ataxias (SCA) NBIA syndromes Complex lipid synthesis and remodeling defects Infantile neuronal ceroid lipofuscinosis Metal disorders	Basal laboratory investigations (including blood gases, lactate, ammonia, and albumin, uric acid), erythrocyte morphology Plasma amino acids Urine organic acids CSF and plasma glucose CSF lactate (and pyruvate) CSF folate Ceruloplasmin Creatine metabolites Consider lysosomal studies if regression Consider genetic panel testing
Spasticity	**Treatable causes** HHH-, homocysteine- and folate-related disorders Biotinidase deficiency Vitamin E deficiency (ataxia is more characteristic) Cerebrotendinous xanthomatosis **With neurodegeneration**	Plasma ammonia, plasma and urine amino acids. Biotinidase activity (plasma). Folate and total. homocysteine (blood). Cholestanol (plasma), bile acid precursors (urine and plasma), plasma lipidome. Vitamin E, triglycerides, cholesterol and fractions, erythrocyte morphology (plasma). Folate and biogenic amine metabolites in CSF. Urine glycosaminoglycans, oligosaccharides, sialic acid. Lysosomal enzymes. Very-long-chain fatty acids. Lactate, pyruvate. Urine organic acids. Consider *PLA2G6* mutation and other NBIA syndromes depending on clinical and MRI findings. Consider complex lipid synthesis and remodeling defects, genes related to hereditary spastic paraplegia.
Tremor	**Generally uncommon but has been described in:** Phenylketonuria, disorders of biogenic amines, galactosemia, mitochondrial disorders, Wilson disease, L-2-hydroxyglutaric aciduria.	Plasma amino acids, urine organic acids CSF neurotransmitters Galactose-1-P, Galactose-1-phosphate uridyltransferase enzyme activity Mitochondrial tests Copper, ceruloplasmin

neuronal ceroid lipofuscinoses, GM1 gangliosidosis, NPC, and cerebrotendinous xanthomatosis; (4) POLG-related disorders and other mitochondrial diseases may exhibit parkinsonism. Some might respond to low doses of levodopa/carbidopa, especially in adolescents and adults [36].

Tremor

Tremor is defined as an abnormal movement with rhythmic oscillation and a fixed frequency that may be postural, resting, or triggered by action. It may affect different parts of the body and can be of small or large amplitude. It is rare in children but can be found as a high-amplitude tremor in early presentations of dopaminergic deficiencies, and in Wilson disease (Table 2.1). Head tremor can be found in GLUT1 deficiency syndrome (late-onset forms) [8].

Myoclonus

Myoclonus is a quick and abrupt movement that can be generalized, focal, or multifocal, and it is not incorporated into a voluntary movement. It can have a cortical origin but also subcortical, in the brainstem or spinal cord. Non-epileptic myoclonus is characteristic of mitochondrial disorders, lysosomal diseases such as GM1 gangliosidosis, and other IEMs (Table 2.1).

Ataxia

Ataxia is defined as an inability to maintain normal posture and smoothness of movement, while force and sensation are intact. Clinical manifestations are diverse, from pure cerebellar dysfunction to mixed patterns. Cerebellar dysfunction and global cerebellar hypoplasia or atrophy are common in IEMs [37]. NGS techniques have enabled the identification of an expanding number of novel genes associated with hereditary ataxia [38]. It is important to first consider the treatable disorders (most of them partially treatable) that give rise to ataxia, including ataxia with vitamin E deficiency, biotinidase deficiency, abetalipoproteinemia, thiamine-responsive pyruvate dehydrogenase (PDH) deficiency, cerebrotendinous xanthomatosis, Refsum disease, GLUT1 deficiency, NPC, Hartnup disease, and coenzyme Q_{10} deficiency.

Intermittent/Episodic Ataxias

The so-called "episodic ataxias" are characterized by episodes of imbalance and incoordination, commonly triggered by exertion and stress, and often associated with channelopathies [39]. If due to a metabolic disorder, these are mainly defects of intermediary metabolism, for example in the setting of a subacute decompensation in amino acid (especially MSUD) or organic acid disorders. Defects of energy metabolism presenting with intermittent ataxia are found in PDH and GLUT1 deficiency syndromes (intermittent ataxia or gait dyspraxia as the main finding, mimicking other episodic ataxias and worsening with fasting in GLUT1 deficiency). Mild forms of biotinidase deficiency and Hartnup disease (neutral amino acid transport defect) may also give rise to intermittent ataxia.

Progressive Ataxia

Many IEMs involve the cerebellum and are accompanied by a more or less prominent ataxia, which is most often progressive (Table 2.1). The treatable (or partially treatable) conditions – vitamin E-responsive ataxia, Refsum disease, cerebrotendinous xanthomatosis, NPC, and coenzyme Q10 deficiency (in which the phenotype ataxia with oculomotor apraxia deserves special attention) – belong to this category. Other disorders frequently associated with progressive ataxia are mitochondrial syndromes. Mitochondrial homeostasis defects, including mtDNA replication and repair, are also common causes of ataxia [38, 40].

Ataxia and gait impairment may be present in diverse IEMs that affect complex-lipid synthesis and remodeling, in particular those related to phospholipid metabolism [12, 38]. Disorders of autophagy-lysosomal activity can also produce progressive ataxias: NPC, ATP13A2, SPG11, and SPG15. Non-progressive ataxias are typically found in CDG syndromes and succinic semialdehyde dehydrogenase (SSADH) deficiency.

Spasticity

Spasticity is the result of damage to upper motor neurons or the corticospinal tract. The main components of the motor system (motor neurons and myelin) are extremely vulnerable to metabolic disturbances. This is the reason why disorders of both small and complex molecules may exhibit spasticity. Disorders that interfere with myelin metabolism, synthesis, and remodeling of complex lipids often cause pyramidal-tract lesions. In fact, almost all progressive neurometabolic diseases may ultimately manifest different degrees of spasticity. Spasticity in metabolic disorders is generally associated with other neurological manifestations (Table 2.1). However, some disorders can start with isolated spastic paraparesis such as X-linked adrenoleukodystrophy, remethylation defects of homocysteine metabolism, hyperammonemia–hyperornithinemia–homocitrullinuria syndrome, arginase deficiency, and Segawa disease. In the emerging category of complex lipid synthesis and remodeling defects, hereditary spastic paraparesis is a relatively common presentation [26].

Conclusions

IEMs disturb the physiology and the connectivity of motor areas in the brain. Thus, movement disorders are frequent in IEM. Pediatric and adult neurologists should be aware of the great diversity of IEMs that cause movement disorders. New genetic technologies allow the identification of the molecular basis for a growing number of conditions and syndromes that were previously unexplained. Additionally, better interdisciplinary characterization provides valuable information about new phenotypes and increased variability even within classic IEMs. A prompt diagnosis may lead to better outcomes, preventing permanent central nervous system injury and resultant movement disorders.

Key Points and Clinical Pearls

- Inborn errors of metabolism (IEMs) disturb the physiology and the connectivity of motor areas in the brain.
- There is a great diversity of IEMs that cause movement disorders.
- New genetic technologies allow the identification of the molecular basis for a growing number of previously unexplained conditions and syndromes.
- Better interdisciplinary characterization provides valuable information about new phenotypes and increased variability.
- A prompt diagnosis may lead to better outcomes.

Directions for Future Research

- Detailed phenotypic characterization of classic and newly discovered IEMs.
- Better delineation of the spectrum of movement disorders in IEMs.
- Better understanding of the contribution of movement disorders to morbidity and mortality in IEMs.
- Development of diagnostic algorithms based on the presenting or predominant signs and symptoms.

References

1. Rosenberg E. Legacies of Garrod's brilliance. One hundred years – and counting.J Inherit Metab Dis. 2008;**31**(5):574–9.
2. Garcia-Cazorla A, Wolf NI, Serrano M, et al. Inborn errors of metabolism and motor disturbances in children. J Inherit Metab Dis. 2009;**32**(5):618–29.
3. Sedel F, Baumann N, Turpin JC, et al. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J Inherit Metab Dis. 2007;**30** (5):631–41.
4. Sedel F, Fontaine B, Saudubray JM, Lyon-Caen O. Hereditary spastic paraparesis in adults associated with inborn errors of metabolism: A diagnostic approach. J Inherit Metab Dis. 2007;**30**(6):855–64.
5. Sedel F, Gourfinkel-An I, Lyon-Caen O, et al. Epilepsy and inborn errors of metabolism in adults: A diagnostic approach. J Inherit Metab Dis. 2007;**30** (6):846–54.
6. Ferreira CR, van Karnebeek CDM, Vockley J, Blau N. A proposed nosology of inborn errors of metabolism. Genet Med. 2019;**21**(1):102–6.
7. Mink JW, Sanger TD. Movement disorders: An overview. In Swaiman K, Ashwal S, Ferriero D, et al., editors. Swaiman's Pediatric Neurology, 6th edn. Elsevier; 2017, pp. 706–17.
8. Christensen CK, Walsh L. Movement disorders and neurometabolic diseases. Semin Pediatr Neurol. 2018;**25**:82–91.
9. Fernandez-Alvarez E, Aicardi J. Movement Disorders in Children. Mac Keith Press; 2001.
10. Yanagisawa N. Functions and dysfunctions of the basal ganglia in humans. Proc Jpn Acad Ser B Phys Biol Sci. 2018;**94**(7):275–304.
11. Balint B, Mencacci NE, Valente EM, et al. Dystonia. Nat Rev Dis Primers. 2018;**4**(1):25.
12. Lamari F, Mochel F, Saudubray JM. An overview of inborn errors of complex lipid biosynthesis and remodelling. J Inherit Metab Dis. 2015;**38**(1): 3–18.
13. Brimblecombe KR, Cragg SJ. The striosome and matrix compartments of the striatum: A path through the labyrinth from neurochemistry toward function. ACS Chem Neurosci. 2017;**8** (2):235–42.
14. Bolam JP, Izzo PN, Graybiel AM. Cellular substrate of the histochemically defined striosome/matrix system of the caudate nucleus: A combined Golgi and immunocytochemical study in cat and ferret. Neuroscience. 1988;**24**(3):853–75.

15. Davis MI, Puhl HL, 3rd. Nr4a1-eGFP is a marker of striosome–matrix architecture, development and activity in the extended striatum. PLoS One. 2011;**6**(1): e16619.

16. Holt DJ, Graybiel AM, Saper CB. Neurochemical architecture of the human striatum. J Comp Neurol. 1997;**384**(1):1-25.

17. Crittenden J, Graybiel AM. Disease-associated changes in the striosome and matrix compartments of the dorsal striatum. In Steine H, Tseng K, editors. Handbook of Basal Ganglia Structure and Function, 2nd edn. Amsterdam: Elsevier; 2016, pp. 801–15.

18. Holmes MJ, Robertson FC, Little F, et al. Longitudinal increases of brain metabolite levels in 5–10 year old children. PLoS One. 2017;**12**(7):e0180973.

19. Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM. N-Acetylaspartate in the CNS: From neurodiagnostics to neurobiology. Prog Neurobiol. 2007;**81**(2):89–131.

20. Benarroch EE. Basic Neurosciences with Clinical Applications. Philadelphia, PA: Butterworth-Heinemann; 2006.

21. Saudubray JM, Garcia-Cazorla A. Inborn errors of metabolism overview: Pathophysiology, manifestations, evaluation, and management. Pediatr Clin North Am. 2018;**65**(2):179-208.

22. Boycott KM, Beaulieu CL, Kernohan KD, et al. Autosomal-recessive intellectual disability with cerebellar atrophy syndrome caused by mutation of the manganese and zinc transporter gene *SLC39A8*. Am J Hum Genet. 2015;**97**(6):886–93.

23. Park JH, Hogrebe M, Gruneberg M, et al. *SLC39A8* Deficiency: A disorder of manganese transport and glycosylation. Am J Hum Genet. 2015;**97**(6):894–903.

24. Harayama T, Riezman H. Understanding the diversity of membrane lipid composition. Nat Rev Mol Cell Biol. 2018;**19**(5):281–96.

25. Sasarman F, Maftei C, Campeau PM, et al. Biosynthesis of glycosaminoglycans: Associated disorders and biochemical tests. J Inherit Metab Dis. 2016;**39**(2):173–88.

26. Garcia-Cazorla A, Mochel F, Lamari F, Saudubray JM. The clinical spectrum of inherited diseases involved in the synthesis and remodeling of complex lipids. A tentative overview.J Inherit Metab Dis. 2015;**38**(1):19–40.

27. Sprecher E, Ishida-Yamamoto A, Mizrahi-Koren M, et al. A mutation in *SNAP29*, coding for a SNARE protein involved in intracellular trafficking, causes a novel neurocutaneous syndrome characterized by cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma. Am J Hum Genet. 2005;**77**(2):242–51.

28. Hirst J, Edgar JR, Esteves T, Darios F, Madeo M, Chang J, et al. Loss of *AP-5* results in accumulation of aberrant endolysosomes: Defining a new type of lysosomal storage disease. Hum Mol Genet. 2015;**24**(17): 4984–96.

29. Stockler S, Corvera S, Lambright D, Fogarty K, Nosova E, Leonard D, et al. Single point mutation in Rabenosyn-5 in a female with intractable seizures and evidence of defective endocytotic trafficking. Orphanet J Rare Dis. 2014;**9**:141.

30. Cortes-Saladelafont E, Lipstein N, Garcia-Cazorla A. Presynaptic disorders: A clinical and pathophysiological approach focused on the synaptic vesicle. J Inherit Metab Dis. 2018;**41**(6):1131–45.

31. Ebrahimi-Fakhari D, Saffari A, Wahlster L, Lu J, Byrne S, Hoffmann GF, et al. Congenital disorders of autophagy: An emerging novel class of inborn errors of neuro-metabolism. Brain. 2016;**139**(Pt 2):317–37.

32. Garcia-Cazorla A, Saudubray JM. Cellular neurometabolism: A tentative to connect cell biology and metabolism in neurology. J Inherit Metab Dis. 2018;**41**(6):1043–54.

33. Mochel F, Sedel F. Inborn errors of metabolism in adults: A diagnostic approach to neurological and psychiatric presentations. In Saudubray JM, Baumgartner M, Walter JH, editors. Inborn Metabolic Diseases: Diagnosis and Treatment. Berlin: Springer-Verlag; 2016, pp. 71–89.

34. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: A consensus update. Mov Disord. 2013;**28**(7):863–73.

35. Jinnah HA, Albanese A. The new classification system for the dystonias: Why was it needed and how was it developed? Mov Disord Clin Pract. 2014;**1**(4):280–4.

36. Garcia-Cazorla A, Duarte ST. Parkinsonism and inborn errors of metabolism. J Inherit Metab Dis. 2014;**37**(4):627–42.

37. Poretti A, Boltshauser E, Huisman TA. Prenatal cerebellar disruptions: Neuroimaging spectrum of findings in correlation with likely mechanisms and etiologies of injury. Neuroimaging Clin N Am. 2016;**26** (3):359–72.

38. Synofzik M, Nemeth AH. Recessive ataxias. Handb Clin Neurol. 2018;**155**:73–89.

39. Jen JC, Wan J. Episodic ataxias. Handb Clin Neurol. 2018;**155**:205–15.

40. Ghaoui R, Sue CM. Movement disorders in mitochondrial disease. J Neurol. 2018;**265**(5):1230–40.

Chapter 3

The Importance of Inborn Errors of Metabolism for Movement Disorders

Colin Wilbur, Darius Ebrahimi-Fakhari, Saadet Mercimek-Andrews, and Anthony E. Lang

Introduction

Movement disorders can present a diagnostic challenge, particularly those with onset at an early age as one component of a complex neurodevelopmental disorder. With advances in next-generation sequencing technologies, the number of genes associated with movement disorders has been rapidly increasing over the last few years. Some of these genes encode transport proteins or enzymes within well-characterized metabolic pathways and their abnormal function results in disorders defined as inborn errors of metabolism (IEMs). Although individually rare, IEMs have a collective estimated incidence of 1:800 to 1:2,500 live births [1]. Movement disorders are a common symptom in IEMs affecting the central nervous system [2]. In general, movement disorders are not the sole symptom of these disorders, but are more often part of complex phenotypes that include other neurological and systemic signs and symptoms. The ability to recognize IEMs is crucial for clinicians evaluating patients presenting with movement disorders, as some IEMs are amenable to therapy, including specific dietary therapies or supplementation with vitamins, minerals, or cofactors that can prevent intoxication or treat deficiencies [3]. The early recognition of IEMs and initiation of appropriate treatment, where available, thus has the potential to profoundly impact outcomes (Box 3.1). Furthermore, many IEMs require long-term surveillance and screening for complications and "harm avoidance" approaches (e.g. avoiding metabolic stressors and selected medications). The details of these important diagnoses and management issues will be dealt with in later chapters.

This chapter will serve as a gateway to the subsequent chapters on "a phenomenology-based approach" and takes the perspective of a neurologist or movement disorder specialist who is confronted with two tasks when evaluating a patient with a movement disorder and suspected genetic or metabolic condition: (1) identifying the correct movement disorder phenomenology; and (2) developing a differential diagnosis and rational approach to counseling and testing. The first task is similar to the general approach to any patient with a movement disorder but, in addition, is guided by the principles outlined below (Box 3.2). The second task is challenged by the need to identify treatable conditions quickly in order to prevent irreversible complications and to reduce long-term morbidity.

In this chapter, we provide a framework to patients presenting with a movement disorder and when to suspect an IEM, with an emphasis on treatable conditions. Such an approach begins by appropriately

Box 3.1 Treatable IEMs not to miss: disorders in which appropriate treatment may prevent irreversible neurological injury or significantly improve neurological symptoms

- Disorders of monoamine neurotransmission
- Disorders of amino acid metabolism – e.g. glutaric aciduria type 1 (GA-1), organic acidurias, maple syrup urine disease, homocystinuria
- Hypermanganesemia with dystonia
- Wilson disease
- Aceruluplasminemia
- Glucose transporter type 1 (GLUT1) deficiency
- Neuronal ceroid lipofuscinosis type 2 (CLN2/*TPP1*)
- Ataxia with vitamin E deficiency
- Niemann–Pick disease type C (NPC)
- Cerebral creatine deficiency syndromes
- Biotin–thiamine-responsive basal ganglia disease
- Primary cerebral folate deficiency
- Primary coenzyme Q10 deficiency
- Biotinidase deficiency
- Refsum disease
- Pyruvate dehydrogenase (PDH) deficiency

Box 3.2 General principles

1. Most IEMs are individually rare or even extraordinarily rare.
2. Most IEMs present in childhood but atypical cases with presentation in adulthood are recognized.
3. Most IEMs are multisystem diseases with neurological and non-neurological manifestations.
4. Most IEMs initially present with non-specific findings.
5. In most IEMs, phenotypes are variable and prototypical features are usually in the "worst-case scenario."
6. In most IEMs, movement disorders are not the only or presenting symptom but their recognition can facilitate a diagnosis.
7. In most IEMs, movement disorders contribute substantially to the morbidity and can have a significant impact on quality of life.
8. Most IEMs present with more than one movement disorder.
9. Some IEMs that present with movement disorders are treatable and early diagnosis and treatment can improve outcomes.
10. All IEMs that present with movement disorders require interdisciplinary care and collaboration between pediatric neurologists, neurologists, geneticists, and experts in metabolism.

recognizing the phenomenology of the presenting movement disorder(s) and the IEMs potentially associated with the movement disorder phenotype. Next, phenotypic clues to specific IEMs may be sought through a careful evaluation for other neurological manifestations and involvement outside of the nervous system, along with defining the inheritance patterns within families. Accurately defining the phenotype in this manner may then guide the use of appropriate directed testing to identify the potentially causative IEM. A systematic approach to the diagnosis of IEMs presenting with movement disorders will lead to an early diagnosis and early therapeutic intervention that may reduce neurological and systemic morbidities.

Movement Disorder Phenomenology

Movement disorders are broadly classified into those presenting with an excess of involuntary movement – hyperkinetic movement disorders – and those characterized by a decrease in automatic and voluntary movement – hypokinetic disorders. Hyperkinetic movement disorders associated with IEMs include dystonia, ataxia, tremor, myoclonus, and chorea. The prototypical hypokinetic movement disorder is parkinsonism, often termed an akinetic–rigid syndrome. Usually, clinical suspicion for an underlying IEM should arise when a patient presents with various types of movement disorders (often a mixed phenotype) or movement disorders occurring in association with intercurrent illnesses or other stressors, in addition to other neurological or systemic manifestations. Signs and symptoms suggesting an underlying IEM etiology are listed in Table 3.1, based on the clinical history, family history, and physical examination features. In addition, patterns of neuroimaging abnormalities – particularly abnormal signal within the basal ganglia – may provide supportive evidence for an underlying IEM.

The International Parkinson and Movement Disorder Society Task Force for Nomenclature of Genetic Movement Disorders recently published a review of the classification and nomenclature of genetically determined movement disorders, including IEM [4]. More than 30 genes associated with IEMs were included in this review and categorized, based on their prominent movement disorder(s). We refer the reader to this review article for a detailed discussion of movement disorder classification, but have summarized the IEMs associated with movement disorders based on the most prominent movement disorder phenomenology in Table 3.2.

An Approach to Ataxia

Ataxia is characterized by disturbed coordination with errors and variability in movement rate, rhythm, and force. Ataxia may arise as a result of dysfunction in multiple neurological pathways, including sensory or vestibular ataxia, but most commonly is the result of cerebellar dysfunction and may be accompanied by other cerebellar signs such as dysarthria, intention tremor, eye movement abnormalities, limb incoordination, and a wide-based unsteady gait. Cerebellar ataxia is common in IEM and often signifies a degenerative process involving the cerebellum. When eliciting the history it is important to establish the timeline and nature of any ataxic movements: Did the ataxia develop suddenly after a concurrent illness or episode of starvation? Is the ataxia gradual in onset and preceded by other signs of cerebellar dysfunction?

Table 3.1 Features suggestive of IEM disorders based on clinical history, family history, and physical examination features

	Features	Associated IEMs
Clinical history	Recurrent encephalopathy triggered by intercurrent illness or stress	Mitochondrial disorders, disorders of amino acid metabolism
	Failure to thrive or short stature	Disorders of monoamine neurotransmission, mitochondrial disorders, disorders of amino acid metabolism
	Protein aversion	Disorders of amino acid metabolism
	Developmental delay, developmental regression, or cognitive decline	Various
	Seizures	GLUT1 deficiency, mitochondrial disorders, Lafora disease, disorders of amino acid metabolism, lysosomal storage disorders, cerebral creatinine deficiency syndromes, disorders of monoamine neurotransmission, cerebral folate deficiency, biotin–thiamine-responsive basal ganglia disease, biotinidase deficiency, molybdenum cofactor deficiency, cerebrotendinous xanthomatosis, congenital disorders of glycosylation
	Hearing loss	Mitochondrial disorders, Refsum disease, biotinidase deficiency
	Progressive visual loss	Neuronal ceroid lipofuscinosis, mitochondrial disease, ataxia with vitamin E deficiency, abetalipoproteinemia, PKAN, aceruloplasminemia, Refsum disease
	Abnormal urine or body odour	Maple syrup urine disease, phenylketonuria
	Psychiatric disturbance	Disorders of amino acid metabolism, Wilson disease, cerebrotendinous xanthomatosis, mitochondrial disorders, lysosomal storage disorders, cerebral creatinine deficiency syndromes, NBIA syndromes, neuroferritinopathy, aceruloplasminemia
	Movement disorders with sudden onset or paroxysmal course	GLUT1 deficiency, PDH deficiency, maple syrup urine disease, GA-1, biotin–thiamine-responsive basal ganglia disease, mitochondrial disorders, Hartnup disease
Family history (extended three generation)	Including developmental delay, cognitive dysfunction, psychiatric disease, movement disorder, early death, repeated pregnancy losses, consanguinity	Will depend on inheritance pattern: autosomal-recessive, autosomal-dominant, X-linked, maternal
Physical examination and organ involvement	Dysmorphic features	Lysosomal storage disorders, molybdenum cofactor deficiency, PDH deficiency, congenital disorders of glycosylation, cerebral creatine deficiency syndromes
	Macrocephaly or microcephaly	Macrocephaly: Alexander disease, GM2 gangliosidosis, GA-1, L-2-hydroxyglutaric aciduria Microcephaly: GLUT1 deficiency, cerebral folate deficiency, molybdenum cofactor deficiency, PDH deficiency, mitochondrial disorders, cerebral creatinine deficiency syndromes, disorders of amino acid metabolism
	Skeletal dysplasia	Lysosomal storage disorders, congenital disorders of glycosylation
	Skin abnormalities	Biotinidase deficiency, congenital disorders of glycosylation, Hartnup disease
	Ocular abnormalities	Lysosomal storage disorders, homocystinuria, molybdenum cofactor deficiency, Wilson disease, mitochondrial disorders, Refsum disease, PKAN, neuronal ceroid lipofuscinosis, cerebrotendinous xanthomatosis
	Hepatosplenomegaly or hepatic dysfunction	Lysosomal storage disorders, Wilson disease, mitochondrial disorders, congenital disorders of glycosylation, hypermanganesemia with dystonia, disorders of amino acid metabolism

Table 3.1 (cont.)

Features	Associated IEMs
Cardiac involvement	Mitochondrial disorders, lysosomal storage disorders, Wilson disease, organic acidurias, Refsum disease, congenital disorders of glycosylation
Myopathy	Mitochondrial disorders, cerebral creatine deficiency syndrome (GAMT)
Renal involvement	Mitochondrial disorders, Wilson disease, Lesch–Nyhan disease, coenzyme Q10 deficiency, congenital disorders of glycosylation, Fabry disease, organic acidurias (renal failure especially in methylmalonic acidemia)
Endocrine dysfunction	Mitochondrial disorders, aceruloplasminemia, Woodhouse–Sakati syndrome, congenital disorders of glycosylation

Abbreviations: GA-1, glutaric aciduria type 1; GLUT1, glucose transporter type 1; PKAN, pantothenate kinase-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PDH, pyruvate dehydrogenase; GAMT, guanidinoacetate methyltransferase deficiency.

Is the presentation episodic or do ataxic movements persist? General diagnostic clues that point to a metabolic etiology secondary to an intoxication-type IEM are: (1) an acute presentation or exacerbation in the setting of a catabolic state (i.e. with a febrile illness); and (2) worsening after a high intake of protein. General diagnostic clues to a metabolic movement disorder secondary to a slower degenerative process such as with lysosomal storage diseases or metal storage diseases include eye movement abnormalities, cerebellar findings preceding ataxia, intellectual disability, and neuropsychiatric symptoms. Important treatable IEMs that present with ataxia are listed in Table 3.2. Ataxia is a prominent feature of vitamin E deficiency arising from a genetic defect in the alpha-tocopherol transfer protein [5]. The onset of ataxia ranges from childhood to young adulthood and commonly occurs along with dysarthria, head tremor, peripheral neuropathy, impaired proprioception, and a Babinski sign. Abetalipoproteinemia – a disorder of lipid trafficking – results in deficiency in fat-soluble vitamins, including vitamin E, and may thus present with a similar ataxic phenotype [6]. Recognition of these disorders is important, as high-dose vitamin E supplementation can prevent neurological deterioration. Ataxia may also be a prominent symptom in other IEMs including Wilson disease, NPC, cerebrotendinous xanthomatosis, cerebral creatine deficiency syndromes, Refsum disease, biotinidase deficiency, and coenzyme Q10 deficiency. Progressive myoclonus ataxia is discussed later.

An Approach to Dystonia

Dystonia is characterized by sustained or intermittent muscle contractions that cause abnormal, often repetitive movements (including tremor), postures, or both [7]. Dystonia is often provoked or worsened by voluntary movements and is associated with overflow muscle activation. It may be further described by its anatomic distribution, whether involving a single body region (focal), two or more contiguous (segmental) or non-contiguous (multifocal) body regions, or two or more body regions along with the trunk (generalized). Dystonia is the second most common movement disorder in IEMs and, in some diseases, a presenting symptom. It is often found in combination with other movement disorders such as parkinsonism or chorea. In this context, it is important to note that dopamine deficiency in childhood often primarily presents with dystonia as opposed to parkinsonism. Dystonia is commonly seen in monoamine neurotransmitter metabolism disorders such as tyrosine hydroxylase deficiency, aromatic L-amino acid decarboxylase deficiency, or defects of biopterin synthesis or recycling such as GTP cyclohydrolase 1 (GTPCH1: the commonest cause of "dopa-responsive dystonia") or dihydropteridine reductase deficiencies [8]. A prominent response to levodopa is characteristic of these disorders. As discussed below, parkinsonism is also a common feature of monoamine neurotransmitter metabolism disorders, and the observation of brisk lower-extremity reflexes or a dystonic dorsiflexed "striatal toe" commonly leads to an initial misdiagnosis as cerebral palsy. Other

Table 3.2 Clinical features of IEMs associated with movement disorders, classified by the most common/prominent movement disorder[a]

Disorder (*gene*)	Associated movement disorders	Other neurological features	Systemic features	Brain MRI pattern[b]	Treatment
Dystonia					
GTP cyclohydrolase type 1 (GTPCH1) deficiency (*GCH1*)	Dystonia, parkinsonism	Pyramidal signs, spasticity		Normal	Levodopa
Tyrosine hydroxylase deficiency (*TH*)	Dystonia, parkinsonism, oculogyric crisis, tremor, myoclonus	Pyramidal signs, spasticity, hypotonia, ptosis, autonomic dysfunction, encephalopathy, global developmental delay		Normal or non-specific atrophy/WM changes	Levodopa
Aromatic L-amino acid decarboxylase deficiency (*DDC*)	Dystonia, oculogyric crisis, parkinsonism, chorea, tremor, myoclonus	Hypotonia, irritability, autonomic dysfunction, ptosis, sleep disturbance, seizures, global developmental delay		Normal or non-specific atrophy/WM changes	Pyridoxine, dopamine agonists, monoamine oxidase inhibitors
Sepiapterin reductase deficiency (*SPR*)	Dystonia, oculogyric crisis, parkinsonism	Hypotonia, autonomic dysfunction, sleep disturbance		Normal or delayed myelination	Levodopa, 5-hydroxytryptophan
6-Pyruvoyl-tetrahydropterin synthase deficiency (*PTS*)	Dystonia, oculogyric crisis, parkinsonism	Hypotonia, spasticity, seizures, global developmental delay		Normal	Levodopa, 5-hydroxytryptophan, tetrahydrobiopterin
Dihydropteridine reductase deficiency (*QDPR*)	Dystonia, chorea, tremor	Hypotonia, seizures, bulbar dysfunction, hypersalivation, global developmental delay		Normal or non-specific WM changes, BG calcifications	Levodopa, 5-hydroxytryptophan, monoamine oxidase inhibitors, folinic acid
Neurodegeneration with brain iron accumulation (NBIA) disorders (*PANK2*, *PLA2G6*, *C19orf12*, *FA2H*, *COASY*, *ATP13A2*, *DCAF17*, *WDR45*)	Dystonia, parkinsonism, chorea	Pyramidal signs, spasticity, abnormal eye movements, dysarthria, peripheral neuropathy, seizures, optic atrophy, cognitive decline, behavior/psychiatric disturbance	Pigmentary retinopathy (*PANK2*) Hypogonadism, alopecia, diabetes mellitus (*DCAF17*)	T2 hypointentensity within BG, substantia nigra	Symptomatic (deferiprone and fosmetpantotenate currently in clinical trials for PKAN)
GM1 gangliosidosis (*GLB1*)	Parkinsonism, dystonia	Hypotonia, spasticity, psychomotor regression, seizures	Cherry-red spot, skeletal dysplasia, short stature, cardiomyopathy, hepatosplenomegaly, coarse facial features	WM, BG, cerebral/cerebellar atrophy	Symptomatic
Lesch–Nyhan disease (*HPRT1*)	Dystonia, chorea	Hypotonia, self-injurious behavior, dysarthria, dysphagia, pyramidal signs, spasticity, global developmental delay	Nephrolithiasis, gout	Normal or cerebral atrophy	Allopurinol
Hypermanganesemia with dystonia (*SLC30A10*)	Dystonia, parkinsonism	Dysarthria, spasticity	Liver dysfunction, polycythemia	T1 hyperintensity within BG, BS, DN	Chelation therapy

Homocystinuria (*CBS*)	Dystonia	Seizures, global developmental delay, psychiatric disturbance, cerebrovascular events	Ectopia lentis, high myopia, thromboembolism, marfanoid body habitus, hypopigmentation of skin/hair.	Normal or WM	Methionine-restricted diet, pyridoxine, folate, betaine, vitamin B12
Glutaric aciduria type 1 (GA-1) (*GCDH*)	Dystonia, parkinsonism, chorea	Acute encephalopathic crises, spasticity	Macrocephaly	Frontotemporal atrophy, BG, WM, DN	Lysine-restricted diet, carnitine, emergency treatment protocol
Organic acidurias (methylmalonic aciduria, proprionic aciduria) (*MUT*, *MMAA*, *MMAB*, *MMADHC*, *MCEE*, *PCCA*, *PCCB*)	Dystonia, ataxia, chorea	Hypotonia, spasticity, seizures, episodic encephalopathy, metabolic stroke, myopathy, optic atrophy, global developmental delay	Cardiomyopathy, acquired microcephaly, cytopenias, renal failure	WM, BG (including calcification), BS, cerebral/cerebellar atrophy	Dietary protein restriction, carnitine
Molybdenum cofactor deficiency (*MOCS1*, *MOCS2*, *MOCS3*, *GPHN*)	Dystonia, parkinsonism	Seizures, encephalopathy, global developmental delay	Microcephaly, dysmorphic features, ectopia lentis	WM (including cystic changes), BG, cerebellum, cerebral/cerebellar atrophy	Cyclic pyranopterin monophosphate (if *MOCS1*)
Glucose transporter type 1 (GLUT1) deficiency syndrome (*SLC2A1*)	Dystonia, ataxia chorea, tremor, myoclonus May be paroxysmal (including paroxysmal exercise-induced dyskinesia)	Seizures, dysarthria, spasticity, global developmental delay	Acquired microcephaly	WM, DN, cerebellar atrophy	Ketogenic diet
Leber hereditary optic neuropathy (*MT-ND1*, *MT-ND4*, *MT-ND6*)	Dystonia, tremor, parkinsonism, myoclonus	Myopathy, peripheral neuropathy, optic neuropathy, spasticity	Cardiac involvement	Normal or WM, cerebral atrophy	Symptomatic
Leigh syndrome (subacute necrotizing encephalomyelopathy) (Numerous)	Dystonia, ataxia, chorea, myoclonus	Encephalopathy with episodic deterioration, hypotonia, spasticity, seizures, eye movement abnormalities, weakness, bulbar dysfunction, peripheral neuropathy, optic atrophy, global developmental delay	Retinitis pigmentosa, cardiac involvement, liver involvement, renal involvement	BG, BS, cerebellum, WM, cerebral/cerebellar atrophy, lactate peak on magnetic resonance spectroscopy	Symptomatic
Tremor					
Wilson disease (*ATP7B*)	Tremor, dystonia, ataxia, parkinsonism, chorea	Dysarthria, dysphagia, drooling, psychiatric disturbance	Hepatic dysfunction, Kayser–Fleischer rings, hemolytic anemia, renal disease, cardiomyopathy, sunflower cataracts, arthritis	BG, BS (including "face of the giant panda" in the midbrain)	Copper chelation, zinc
Phenylketonuria (*PAH*)	Tremor, parkinsonism	Cognitive impairment, psychiatric disturbance, spasticity, seizures	Musty odor, microcephaly, decreased skin/hair pigmentation	WM, cerebral atrophy	Phenylalanine-restricted diet, tetrahydrobiopterin trial

Table 3.2 (cont.)

Disorder (*gene*)	Associated movement disorders	Other neurological features	Systemic features	Brain MRI pattern[b]	Treatment
Alexander disease (*GFAP*)	Palatal tremor, ataxia	Seizures, pyramidal signs, spasticity, hydrocephalus, cognitive decline, bulbar dysfunction	Macrocephaly	WM, BG, BS May show contrast enhancement	Symptomatic
Myoclonus					
Lafora disease (*EPM2A*, *NHLRC1*)	Myoclonus, ataxia	Seizures, dysarthria, dementia		Normal or cerebral/ cerebellar atrophy	Symptomatic
Neuronal ceroid lipofuscinoses (*PPT1*, *TPP1*, *CLN3*, *DNAJC5*, *CLN5*, *CLN6*, *MFSD8*, *CLN8*, *CTSD*, *GRN*, *ATP13A2*, *CTSF*, *KCTD7*)	Myoclonus, ataxia, parkinsonism	Seizures, psychomotor regression, pyramidal signs, spasticity, psychiatric/ behavior disturbance, dysarthria	Vision loss, cardiac involvement (uncommon).	Cerebral/cerebellar atrophy. BG or WM in some forms	Intrathecal cerliponase alfa (if *TPP1*)
Gaucher disease (*GBA*)	Myoclonus, ataxia, parkinsonism, retroflexion of neck	Eye movement abnormalities, horizontal supranuclear gaze palsy, spasticity, seizures, apnea, bulbar dysfunction, global developmental delay / dementia	Hepatosplenomegaly, cytopenias, pulmonary involvement	Normal	Enzyme-replacement therapy
Myoclonic epilepsy with ragged red fibres (MERRF) (*MT-TK*, *MT-TF*, *MT-TL1*, *MT-TI*, *MT-TP*)	Myoclonus, ataxia	Epilepsy, myopathy, peripheral neuropathy, pyramidal signs, dementia, ophthalmoparesis, pyramidal signs, optic atrophy, hearing loss	Retinitis pigmentosa, short stature, cardiac involvement	Cerebral/cerebellar atrophy, BG (including calcifications), BS, WM	Symptomatic
Sialidosis type 1 (*NEU1*)	Myoclonus, ataxia	Seizures, visual loss	Cherry-red spot macula, cataracts, corneal opacities	Diffuse atrophy	Symptomatic
Chorea					
Neuroferritinopathy (*FTL1*)	Chorea, dystonia, ataxia, parkinsonism, orofacial/ orolingual dyskinesias, tremor	Dysarthria, dysphagia, abnormal eye movements, cognitive dysfunction, psychiatric disturbance		T2 hypointensity within BG, substantia nigra, DN Cystic degeneration late	Symptomatic
Parkinsonism					
Primary familial brain calcification (*SLC20A2*, *PDGFB*, *PDGFRB*, *XPR1*)	Parkinsonism, dystonia, ataxia	Dementia, seizures, psychiatric disturbance		Calcifications in BG, DN/ cerebellum, BS, subcortical WM	Symptomatic
Ataxia					
Ataxia with vitamin E deficiency (*TTPA*)	Ataxia, dystonia, head tremor	Proprioceptive loss, areflexia, dysarthria, peripheral neuropathy, pyramidal signs	Retinitis pigmentosa	Cerebellar atrophy, WM	Vitamin E
Abetalipoproteinemia (*MTP*)	Ataxia	Dysarthria, peripheral neuropathy, proprioceptive loss, areflexia	Steatorrhea, retinitis pigmentosa	Normal	Dietary fat restriction, vitamins E, D, K, and A
GM2 gangliosidosis (*HEXA*, *HEXB*)	Ataxia, myoclonus, dystonia, chorea, parkinsonism	Hypotonia, pyramidal signs, spasticity, psychomotor regression, seizures, motor neuron disease, dysarthria	Cherry red spot, vision loss, macrocephaly, hepatosplenomegaly, skeletal dysplasia, doll-like facies	BG, WM, cerebral/ cerebellar atrophy	Symptomatic

Niemann–Pick disease type C (NPC) (*NPC1*, *NPC2*)	Ataxia, dystonia, myoclonus, tremor, chorea, parkinsonism	Vertical supranuclear gaze palsy, hypotonia, dysarthria, dysphagia, deafness, gelastic cataplexy, spasticity, seizures, cognitive decline/dementia, psychosis and other psychiatric symptoms	Hepatosplenomegaly, neonatal jaundice	Normal or cerebral/cerebellar atrophy, WM	Miglustat
Metachromatic leukodystrophy (*ARSA*)	Ataxia	Hypotonia, pyramidal signs, spasticity, peripheral neuropathy, dysarthria, seizures, cognitive decline, behavioral/psychiatric disturbance	Gallbladder involvement	WM (initially periventricular), cerebral/cerebellar atrophy	Hematopoietic stem-cell transplantation
Aceruloplasminemia (*CP*)	Ataxia, dystonia, chorea, tremor, parkinsonism	Dysarthria, cognitive decline	Retinal degeneration, diabetes mellitus, anemia	T2 hypointensity within BG, substantia nigra, red nuclei, DN	Iron chelation
Cerebrotendinous xanthomatosis (*CYP27A1*)	Ataxia, parkinsonism, dystonia	Dysarthria, pyramidal signs, spasticity, seizures, peripheral neuropathy, cognitive impairment/dementia, psychiatric disturbance	Chronic diarrhea, cataracts, tendon xanthomas	DN/cerebellum, WM, cerebral/cerebellar atrophy	Chenodeoxycholic acid
Cerebral creatine deficiency syndromes (*GAMT*, *GATM*, *SLC6A8*)	Ataxia, dystonia, chorea	Language delay, intellectual disability, seizures, spasticity, hypotonia, myopathy (*GATM*), behavioral/psychiatric disturbance	Microcephaly, dysmorphic features (*SLC6A8*).	Reduced creatine on MRS, BG	Creatine monohydrate; ornithine supplementation, arginine restriction (if *GAMT*); arginine, glycine (if *SLC6A8*)
Biotin-thiamine-responsive basal ganglia disease (*SLC19A3*)	Ataxia, dystonia, rigidity	Subacute encephalopathy, seizures, pyramidal signs, dysarthria, dysphagia, eye movement abnormalities, facial palsy		BG, BS, cerebral/cerebellar atrophy	Biotin, thiamine
Primary cerebral folate deficiency *(SLC46A1, FOLR1)*	Ataxia, chorea, tremor	Seizures, global developmental delay	Microcephaly, megaloblastic anemia, diarrhea, oral ulcers, immunodeficiency (*SLC46A1*)	WM, cerebral/cerebellar atrophy; intracranial calcifications (*SLC46A1*)	Folinic acid
Primary coenzyme Q10 deficiency (*COQ2*, *COQ4*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, *PDSS1*, *PDSS2*)	Ataxia, dystonia, tremor, spasticity, parkinsonism, myoclonus	Encephalopathy, seizures, hypotonia, peripheral neuropathy, myopathy, stroke-like episodes, optic atrophy, global developmental delay	Cardiac involvement, nephrotic syndrome, retinopathy	Cerebral/cerebellar atrophy, BG, cortex	Coenzyme Q10
Hartnup disease *(SLC6A19)*	Ataxia, dystonia, tremor; may be paroxysmal	Psychiatric disturbance	Dermatitis	Normal or diffuse atrophy	Nicotinamide
L-2-hydroxyglutaric aciduria (*LTHGDH*)	Ataxia, dystonia	Seizures, pyramidal signs, spasticity, hypotonia, global developmental delay, brain tumors	Macrocephaly	Subcortical WM, BG, DN, cerebral/cerebellar atrophy	Dietary protein restriction, carnitine, riboflavin
Maple syrup urine disease (*BCKDHA, BCKDHB, DBT*)	Ataxia, dystonia, tremor, chorea, parkinsonism. May be paroxysmal	Episodic encephalopathy, spasticity, cognitive impairment, psychiatric disturbance	Maple syrup odor, anorexia, vomiting.	Diffusion restriction in WM, BG, BS, dentate/cerebellum.	Leucine-restricted diet

Table 3.2 (cont.)

Disorder (*gene*)	Associated movement disorders	Other neurological features	Systemic features	Brain MRI pattern[b]	Treatment
Biotinidase deficiency (*BTD*)	Ataxia	Seizures, hypotonia, myelopathy, spasticity, hearing loss, optic neuropathy, global developmental delay	Rash, alopecia	Normal or cerebral/ cerebellar atrophy, BG	Biotin
Succinic semialdehyde dehydrogenase deficiency (*ALDH5A1*)	Ataxia, chorea	Hypotonia, seizures, global developmental delay, behavior disturbance		Normal or BG, WM, BS, DN, cerebellum	Symptomatic
Refsum disease (*PHYH*, *PEX7*)	Ataxia	Peripheral neuropathy, hearing loss	Retinitis pigmentosa, anosmia, icthyosis, cardiac involvement	Normal or cerebral atrophy	Phytanic acid-restricted diet
Congenital disorders of glycosylation (*PMM2*, many others)	Ataxia	Hypotonia, seizures, peripheral neuropathy, myopathy, abnormal eye movements, stroke-like events, global developmental delay	Eye abnormalities, dysmorphic features, skin abnormalities, liver involvement, heart involvement, skeletal abnormalities, endocrine dysfunction, renal involvement, immune dysfunction	Cerebellar hypoplasia/ atrophy	Symptomatic
Pyruvate dehydrogenase (PDH) deficiency (*PDHB*, *DLAT*, *PDHX*, *DLD*, *PDP1*, *PDHA1*)	Ataxia, dystonia, chorea (may be paroxysmal)	Hypotonia, seizures, encephalopathy, spasticity, peripheral neuropathy, global developmental delay	Microcephaly, dysmorphic features	BG, BS, cerebellum, corpus callosum, cerebral atrophy	Ketogenic diet, thiamine, dichloroacetate
POLG-related disorders (*POLG*)	Ataxia, chorea, myoclonus, parkinsonism	Hypotonia, encephalopathy, seizures, peripheral neuropathy, progressive external ophthalmoplegia, myopathy, hearing loss, global developmental delay, psychiatric disturbance	Liver involvement, endocrine dysfunction, cardiac involvement, retinopathy.	Cerebral/cerebellar atrophy, DN/ cerebellum, WM, BG, BS.	Symptomatic
Neuropathy, ataxia, retinitis pigmentosa (*MT-ATP6*)	Ataxia	Peripheral neuropathy, seizures, optic atrophy, learning difficulties	Retinitis pigmentosa.	Cerebral/cerebellar atrophy, BG, WM	Symptomatic

[a] Abbreviations: BG = basal ganglia/thalamus; BS = brainstem; DN = dentate nucleus; WM = white matter.

[b] See Chapter 4 for a more detailed discussion.

potentially treatable IEMs that may present with prominent dystonia include disorders of amino acid metabolism, glucose transporter type 1 (GLUT1) deficiency (often with dystonia induced by prolonged exercise), hypermanganesemia with dystonia, Lesch–Nyhan disease, and Wilson disease. When developing a differential diagnosis, it is helpful to consider the age at onset: IEMs that present with early-onset dystonia, often in infancy, include the organic acidurias [9, 10], many mitochondrial disorders [11], monoamine neurotransmitter disorders [12], Lesch–Nyhan [13], and creatine deficiency syndromes [14]. An acute-onset generalized dystonia is seen in disorders that acutely damage the basal ganglia such as the organic acidurias, most commonly GA-1, biotin–thiamine-responsive basal ganglia disease, or Leigh syndrome. Acute worsening including presentations with life-threatening status dystonicus are possible [15]. Timely recognition and treatment are key to prevent irreversible damage that often leads to a severe generalized and fixed dystonia later on.

An Approach to Chorea

Chorea is an ongoing, random-appearing sequence of discrete involuntary movements or movement fragments [16]. Choreatic movements arise from injury to the striatum, subthalamic nuclei, or more widespread areas [17]. First and foremost, pathological chorea needs to be distinguished from benign choreatic movements that occur transiently during motor development in young children. For example, between the age 6 months and 12 months most infants show rapid unpredictable movements resembling chorea, particularly in the upper limbs and mostly during excitement, anger, or frustration. Such physiological transient infantile chorea can be misinterpreted as a sign of disease [18].

Chorea affecting proximal muscle groups may result in large-amplitude flinging movements of the limbs, termed ballismus. Chorea often occurs in association with athetosis, which involves slow, continuous, writhing movements that prevent maintenance of a stable posture. Chorea is common in many IEMs, in particularly in the organic acidurias [9], in GLUT1 deficiency syndrome [19], cerebral creatine deficiency syndromes [14], lysosomal storage diseases, Lesch–Nyhan disease [13], urea cycle disorders, neurodegeneration with brain iron accumulation (NBIA), and mitochondrial diseases. Chorea is rarely the only or presenting movement disorder, thus the differential diagnosis and approach are oriented towards the predominant movement disorder, in many cases ataxia or dystonia. Notably, however, focal-onset chorea has been reported as the most common presenting neurological symptom in populations with neuroferritinopathy, which is a type of NBIA with typical onset in adulthood that evolves into a complex neurological phenotype that may also include dystonia, orolingual dyskinesia, and bradykinesia [20].

An Approach to Parkinsonism

Parkinsonism is defined as bradykinesia (slowness of movement), usually in combination with rigidity (velocity-independent resistance to passive movement) [21]. Gait disturbance and postural instability are not uncommon in more severe forms of parkinsonism. In general, hypokinetic movement disorders like parkinsonism are rare in childhood and similarly are rare in IEMs. Nevertheless, IEMs are the most common cause of parkinsonism in childhood and any child that presents with parkinsonism should be evaluated for an underlying metabolic disorder. Parkinsonism in IEMs most commonly presents as a hypokinetic–rigid syndrome; although a typical parkinsonian resting tremor is rare, a low-amplitude postural and action tremor is sometimes present. As discussed above, dopamine deficiency more commonly leads to dystonia in children and thus a mixed phenomenology of parkinsonism and dystonia is usually found.

Parkinsonism can be subdivided based on its response to the precursor of dopamine, levodopa. Where the disorder is characterized by a metabolic or degenerative process affecting the nigrostriatal dopamine neurons, a symptomatic benefit from levodopa is often striking. On the other hand, if the dysfunction is downstream from these neurons (e.g. in the striatum or globus pallidus), there may be little or no levodopa response. Parkinsonism presenting in infancy or early childhood should raise suspicion for monoamine neurotransmitter metabolism disorders, in which it is generally associated with severe dystonia and is commonly levodopa responsive (although a direct-acting dopamine agonist is often required in aromatic L-amino acid decarboxylase deficiency) [8]. Later in childhood or adolescence, parkinsonism in association with prominent dystonia is a common manifestation of the NBIA syndromes [22]. Parkinsonism may appear later in adolescence or adulthood as part of a variety of IEMs including

Wilson disease, lysosomal storage disorders (e.g. NPC, the neuronal ceroid lipofuscinoses, Gaucher disease, or GM2 gangliosidosis) [23], primary familial brain calcification, and cerebrotendinous xanthomatosis [24]. Mitochondrial depletion syndrome associated with bi-allelic, likely pathogenic, variants in *POLG* may present with parkinsonism (possibly levodopa-responsive, at times complicated by severe levodopa-induced dyskinesia) in combination with progressive external ophthalmoplegia or peripheral neuropathy [25]. Parkinson disease has also been reported in Gaucher disease carriers and studies have shown that carrier frequency of Gaucher disease is higher in Parkinson disease populations compared to controls [26]. Indeed, *GBA* mutations are now recognized as the commonest genetic risk factor for Parkinson disease.

An Approach to Tremor

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part [27]. Tremor may be further characterized by its body distribution, frequency, and whether it is activated by rest or action (whether kinetic, postural, or intention). The etiology of tremor in IEMs is varied but is often accompanied by other movement disorders such as parkinsonism, dystonia, or ataxia. A "wing-beating" tremor has characteristically been associated with Wilson disease and presents as a coarse, irregular, proximal postural tremor [28]. However, this is relatively uncommon and Wilson disease may be associated with a wide variety of more common or unusual forms of tremor, as well as almost any other movement disorder phenotype. One uncommon form of tremor involves the palate and branchial muscles and is termed palatal tremor (sometimes referred to as palatal myoclonus), which has been reported in Alexander disease and mitochondrial disorders, including in association with *POLG* mutations [29].

An Approach to Myoclonus

Myoclonus involves repeated, brief, shock-like jerks due to sudden involuntary muscle contraction (positive myoclonus) or loss of muscle activity/tone (negative myoclonus) [16]. Myoclonus may be characterized by its distribution (focal, multifocal, or generalized) and whether it occurs at rest or is precipitated by movement (action myoclonus) or other external stimuli (stimulus sensitive or reflex myoclonus). It can also be classified electrophysiologically based on its origin within the central nervous system (e.g. cortical, subcortical/reticular, spinal cord) and rarely in the peripheral nervous system (e.g. plexus, peripheral nerve). Myoclonus is found in IEMs that present with neurodegeneration, and cortical myoclonus is most common.

Myoclonus is a common clinical feature of lysosomal storage disorders such as the neuronal ceroid lipofuscinoses, sialidosis, Gaucher disease, GM2 gangliosidosis, and NPC [30, 31]. Myoclonus may also be prominent in mitochondrial encephalomyopathies – such as myoclonic epilepsy with ragged red fibres (MERRF) – or as part of more varied mitochondrial encephalomyopathy phenotypes including POLG-related disorders or Leigh syndrome [25]. In lysosomal storage disorders and mitochondrial encephalomyopathies, global developmental delay, hepatic dysfunction, or ophthalmological involvement may be expected to be part of the complex clinical picture. "Progressive myoclonus epilepsy" and "progressive myoclonus ataxia" are two overlapping syndromes associated with myoclonus (commonly action-induced) that is often due to IEMs, particularly Lafora disease, NPC, sialidosis, and mitochondrial encephalopathies.

An Approach to Spasticity

Spasticity is a common presentation in child neurology and, in a subset of patients, is secondary to an IEM. Spasticity is associated with a velocity-dependent increase in tone ("clasp-knife"), typically with other pyramidal signs including weakness in a pyramidal distribution (greater in the extensors in the upper limbs and flexors in the lower limbs with posturing due to the stronger muscles), pathologically brisk deep tendon reflexes with clonus and extensor plantar responses. IEMs are among the most common "mimics" of cerebral palsy, a problem that is increasingly recognized [32]. Cerebral palsy is defined as a permanent disorder of the development of movement and posture attributable to a non-progressive disturbance in the developing fetal or infant brain [33]. Cerebral palsy is often accompanied by epilepsy or disturbances of sensation, cognition, or behavior and can be classified according to the predominant motor abnormality as spastic (spasticity defined as velocity-dependent increase in muscle tone), dyskinetic, or ataxic. More than 50 treatable IEMs have been reported to present with a phenotype that may mimic cerebral palsy in early childhood, in addition to

many IEMs that are not currently treatable [32]. IEMs that can present with isolated spastic diplegia, at least initially, include X-linked adrenoleukodystrophy, urea cycle disorders, homocysteine remethylation defects, and some of the neurotransmitter diseases (particularly autosomal-dominant GTPCH1 deficiency). Treatable conditions that present with prominent spasticity, in addition to other neurological manifestations, include cerebral folate deficiency, biotinidase deficiency, and cerebrotendinous xanthomatosis. Consideration of the diagnosis of these treatable IEMs should be given in all children with a cerebral palsy phenotype in the absence of another clearly identified etiology or in those who show a progressive course.

Movement Disorders: Temporal Pattern

The majority of movement disorders associated with IEMs exhibit a chronic, slowly progressive course. A subset of IEM disorders may present with movement disorders and other neurological symptoms with an acute or subacute onset, often triggered by intercurrent illness or catabolism. For example, GA-1 may present in the first few years of life with an acute encephalopathic crisis and bilateral striatal necrosis. As a result, patients later develop complex movement disorders including severe dystonia, chorea, or parkinsonism [34]. Similarly, biotin–thiamine-responsive basal ganglia disease presents in early childhood with subacute onset of encephalopathy and ataxia, often accompanied by dystonia and seizures [35]. In GA-1, permanent central nervous system damage can be prevented by illness management and a protein-restricted diet, whereas biotin–thiamine-responsive basal ganglia disease is treatable with thiamin and biotin supplementation. Leigh syndrome, a severe mitochondrial encephalomyopathy, also presents with subacute neurological decline that may include ataxia, dystonia, or other hyperkinetic movement disorders along with brainstem dysfunction [25].

Some IEMs may manifest as paroxysmal movement disorders with sudden onset associated with a trigger and may or may not return to a neurological baseline in between such episodes. GLUT1 deficiency syndrome can present with paroxysmal exercise-induced dyskinesia/dystonia with or without epilepsy, in which dyskinesias are triggered by prolonged exercise, often with a normal neurological examination between events [36]. A variety of other paroxysmal events have also been reported in GLUT1 deficiency syndrome including ataxia, choreoathetosis, dystonia, parkinsonism, weakness, or altered behavior. Events typically last minutes or hours and may be triggered by exercise, fasting, or intercurrent illness. In more severe phenotypes, persistent neurological abnormalities are seen between paroxysmal events, including movement disorders, seizures, developmental delay, spasticity, and microcephaly. Early diagnosis is important, as neurological symptoms can respond well to the ketogenic diet. PDH deficiency, a cellular energy metabolism disorder, presents with severe encephalopathy and lactic acidosis or paroxysmal ataxia or dystonia triggered by exercise, carbohydrate-rich meals, or intercurrent illness [37]. Paroxysmal episodes of ataxia or dystonia may also occur in amino acid metabolism disorders, such as Hartnup disease and maple syrup urine disease, particularly during periods of metabolic decompensation [38, 39]. Occasionally, true strokes or stroke-like episodes resulting in movement disorders are the result of an IEM, as in Fabry disease or mitochondrial encephalopathies.

One unique paroxysmal movement disorder that may be seen in selected IEMs is oculogyric crisis [40]. This is considered a form of dystonic movement disorder, characterized by the sustained contraction of extraocular muscles resulting in paroxysmal, tonic, conjugate (most commonly upward) eye deviation. Oculogyric crises typically last minutes-to-hours, may be accompanied by other dystonic symptoms, and are often distressing to the affected individual. Most notably, oculogyric crises can be a prominent clinical feature of disorders of monoamine neurotransmission, particularly aromatic L-amino acid decarboxylase deficiency, sepiapterin reductase deficiency, tyrosine hydroxylase deficiency, and vesicular monoamine transporter 2 deficiency.

Phenotypic Clues to IEMs

Other Neurological Features

Some neurological features accompanying movement disorders in IEMs are non-specific, such as developmental delay or regression, cognitive dysfunction, or pyramidal signs. However, other neurological features, such as seizures, can help distinguish particular neurometabolic phenotypes (Figure 3.1). Seizures in association with myoclonus are suggestive of

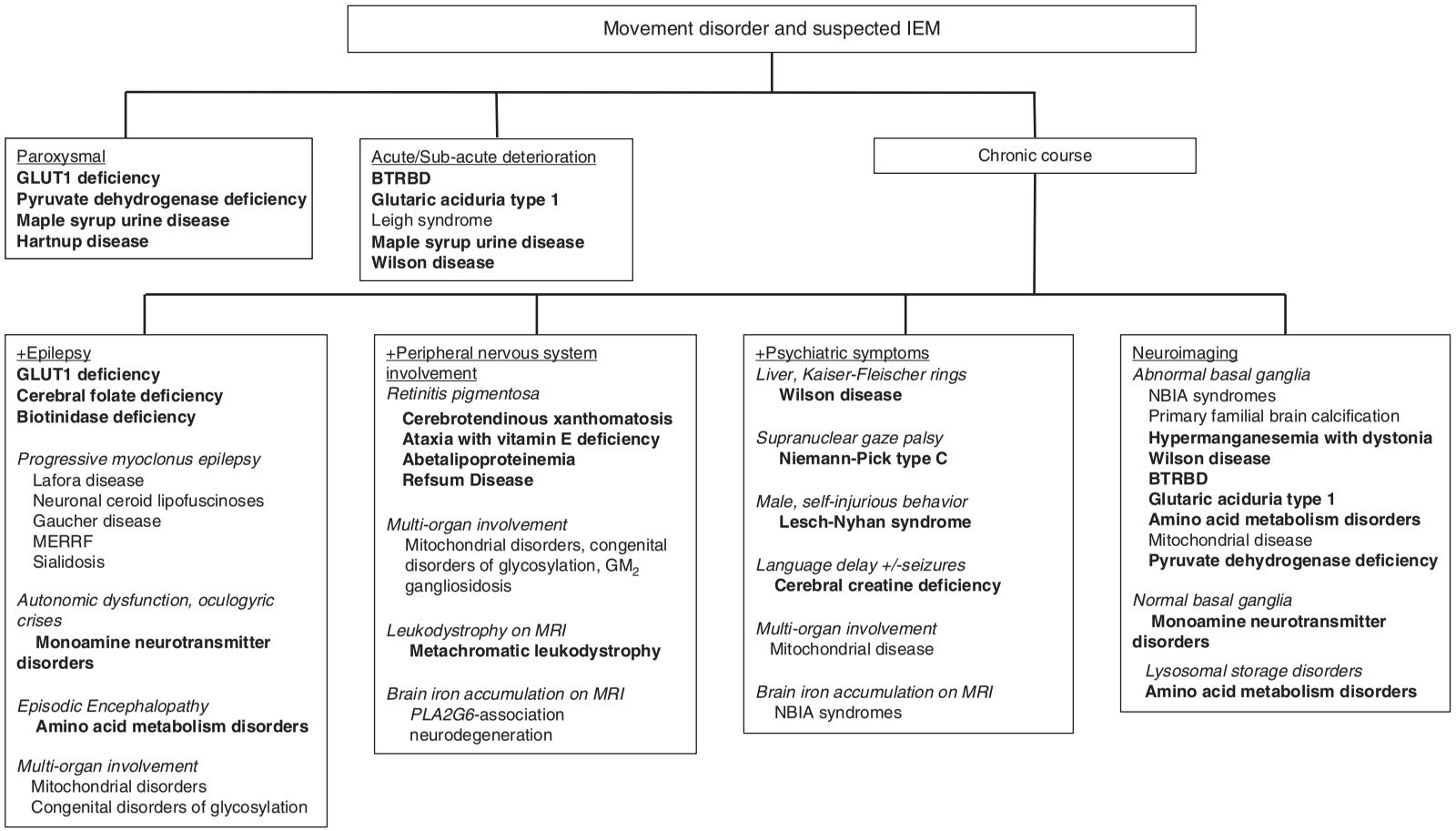

Figure 3.1 Diagnostic approach to patients presenting with a movement disorder and suspected IEM disorders. Potentially treatable disorders are noted in bold type.

progressive myoclonus epilepsies such as Lafora disease, the neuronal ceroid lipofuscinoses, sialidosis, Gaucher disease, and MERRF. Seizures occur in the majority of individuals with GLUT1 deficiency syndrome and may be either focal or generalized, including atypical absence seizures. Seizures also can be part of the complex phenotype in amino acid metabolism disorders, Niemann–Pick disease type C (NPC), cerebral creatine deficiency syndromes, cerebral folate deficiency, biotinidase deficiency, and mitochondrial encephalomyopathies. Gelastic cataplexy, often part of the differential diagnosis of seizures, strongly suggests NPC.

Neuro-ophthalmological features are commonly associated with IEMs. A vertical supranuclear gaze palsy is an important sign of NPC, while oculomotor apraxia is a common finding in neuronopathic Gaucher disease. Nystagmus or ophthalmoparesis can be associated with mitochondrial encephalomyopathies, PDH deficiency, NBIA syndromes, biotin–thiamine-responsive basal ganglia disease, and congenital disorders of glycosylation. Optic atrophy may be seen in selected NBIA syndromes, particularly *PLA2G6*-associated neurodegeneration and mitochondrial membrane protein-associated neurodegeneration, mitochondrial encephalomyopathies, PDH deficiency, biotinidase deficiency, disorders of amino acid metabolism, and the neuronal ceroid lipofuscinoses.

Sensorineural hearing loss is seen in a more limited number of IEMs, including mitochondrial encephalomyopathies, biotinidase deficiency, NPC, and Refsum disease.

Neuropsychiatric disorders – such as psychosis or mood disorders– are common in IEMs associated with movement disorders. Psychiatric manifestations may occur as an initial presentation prior to the development of other significant neurological abnormalities in Wilson disease, NPC, metachromatic leukodystrophy, the neuronal ceroid lipofuscinoses, mitochondrial encephalomyopathies, NBIA syndromes, and cerebrotendinous xanthomatosis. Psychiatric manifestations may also occur in association with developmental delay or cognitive dysfunction in Lesch–Nyhan disease (also associated with self-mutilatory behavior), cerebral creatinine deficiency syndromes, and amino acid metabolism disorders.

Finally, peripheral nervous system involvement may manifest as hyporeflexia, weakness, muscle atrophy, or sensory impairment. The presence of a sensory or sensorimotor neuropathy in association with a movement disorder should raise suspicion for IEMs such as mitochondrial encephalomyopathies, PDH deficiency, *PLA2G6*-associated neurodegeneration, metachromatic leukodystrophy, cerebrotendinous xanthomatosis, ataxia with vitamin E deficiency, abetalipoproteinemia, Refsum disease, or congenital disorders of glycosylation. Notably, mitochondrial membrane protein-associated neurodegeneration may be associated with a primarily motor axonal neuropathy [22], while GM2 gangliosidosis can present with a motor neuron disorder phenotype [31].

Systemic Features

The presence of organ involvement outside of the nervous system in a patient presenting with a movement disorder should raise clinical suspicion for an underlying IEM. Visceral involvement is a common feature. Hepatosplenomegaly in association with a movement disorder is suggestive of lysosomal storage disorders such as GM1 and GM2 gangliosidoses, Gaucher disease, and NPC. Synthetic or hepatocellular liver dysfunction may be seen in Wilson disease, mitochondrial encephalomyopathies, hypermanganesemia with dystonia, and congenital disorders of glycosylation. Cardiomyopathy or cardiac conduction abnormalities can occur in lysosomal storage disorders, Wilson disease, organic acidurias, mitochondrial encephalomyopathies, Refsum disease, and congenital disorders of glycosylation. Renal involvement can include nephrolithiasis (as in Lesch–Nyhan disease), renal tubulopathy (as in Wilson disease and mitochondrial encephalomyopathies), nephrotic syndrome (as in coenzyme Q10 deficiency), or tubulointerstitial disease (as in methylmalonic acidemia).

Careful ophthalmological assessment can reveal findings suggestive of an IEM. A cherry-red spot on funduscopic examination is suggestive of lysosomal storage disorders such as GM1 or GM2 gangliosidosis and sialidosis, or metachromatic leukodystrophy, among others. Retinitis pigmentosa may result in visual loss and is seen in ataxia with vitamin E deficiency, abetalipoproteinemia, aceruloplasminemia, Refsum disease, pantothenate kinase-associated neurodegeneration, the neuronal ceroid lipofuscinoses, and mitochondrial encephalomyopathies. Lens dislocation (ectopia lentis) can occur in homocystinuria and molybdenum cofactor deficiency. Cataracts can be seen

in cerebrotendinous xanthomatosis and sunflower cataracts in Wilson disease. Kayser–Fleischer rings – copper deposition within Descemet's membrane of the cornea on slit lamp examination – are a key physical sign of Wilson disease and are found in approximately 95% of patients with neurological disease [28].

Physical examination should also include assessment of growth parameters, dysmorphic features, and dermatological features. Acquired microcephaly is suggestive of IEMs including GLUT1 deficiency, PDH deficiency, and cerebral folate deficiency syndromes. Macrocephaly is seen in GA-1, L-2-hydroxyglutaric aciduria, Alexander disease, and GM2 gangliosidosis. Short stature is suggestive of mitochondrial encephalomyopathies or GM1 gangliosidosis, while a marfanoid body habitus is seen in homocystinuria. Dysmorphic facial features may be seen in a variety of IEMs, for example in GM1 and GM2 gangliosidoses, molybdenum cofactor deficiency, congenital disorders of glycosylation, and PDH deficiency. Skin abnormalities can include dermatitis or icthyosis and may be seen in biotinidase deficiency, Refsum disease, and congenital disorders of glycosylation. Tendon xanthomas are strongly suggestive of cerebrotendinous xanthomatosis.

Inheritance Patterns

A detailed family history is important to establish inheritance patterns within a family. The majority of IEMs are inherited in an autosomal-recessive manner, requiring bi-allelic pathogenic variants. In such cases, the family history can be unremarkable in non-consanguineous pedigrees. The presence of consanguinity or origin from a region or ethnic group with high rates of consanguinity should increase suspicion for an IEM. Autosomal-dominant inheritance can be seen in a few IEMs, including GTPCH1 deficiency, GLUT1 deficiency, neuroferritinopathy, and primary familial brain calcification. X-Linked inheritance should be suspected when the family history reveals a pattern of more severely affected males without male-to-male transmission, such as Lesch–Nyhan disease and creatine transporter deficiency. Notably, beta-propeller protein-associated neurodegeneration (a form of NBIA) is an X-linked disorder in which the majority of affected individuals are female, which may reflect non-viability in most affected male conceptuses [22]. Finally, maternal inheritance is seen in mitochondrial encephalomyopathies. However, because many mitochondrial proteins are encoded by nuclear genes, mitochondrial encephalomyopathies may also be inherited in an autosomal-recessive, -dominant, or X-linked manner.

Newborn Screening

Newborn screening has the ability to identify affected children prior to the development of symptoms and to thus improve long-term clinical outcomes through early therapeutic interventions [41]. Amino acid metabolism disorders, biotinidase deficiency, and defects of biopterin synthesis or recycling are included in the majority of newborn screening programs. Some of the more expanded newborn screening programs also screen for lysosomal storage disorders or X-linked adrenoleukodystrophy [42]. In countries where newborn screening is not universal, these disorders should be suspected in patients with movement disorders.

Conclusions

IEMs are an important diagnostic category to consider in both children and adults presenting with movement disorders, particular in those with complex or mixed movement disorder phenotypes, paroxysmal movement disorders, and those associated with additional neurological or systemic manifestations. The early identification of IEM is key to provide early therapeutic intervention (where available) that may reduce long-term neurological morbidity and mortality. In those IEMs without specific therapies, accurate diagnosis remains important to monitor for clinically relevant disease manifestations and to provide genetic counseling to parents or at-risk family members. Targeted next-generation sequencing and whole-exome sequencing have reported genetic diagnostic yields in approximately 15–20% of cases with movement disorders [43, 44]. However, these molecular testing techniques may miss certain genetic etiologies such as deletions/duplications or abnormalities within non-coding regions. Thus, even as broad genetic testing becomes more available, thorough and accurate documentation of the clinical phenotype remains necessary for the appropriate interpretation of genetic testing results and to identify new genotype–phenotype associations. Improving understanding of the genetic and physiological underpinnings of IEMs is expected to lead to new therapeutic strategies and will broaden the scope of IEMs that are considered treatable.

Key Points and Clinical Pearls

- Inborn errors of metabolism (IEMs) are an important potentially treatable cause of movement disorders in both children and adults.
- IEMs should be suspected in cases presenting with complex/mixed movement disorder phenotypes in association with other neurological or systemic manifestations or a positive family history.

Directions for Future Research

- Expanding use of next-generation sequencing is expected to facilitate the diagnosis of genetic movement disorders and broaden the phenotypes associated with IEMs.
- New therapeutic techniques will increase the number of IEMs considered treatable.

References

1. Sanderson S, Green A, Preece MA, Burton H. The incidence of inherited metabolic disorders in the West Midlands, UK. Arch Dis Child. 2006;**91**(11):896–9.
2. Gouider-Khouja N, Kraoua I, Benrhouma H, Fraj N, Rouissi A. Movement disorders in neuro-metabolic diseases. Eur J Paediatr Neurol. 2010;**14**(4):304–7.
3. Jinnah HA, Albanese A, Bhatia KP, et al. Treatable inherited rare movement disorders. Mov Disord. 2018;**33**(1):21–35.
4. Marras C, Lang A, van de Warrenburg BP, et al. Nomenclature of genetic movement disorders: Recommendations of the international Parkinson and movement disorder society task force. Mov Disord. 2016;**31**(4):436–57.
5. El Euch-Fayache G, Bouhlal Y, Amouri R, Feki M, Hentati F. Molecular, clinical and peripheral neuropathy study of Tunisian patients with ataxia with vitamin E deficiency. Brain. 2014;**137**(Pt 2):402–10.
6. Lee J, Hegele RA. Abetalipoproteinemia and homozygous hypobetalipoproteinemia: A framework for diagnosis and management. J Inherit Metab Dis. 2014;**37**(3):333–9.
7. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: A consensus update. Mov Disord. 2013;**28**(7):863–73.
8. Wijemanne S, Jankovic J. Dopa-responsive dystonia: Clinical and genetic heterogeneity. Nat Rev Neurol. 2015;**11**(7):414–24.
9. Gitiaux C, Roze E, Kinugawa K, et al. Spectrum of movement disorders associated with glutaric aciduria type 1: A study of 16 patients. Mov Disord. 2008;**23**(16):2392–7.
10. Kolker S, Valayannopoulos V, Burlina AB, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: The evolving clinical phenotype. J Inherit Metab Dis. 2015;**38**(6):1059–74.
11. Martikainen MH, Ng YS, Gorman GS, et al. Clinical, genetic, and radiological features of extrapyramidal movement disorders in mitochondrial disease. JAMA Neurol. 2016;**73**(6):668–74.
12. Ng J, Heales SJ, Kurian MA. Clinical features and pharmacotherapy of childhood monoamine neurotransmitter disorders. Paediatr Drugs. 2014;**16**(4):275–91.
13. Jinnah HA, Visser JE, Harris JC, et al. Delineation of the motor disorder of Lesch–Nyhan disease. Brain. 2006;**129**(Pt 5):1201–17.
14. Mercimek-Mahmutoglu S, Stoeckler-Ipsiroglu S, Adami A, et al. GAMT deficiency: Features, treatment, and outcome in an inborn error of creatine synthesis. Neurology. 2006;**67**(3):480–4.
15. Allen NM, Lin JP, Lynch T, King MD. Status dystonicus: A practice guide. Dev Med Child Neurol. 2014;**56**(2):105–12.
16. Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. Mov Disord. 2010;**25**(11):1538–49.
17. Crossman AR. Functional anatomy of movement disorders. J Anat. 2000;**196** (Pt 4):519–25.
18. Munchau A. Transient (benign) infantile chorea – a physiological phenomenon during motor development? International Symposium on Pediatric Movement Disorders. Barcelona: The Movement Disorder Society; 2004.
19. Klepper J, Leiendecker B, Eltze C, Heussinger N. Paroxysmal nonepileptic events in Glut1 deficiency. Mov Disord Clin Pract. 2016;**3**(6):607–10.
20. Keogh MJ, Morris CM, Chinnery PF. Neuroferritinopathy. Int Rev Neurobiol. 2013;**110**:91–123.
21. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;**30**(12):1591–601.
22. Di Meo I, Tiranti V. Classification and molecular pathogenesis of NBIA syndromes. Eur J Paediatr Neurol. 2018;**22**(2):272–84.

23. Ebrahimi-Fakhari D, Hildebrandt C, Davis PE, et al. The spectrum of movement disorders in childhood-onset lysosomal storage diseases. Mov Disord Clin Pract. 2018;**5**(2):149–55.
24. Garcia-Cazorla A, Duarte ST. Parkinsonism and inborn errors of metabolism. J Inherit Metab Dis. 2014;**37**(4):627–42.
25. Ghaoui R, Sue CM. Movement disorders in mitochondrial disease. J Neurol. 2018;**265**(5):1230–40.
26. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009;**361**(17):1651–61.
27. Bhatia KP, Bain P, Bajaj N, et al. Consensus statement on the classification of tremors from the Task Force on Tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;**33**(1):75–87.
28. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;**56**(3):671–85.
29. Tilikete C, Desestret V. Hypertrophic olivary degeneration and palatal or oculopalatal tremor. Front Neurol. 2017;**8**:302.
30. Mink JW, Augustine EF, Adams HR, Marshall FJ, Kwon JM. Classification and natural history of the neuronal ceroid lipofuscinoses. J Child Neurol. 2013;**28**(9):1101–5.
31. Ferreira CR, Gahl WA. Lysosomal storage diseases. Transl Sci Rare Dis. 2017;**2**(1–2):1–71.
32. Leach EL, Shevell M, Bowden K, Stockler-Ipsiroglu S, van Karnebeek CD. Treatable inborn errors of metabolism presenting as cerebral palsy mimics: Systematic literature review. Orphanet J Rare Dis. 2014;**9**:197.
33. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;**109**:8–14.
34. Kolker S, Christensen E, Leonard JV, et al. Diagnosis and management of glutaric aciduria type I: Revised recommendations. J Inherit Metab Dis. 2011;**34**(3):677–94.
35. Alfadhel M, Almuntashri M, Jadah RH, et al. Biotin-responsive basal ganglia disease should be renamed biotin–thiamine-responsive basal ganglia disease: A retrospective review of the clinical, radiological and molecular findings of 18 new cases. Orphanet J Rare Dis. 2013;**8**:83.
36. Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in Glut-1 deficiency. Mov Disord. 2010;**25**(3):275–81.
37. Castiglioni C, Verrigni D, Okuma C, et al. Pyruvate dehydrogenase deficiency presenting as isolated paroxysmal exercise induced dystonia successfully reversed with thiamine supplementation. Case report and mini-review. Eur J Paediatr Neurol. 2015;**19**(5):497–503.
38. Darras BT, Ampola MG, Dietz WH, Gilmore HE. Intermittent dystonia in Hartnup disease. Pediatr Neurol. 1989;**5**(2):118–20.
39. Carecchio M, Schneider SA, Chan H, et al. Movement disorders in adult surviving patients with maple syrup urine disease. Mov Disord. 2011;**26**(7):1324–8.
40. Slow EJ, Lang AE. Oculogyric crises: A review of phenomenology, etiology, pathogenesis, and treatment. Mov Disord. 2017;**32**(2):193–202.
41. Watson MS, Mann MY, Lloyd-Puryear MA, Rinaldo P, Howell RR.Executive summary. Genet Med. 2006;**8**:1S.
42. Therrell BL, Padilla CD, Loeber JG, et al. Current status of newborn screening worldwide: 2015. Semin Perinatol. 2015;**39**(3):171–87.
43. Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of Sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. 2013;**34**(12):1721–6.
44. van Egmond ME, Lugtenberg CHA, Brouwer OF, et al. A post hoc study on gene panel analysis for the diagnosis of dystonia. Mov Disord. 2017;**32**(4):569–75.

Chapter 4

Imaging in Metabolic Movement Disorders

Lance Rodan and Edward Yang

Introduction

During the evaluation of a patient with a movement disorder, advanced neuroimaging is often obtained to narrow the diagnostic possibilities and also to assess the status of what is frequently a neurodegenerative process. In the other chapters of this monograph, specific metabolic causes of movement disorders are discussed in detail. In this chapter, we provide a pragmatic approach for integrating imaging data into the work-up of a patient with a movement disorder of uncertain etiology, heavily emphasizing brain MRI which is the cornerstone of imaging work-up for this indication. Our focus is on pediatric-onset disorders manifesting as dystonia, chorea, athetosis, tremor, parkinsonism, and myoclonus. Since spasticity is a common end-state of many neurodegenerative conditions, it is not emphasized in this review, and likewise we omit disorders for which the primary manifestation is ataxia. Several review articles provide complementary information on adult-onset metabolic movement disorders or imaging algorithms for metabolic conditions or leukodystrophies more generally [1–6].

We begin by reviewing a standard brain MRI protocol for a patient undergoing evaluation of a movement disorder, and we briefly detail the normal developmental trajectory of the brain, since many metabolic conditions present at a time of ongoing developmental changes in brain signal (e.g. myelination). Metabolic conditions which cause movement disorders are then discussed according to imaging patterns: basal ganglia T2 hyperintensity, abnormal basal ganglia mineralization, diffuse white matter signal abnormality, and disorders without specific brain imaging findings. We contrast these disorders with acquired conditions which may mimic metabolic movement disorders, either on imaging or by clinical presentation. A graphical overview of the approach in this chapter is provided in Figure 4.1.

Imaging for Movement Disorders and Normal Brain Development

A brain MRI obtained for evaluation of a movement disorder will usually be protocoled to screen broadly for underlying injuries, neoplasm, and evidence of a genetic condition. While a number of protocols can be devised to evaluate these possibilities, our institutional protocol for evaluation of a patient with movement disorders (Box 4.1) includes isotropic T1-weighted imaging, high resolution axial/coronal T2-weighted imaging, susceptibility-weighted imaging (SWI), and diffusion tensor imaging. For patients older than 6–12 months, axial fluid-attenuated inversion recovery (FLAIR) imaging will also be routinely performed, and since studies are monitored in real time in our practice, there is always the option of injecting contrast should the non-contrast imaging warrant it. If there is a strong suspicion of a metabolic condition as the basis of a movement

Box 4.1 Local protocol for metabolic disease evaluation

3 Tesla MRI

32- or 64-channel head coil

Sagittal T1 MPRAGE (magnetization-prepared rapid gradient echo) or IR-SPGR (fast spoiled GRASS sequence with IR preparation) at isotropic resolution (0.9 mm)

Axial T2 (0.4 × 0.5 × 2.5 mm skip 0 mm)

Coronal T2 (0.4 × 0.5 × 2.5 mm skip 0 mm)

Axial FLAIR (0.6 × 0.6 × 4 mm skip 1 mm)

Axial susceptibility weighted imaging (SWI), susceptibility weighted angiography (SWAN), or venous blood oxygen level dependent (VEN-BOLD) (0.8 × 0.9 × 1.25 mm)

Three-dimensional spiral chemical shift imaging MR spectroscopy (30 ms, 135 ms echo time)

Simultaneous multislice diffusion tensor imaging (35 directions, 1.5 × 1.5 × 2 mm skip 0 mm)

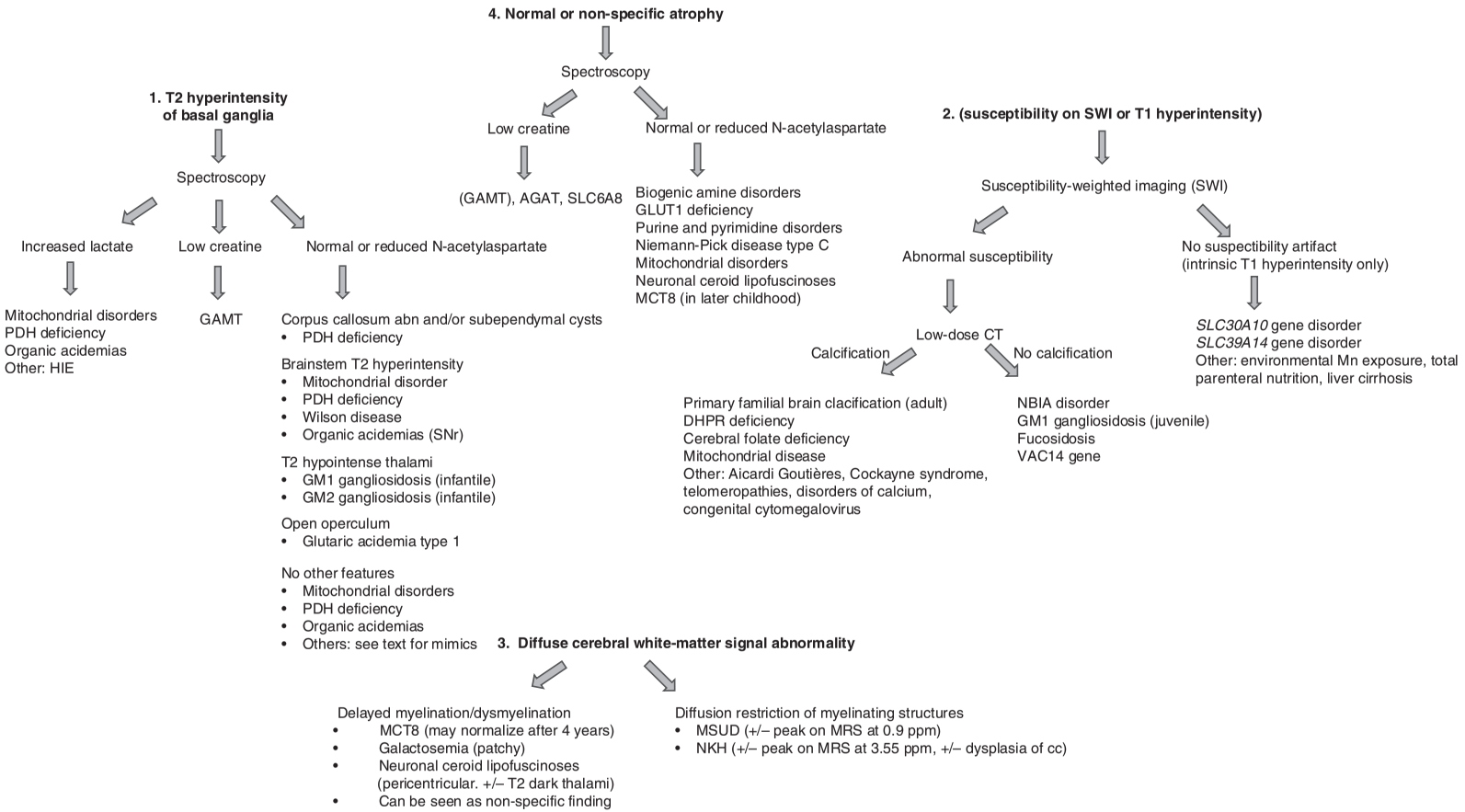

Figure 4.1 Proposed diagnostic approach to movement disorders based on imaging findings: (1) basal ganglia T2 hyperintensity; (2) mineralization of the basal ganglia; (3) diffusely abnormal white matter signal; (4) normal or non-specific atrophy.

disorder, multivoxel MRS at short and intermediate echo times is also obtained, and in cases where deep brain stimulator placement is likely to be recommended, surgical navigation sequences as well as an MR angiogram will be obtained. The described imaging protocol is of sufficient detail to detect congenital structural abnormalities (e.g. polymicrogyria), injuries (e.g. hypoxic ischemic insult), neoplasms, and patterns of signal abnormality typical of particular genetic conditions (discussed below).

T1, T2, and SWI characteristics of the brain evolve throughout childhood due to normal myelination and physiological iron deposition. A basic understanding of these changes is therefore essential to detecting abnormalities on brain MRI in young patients.

Dramatic changes in brain myelination occur during the first 2 years of life, most conspicuous on T1-weighted sequences during the first 7–8 months and later most conspicuous on T2-weighted imaging. With myelination, any given brain structure develops increased T1 hyperintensity and decreased T2 hyperintensity, which can be conceptualized as a transition from watery to more proteinaceous brain matter. Complex tables listing normative myelination milestones for specific brain structures are available [7], but an understanding of brain myelination at three early time points usually suffices for most day to day evaluations of brain myelination (Figure 4.2a–f). At birth (Figure 4.2a, b), the brain is largely unmyelinated apart from small areas of myelinated brain (high T1 and low T2 signal) in the ventrolateral thalamus, posterior putamen, and posterior limb of the internal capsule; the dorsal brainstem, perirolandic cortex, and primary visual cortex are also myelinated at birth. By 6–8 months of age, myelination on T1-weighted imaging has reached the subcortical white matter (Figure 4.2c) though myelination on T2-weighted imaging is limited to the internal capsule and corpus callosum (Figure 4.2d); myelination of the posterior fossa structures will be complete on both T1 and T2, having typically reached maturity by 3 months. By 18–20 months, the myelination in the subcortical white matter has further matured on T1 imaging (Figure 4.2e) and the myelination on T2 imaging has reached the subcortical white matter (Figure 4.2f). Thereafter, minimal incremental myelination will occur in the subcortical white matter (perceptible changes through the first 5 years) and the periatrial white matter (periatrial "terminal zones" can persist through adolescence). An important consequence of this evolution of signal intensity is that T2 hyperintensity can be obscured during the first 2 years of life due to the intrinsically T2 hyperintense signal of unmyelinated brain parenchyma, and conversely pathological T2 hyperintensity of the globus pallidus can be falsely suggested around 6–8 months due to relative differences in the rates of internal capsule versus basal ganglia myelination (Figure 4.2d). As illustrated in specific cases discussed later, these limitations can be partly addressed using diffusion imaging.

With SWI, local disturbances in tissue magnetization (e.g. from iron or calcium deposition) result in a loss of MRI signal. As typically implemented, SWI sequences employ a gradient echo sequence that has both T1 and T2 weighting [8, 9], providing a relatively low-contrast image of the normal brain with the exception of brain nuclei with physiological mineralization: globus pallidi, subthalamic nuclei, substantia nigra, red nuclei, and dentate nuclei. In these locations, there is no detectable mineralization at birth but faint physiological iron deposition is seen by school age and this increases with age (Figure 4.3). Normative measures of this process are scarce [10–12]. Therefore, assessing for abnormal iron deposition in brain nuclei is a somewhat subjective exercise on routine clinical imaging, reflecting scanner-specific effects as well as interindividual variation. Calcification also accumulates in the basal ganglia with age and can be detected on SWI. As with iron deposition, normative data are scarce though it is rare to see calcification in the basal ganglia before adolescence [13, 14]. By clinical experience, calcifications are more likely to manifest as focal deposits than diffuse deposition throughout a deep brain nucleus, for example as seen in neurodegeneration with brain iron accumulation (NBIA). Nonetheless, there are instances where confusion about calcium versus iron deposition may persist on MRI. In those cases, the increased magnetization associated with iron and decreased magnetization associated with calcium deposits can be separated using detailed "phase" maps from SWI (Figure 4.4) [15]. CAT scan is a complementary means of detecting calcification.

The relative concentration of metabolites detectable on MRS also changes with age, slowly reaching an adult pattern by 2 years of age [7]. In practice, this changing relationship has a limited application to metabolic movement disorders where the presence of abnormal metabolites (e.g. lactate) or the absence

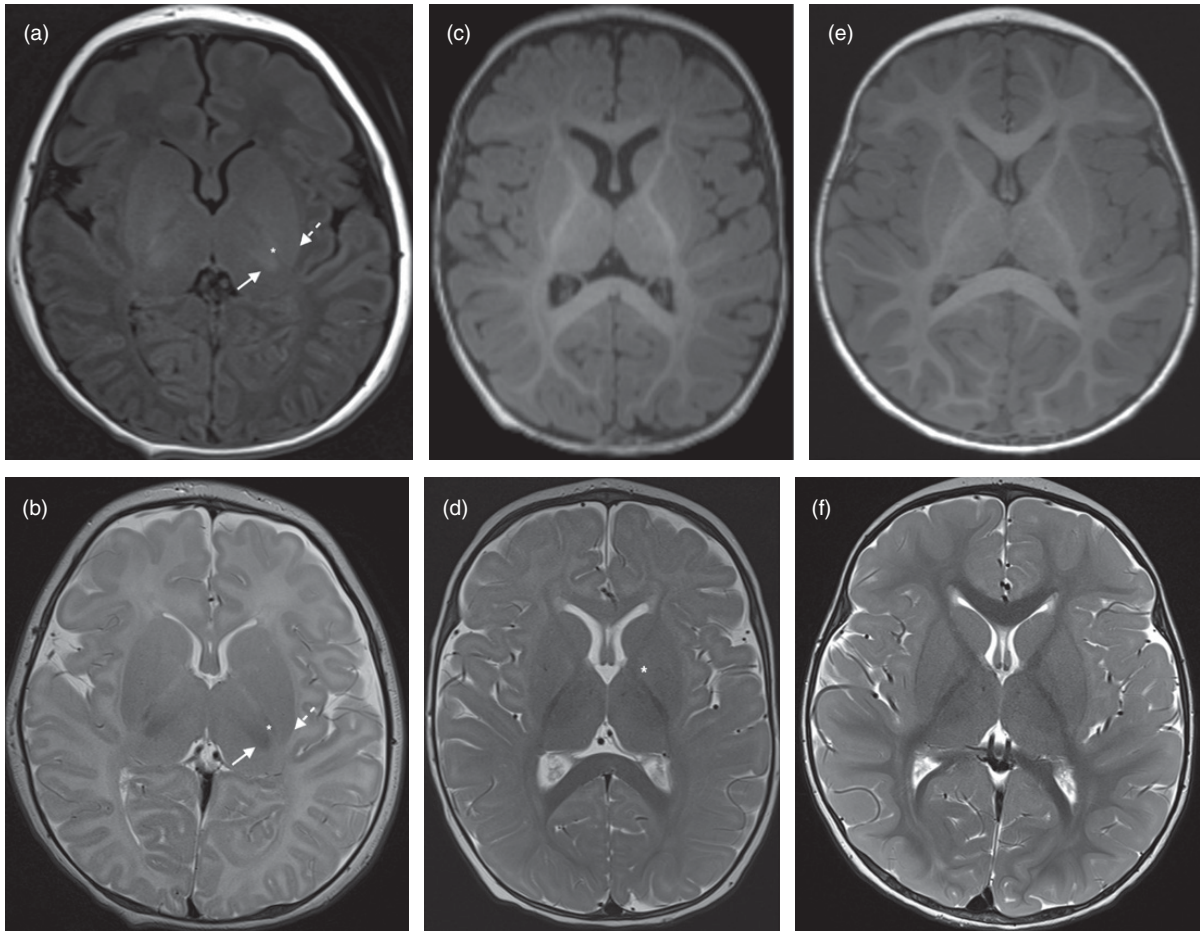

Figure 4.2 Normal brain myelination using T1-weighted (a, c, e) and T2-weighted (b, d, f) sequences. In the normal neonatal brain (a, b), there is T1 hyperintensity and T2 hypointensity from brain myelination at the ventrolateral thalamus (arrow with solid stem on the left), posterior putamen (arrow with dashed stem on the left), and posterior limb of the internal capsule (asterisk on the left). By 6 months of age (c, d), myelination is now visible out to the subcortical white matter throughout the brain on T1-weighted imaging but myelination on T2-weighted imaging is limited to the internal capsule and corpus callosum. Note relative T2 hyperintensity of the globus pallidus at this age (asterisk on the left in d). By 18 months of age (e, f), myelination has further matured in the subcortical white matter on T1-weighted imaging, and myelination on T2-weighted imaging has reached the subcortical white matter.

of normal metabolites (e.g. creatine) is generally more important than quantitative relationships.

Neuroimaging Patterns in Metabolic Movement Disorders

The neuroimaging patterns in inborn errors of metabolism (IEMs) associated with movement disorders can be divided into four general categories: (1) symmetrical T2 hyperintensity of basal ganglia; (2) mineralization of basal ganglia; (3) diffuse abnormalities of cerebral white matter signal; and (4) normal or non-specific patterns.

Symmetrical T2 Hyperintensity of Basal Ganglia

Symmetrical T2 hyperintensity of the basal ganglia is a common neuroimaging pattern in a number of IEMs associated with movement disorders, including organic acidemias, pyruvate dehydrogenase (PDH) deficiency, mitochondrial disorders more generally, infantile forms of GM1 and GM2 gangliosidoses, Wilson's disease, and guanidinoacetate N-methyltransferase (GAMT) deficiency.

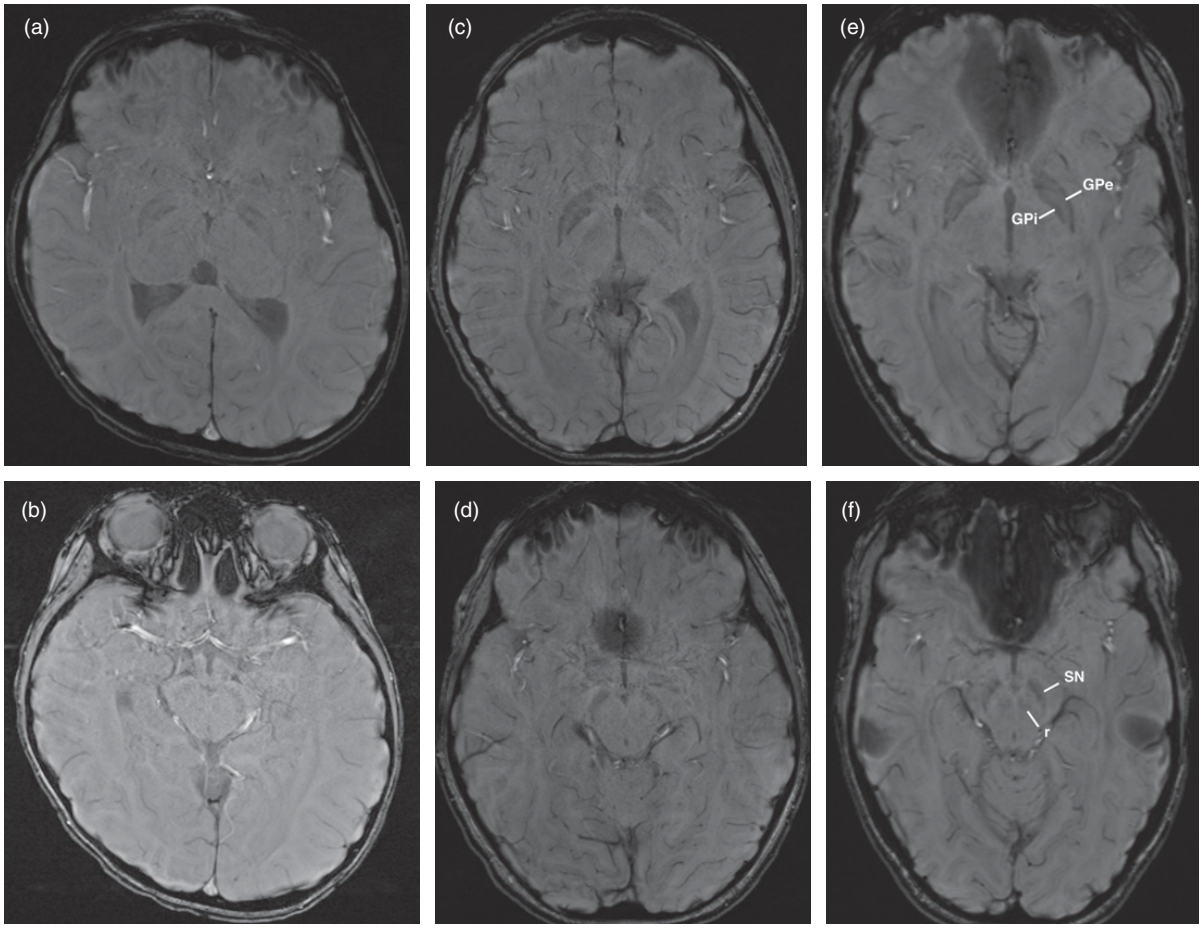

Figure 4.3 Normal brain mineralization and characterization of calcium versus iron using SWI. At 5 years (a, b), 10 years (c, d), and 19 years (e, f) of age, there is progressive physiological iron deposition seen at the level of the basal ganglia (a, c, e) and midbrain (b, d, f). Left-sided nuclei are labelled in e, f: GPi, globus pallidus internus; GPe, globus pallidus externus; r, red nuclei; and SN, substantia nigra.

Organic Acidemias

The organic acidemias are a diverse group of genetic disorders caused by enzymatic deficiencies in the catabolic pathways of amino acids, resulting in the accumulation of specific organic acids in body fluids. They can be divided clinically into **classic** organic acidemias that present with metabolic derangements in blood, including ketoacidosis and hyperammonemia, in addition to neurological symptoms, and **cerebral** organic acidemias that typically manifest with only neurological symptoms. Examples of classic organic acidemias include propionic acidemia, methylmalonic acidemia, isovaleric acidemia, and beta-ketothiolase deficiency. Examples of cerebral organic acidemias include glutaric acidemia type 1, 3-methyl-3-hydroxybutyric acidemia, L2-hydroxyglutaric acidemia, 3-methylglutaric acidemia, and succinate semialdehyde dehydrogenase deficiency. A specific diagnosis is made by measuring urine organic acids, and in some disorders the plasma acylcarnitine profile [16].

The clinical presentations of the various organic acid disorders are distinct. Propionic and methylmalonic acidemia present with recurrent ketoacidosis and hyperammonemia, provoked by high protein load or metabolic stressors like prolonged fasting or illness. Developmental delay, failure to thrive/anorexia, and gastrointestinal dysmotility are common complications. Pancreatitis, sensorineural hearing loss, and optic neuropathy have also been reported. Chronically, patients with propionic acidemia may develop cardiomyopathy and QT prolongation, whereas patients with methylmalonic acidemia may develop renal failure. Patients with

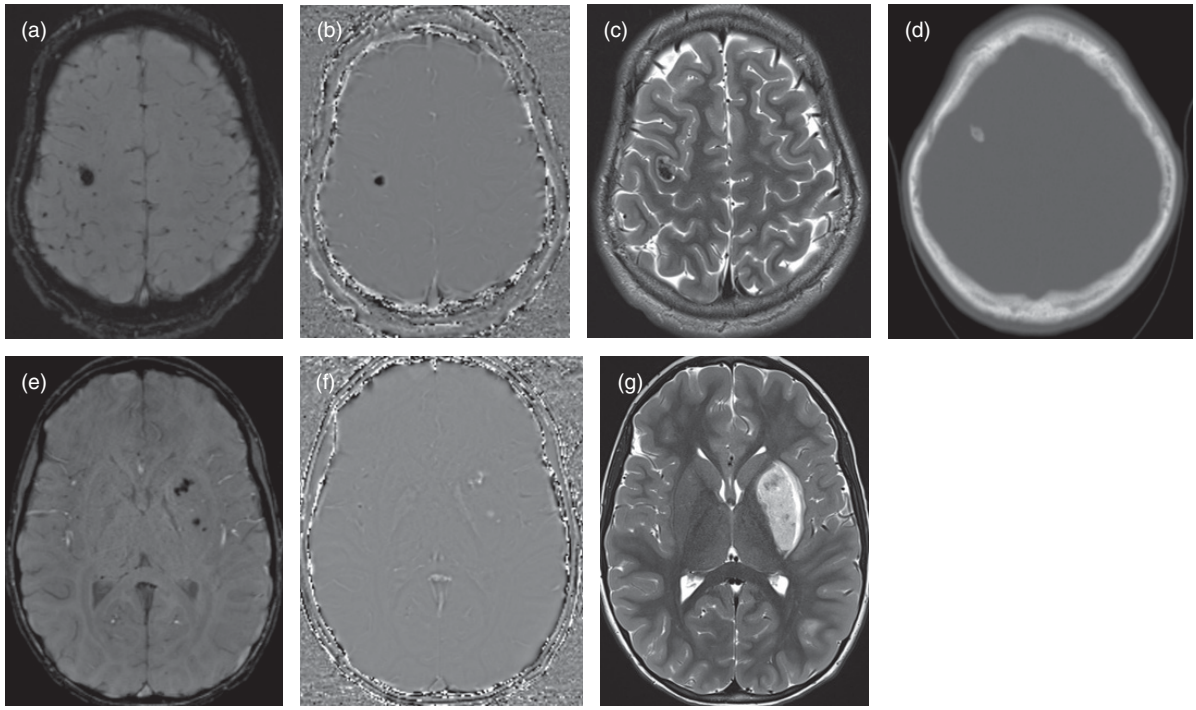

Figure 4.4 Characterization of mineralization by SWI. Susceptibility in a right frontal lesion (a) is characterized by the SWI phase map (b) as opposite phase to blood dephasing (i.e. black rather than white). The phase map enables inference of calcification as the basis of the susceptibility, suggesting that the small mass seen on T2-weighted imaging (c) is calcified as confirmed by non-contrast head CT (d). Conversely, the SWI phase map for a patient with a subacute basal ganglia infarct (e) demonstrates that susceptibility (f) in the infarct seen on T2-weighted imaging (g) represents petechial blood (white on phase map).

glutaric acidemia type 1 are often macrocephalic since infancy. They are typically asymptomatic initially, but are at risk for metabolic stroke in the first 6 years of life, provoked by increased metabolic stress, such as febrile illness. They are also susceptible to subdural hemorrhages due to enlarged extra-axial spaces, which can mimic non-accidental trauma. The most common movement disorder seen in the organic acidemias is dystonia, but choreoathetosis, parkinsonism, and myoclonus have also been reported. These movement abnormalities may develop subacutely following a metabolic stressor such as illness or infection, or more insidiously [16].

In the organic acidemias as a group, neuroimaging may be normal prior to an acute central nervous system event or abnormalities may develop insidiously. The most common pattern of signal abnormality is T2 hyperintensity of the basal ganglia that is almost always symmetric, although unilateral or asymmetrical cases have been encountered. The specific pattern of basal ganglia involvement and whether or not there is additional involvement of substantia nigra pars reticulata, cerebellar dentate nuclei, and cerebral white matter is disease specific (summarized in Table 4.1) [17–21]. There may also be a diffusion restriction of affected structures in the acute stages [22]. Examples of brain MRI of patients with organic acidemias are presented in Figures 4.5–4.7. Spectroscopy is normal or may demonstrate lactate elevation.

Mitochondrial Disorders

Mitochondrial disorders encompass a wide range of genetic defects that affect the assembly of the mitochondrial respiratory chain, function of the citric acid cycle, mitochondrial translation, mitochondrial maintenance, mitochondrial fission/fusion, intra-mitochondrial transport, mitochondrial cofactor synthesis/metabolism, and autophagy. Mitochondrial disorders can result from defects in nuclear or mitochondrially encoded genes. The phenotypic spectrum of mitochondrial disorders is highly pleiomorphic, and may involve vision, hearing, the heart, liver, kidney, endocrine system, central nervous system, and peripheral nervous

Table 4.1 Neuroimaging findings in the organic acidemias

	Basal ganglia/ substantia nigra	White matter	Other
Propionic acidemia	Striatum, substantia nigra	Subcortical U-fibers	No
Methylmalonic acidemia	Globus pallidi, substantia nigra reported	Non-specific gliosis	Dorsal brainstem, cerebellar hemispheres, volume loss
Isovaleric acidemia	Globus pallidi	Yes, non-specific	No
Beta-ketothiolase deficiency	Variable		No
Glutaric acidemias type 1	Striatum	Yes, non-specific	Central tegmental tracts, dentate, thalami, macrocephaly, open operculum, subdural fluid collections
L2-hydroxyglutaric acidemias	Globus pallidus	Subcortical U-fibers (predominantly frontal)	Dentate

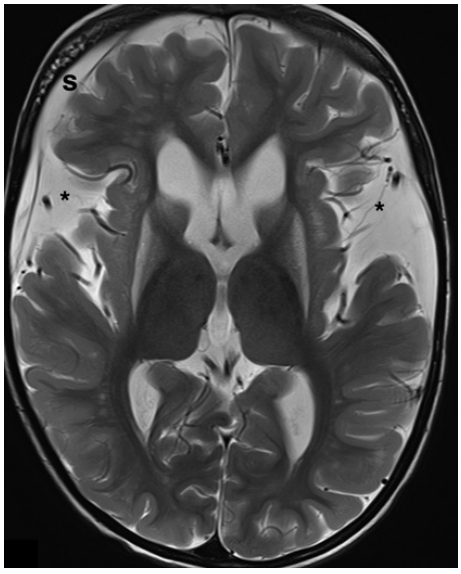

Figure 4.5 Glutaric acidemia type 1 with dystonia and spasticity at 5 years of age. This axial T2 image demonstrates severe volume loss and signal abnormality of the basal ganglia bilaterally, associated with opercular widening (asterisks) and small subdural collections.

system. A wide range of movement disorders have been described in mitochondrial disorders, including dystonia, choreoathetosis, parkinsonism, tremor, ataxia, and myoclonus. Biochemical evaluation may demonstrate elevations in lactic acid with increased lactate:pyruvate ratio, elevations in plasma alanine and/or proline, abnormalities of citric acid cycle metabolites, or the accumulation of specific organic acids in urine. Some mitochondrial disorders have more specific biochemical abnormalities (e.g. elevated lactate with a normal (<20) lactate:pyruvate ratio in PDH deficiency and low plasma arginine in MELAS [mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes] syndrome) [16].

Imaging in mitochondrial disorders is variable, but a common pattern involves symmetrical T2 hyperintensity of deep gray nuclei and brainstem tracts [23–25]. This pattern was initially described, based on specific post-mortem pathology findings, as Leigh syndrome; however, when this distribution of signal abnormality is seen in vivo on MRI, it is best described as "Leigh-like." In addition to an increased T2 signal, the involved structures may show cavitation and necrosis. Affected structures may also demonstrate diffusion restriction, but unlike the typical diffusion changes following ischemia, they may be prolonged (lasting months) in mitochondrial disorders, and may not result in gliosis or atrophy [23]. MRS may demonstrate a lactate doublet at 1.3 ppm that is upright at short and long echo times, and inverts at intermediate echo times. Examples of mitochondrial disorders are shown in Figures 4.8 and 4.9.

Additional neuroimaging patterns in mitochondrial disease include stroke-like, cortically based lesions that cross vascular territories (e.g. mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes [MELAS] syndrome, Alpers syndrome); non-specific cerebral and/or cerebellar atrophy; and prominent white matter signal alterations (e.g. Kearn–Sayre syndrome, mitochondrial neurogastrointestinal encephalopathy syndrome, disorders of mitochondrial aminoacyl transfer RNA synthetases, some complex 1 defects). Mitochondrial disorders may occasionally be associated with calcification of the basal ganglia, and brain malformations (e.g. callosal dysgenesis in pyruvate dehydrogenase deficiency, migrational abnormalities in fumarase deficiency) [5, 24].

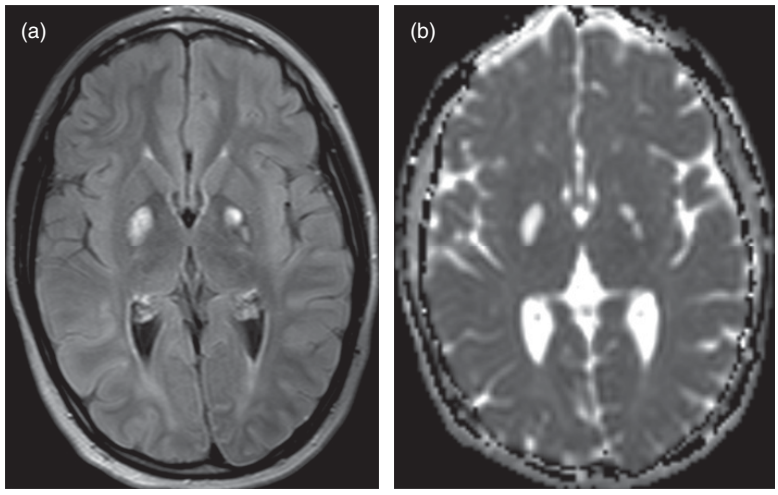

Figure 4.6 12-year-old male with methylmalonic acidemia, global developmental delay, intractable seizures, and new tremors. (a) Axial FLAIR images demonstrate signal abnormality in the basal ganglia and patchy periventricular gliosis, new findings compared to a study performed 4 years prior. (b) Axial apparent diffusion coefficient maps indicate that the signal abnormality has increased diffusivity in keeping with a subacute to chronic metabolic insult.

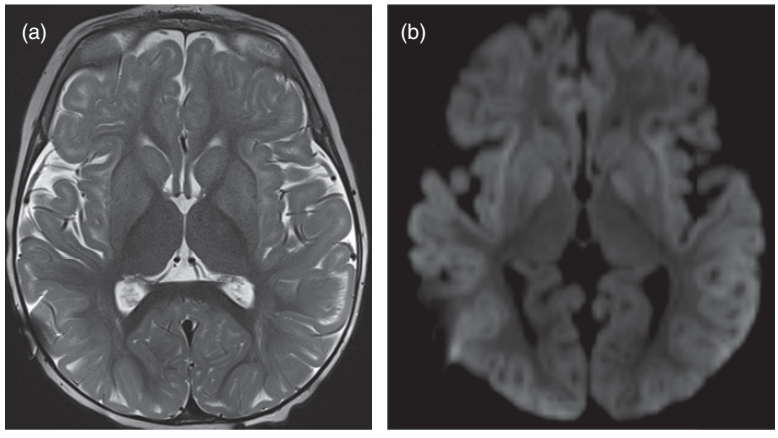

Figure 4.7 Propionic acidemia at 12 months with hypotonia and seizures. (a) Axial T2 and (b) diffusion-weighted images demonstrate T2 prolongation and faint diffusion restriction in the basal ganglia with abnormally accentuated T2 hyperintensity in the subcortical white matter.

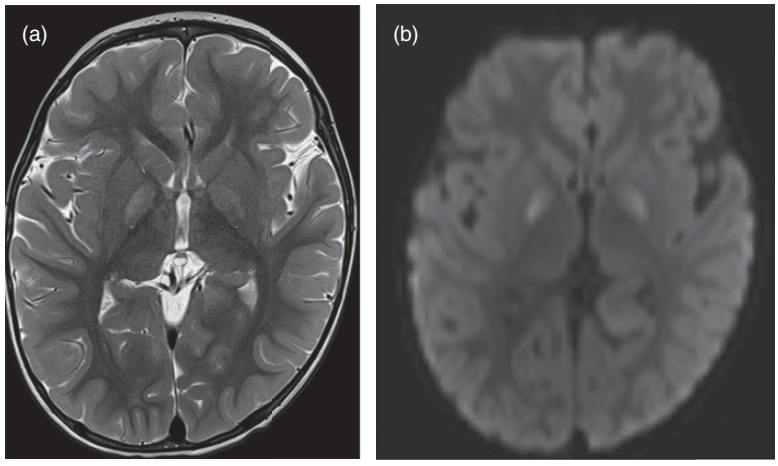

Figure 4.8 PDH deficiency in a 28-month-old child with developmental delay and seizures. (a) Axial T2 and (b) diffusion-weighted images demonstrate diffusion restriction and T2 hyperintensity within the globus pallidi.

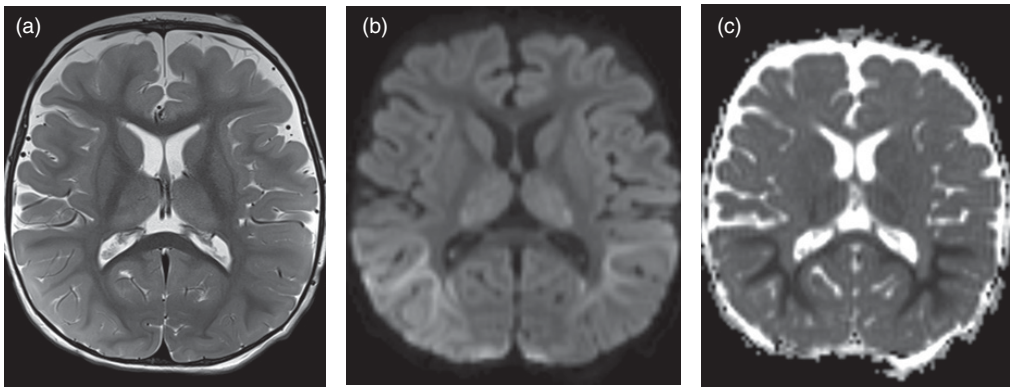

Figure 4.9 A 1-year-old male with POLG-associated Alpers syndrome, manifest as refractory status epilepticus, myoclonus, and liver failure. (a) Axial T2-weighted imaging demonstrates thalamic T2 hyperintensity and posterior quadrant cortical/subcortical T2 prolongation, much more conspicuous on (b) an axial diffusion trace and (c) apparent diffusion coefficient (ADC) maps.

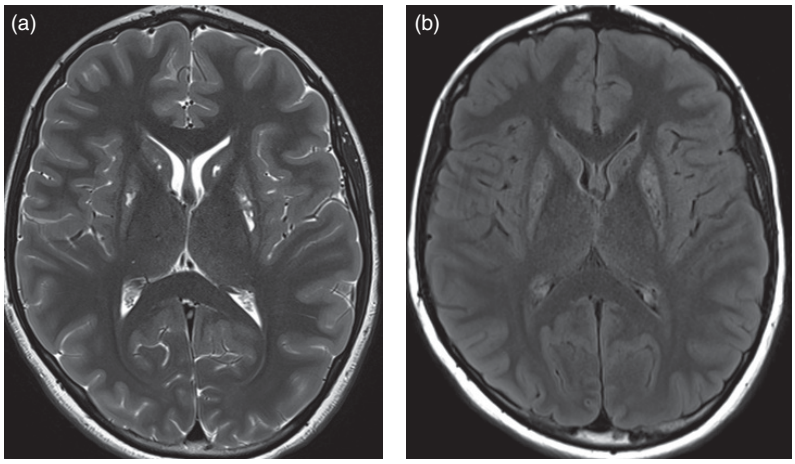

Figure 4.10 Biotin–thiamine responsive basal ganglia disease at 12 months. (a) Axial T2 and (b) FLAIR images demonstrate bilateral striatal necrosis. The patient had a history of paroxysmal episodes of weakness and ataxia responsive to a mitochondrial cocktail including biotin.

One disorder that deserves special attention in this category since it is amenable to therapy is biotin–thiamine-responsive basal ganglia disease [26]. Patients present with episodes of subacute encephalopathy, seizures, ataxia, dystonia, rigidity, and brainstem signs provoked by metabolic stressors. Occasionally, the presentation can be chronically progressive. Neuroimaging demonstrates bilateral T2 hyperintensity in caudate heads, putamen, and, occasionally, globi pallidi, thalami, brainstem tracts, cerebellum, cortex, and subcortical white matter (Figure 4.10). Patients respond favorably to early administration of high-dose biotin and thiamine.

Infantile (Acute) Forms of GM1 and GM2 Gangliosidoses

GM1 and GM2 gangliosidoses are caused by defects in lysosomal hydrolases that result in an accumulation of ganglioside substrates (a form of sphingolipid) within lysosomes [6]. GM1 gangliosidosis results from a deficiency of the enzyme beta-galactosidase; GM2 gangliosidosis type 1 (Tay–Sachs disease) results from a deficiency of the enzyme hexosaminidase A, GM activator protein, or saposin A; and GM2 gangliosidosis type 2 (Sandhoff disease) results from a deficiency of the enzyme hexosaminidase B. The gangliosidoses can be further divided into several subtypes based on the age of onset and rate of disease progression, including infantile/acute, juvenile/subacute, and adult/chronic forms. A specific diagnosis can be made through enzyme analysis in blood or fibroblasts [16].

The infantile forms of both GM1 and GM2 gangliosidoses present in the first year of life with rapidly progressive neurodegeneration, resulting in encephalopathy and spastic quadraplegia. There may be a macular cherry red spot from lipid storage in perimacular

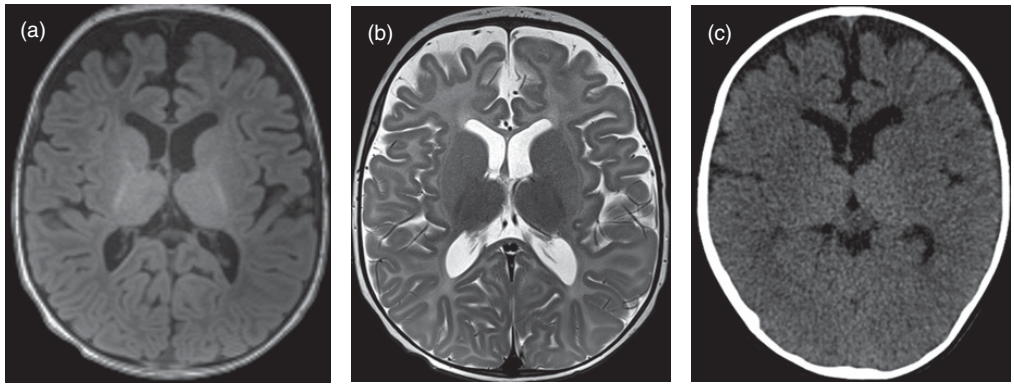

Figure 4.11 GM1 gangliosidosis in a 9-month-old infant with motor delay, hypotonia, hepatomegaly, rickets-like changes on radiographs, and cherry red spots on ophthalmological examination. (a) Axial T1 and (b) axial T2 images demonstrate a markedly delayed myelination pattern for a patient of this age. (c) There is also a question of relative T2 hypointensity of the thalami, correlating with hyperdensity of the thalami on CT, 3 months later.

retinal cells. In addition, in GM1 gangliosidosis and the infantile form of GM2 gangliosidosis type 2 (Sandhoff disease), there may also be extra-neurological features, including hepatosplenomegaly, skeletal anomalies, and coarsening of facial features. Movement disorders include startle-provoked myoclonus and, in the terminal stages, decerebrate posturing [16].

Neuroimaging in infantile GM1 and GM2 gangliosidoses is notable for delayed myelination which may be accompanied by basal ganglia T2 hyperintensity. The thalami demonstrate hyperdensity on CT and relative T2 hypointensity on MRI (Figure 4.11) [27, 28].

Wilson's Disease

Wilson's disease results from defective incorporation of copper into ceruloplasmin and inadequate excretion of biliary copper, producing systemic copper overload. Neurological features include progressive parkinsonism, dystonia (particularly bulbar), "wing-beating" tremor, dementia, and psychiatric symptoms. Extra-neurological features include liver disease, hemolytic anemia, Kaiser–Fleischer rings from accumulation of copper in Descemet's membrane of the eye, and, rarely, cardiomyopathy and renal tubulopathy. Onset may be from childhood to adulthood; childhood forms tend to be dominated by hepatic involvement. Serum copper and ceruloplasmin are often reduced; 24-hour urine copper is increased; and liver biopsy may demonstrate hepatic copper accumulation [16].

While imaging may be normal in presymptomatic patients, typical imaging findings in symptomatic patients include basal ganglia T2 hyperintensity, cerebral atrophy, and brainstem/thalamic signal abnormalities [29]. The brainstem signal abnormality tends to concentrate in the midbrain with near universal involvement of the tectum and less frequent involvement of the midbrain tegmentum (when associated with sparing of the red nuclei, the midbrain tegmentum signal abnormality is dubbed the "giant panda sign") [30]. Co-occurrence of the basal ganglia susceptibility artifact or T1 hyperintensity can sometimes be seen in Wilson's disease, possibly as a result of parenchymal calcification or manganese deposition in the setting of liver dysfunction, respectively [31]. A typical case of adolescent onset Wilson's disease is depicted in Figure 4.12.

Guanidinoacetate N-Methyltransferase Deficiency

GAMT is the second enzyme in the biosynthetic pathway of creatine. GAMT deficiency is associated with developmental delay, particularly affecting language, epilepsy, behavioral abnormalities, and a complex movement disorder that may include chorea, athetosis, dystonia, and ataxia. MR may demonstrate T2 hyperintensity of bilateral globi pallidi [32]. Spectroscopy demonstrates a reduced creatine peak. Of note, the other known disorders of creatine metabolism, namely arginine glycine amidinotranserase (AGAT) deficiency and the creatine transporter defect, do not generally show abnormalities on structural MRI, but do show reduced creatine on MRS (Figure 4.13).

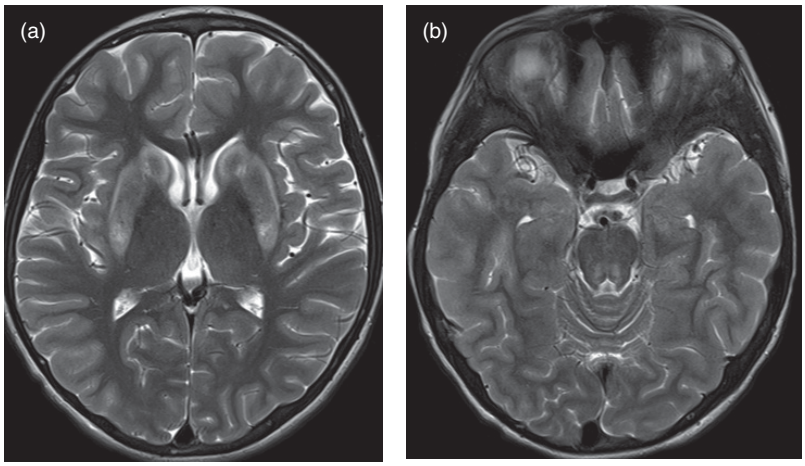

Figure 4.12 Wilson's disease in a 12-year-old adolescent with tremor, micrographia, and dysarthria. Axial T2-weighted images demonstrate T2 hyperintensity within (a) the corpus striatum and (b) the dorsal brainstem.

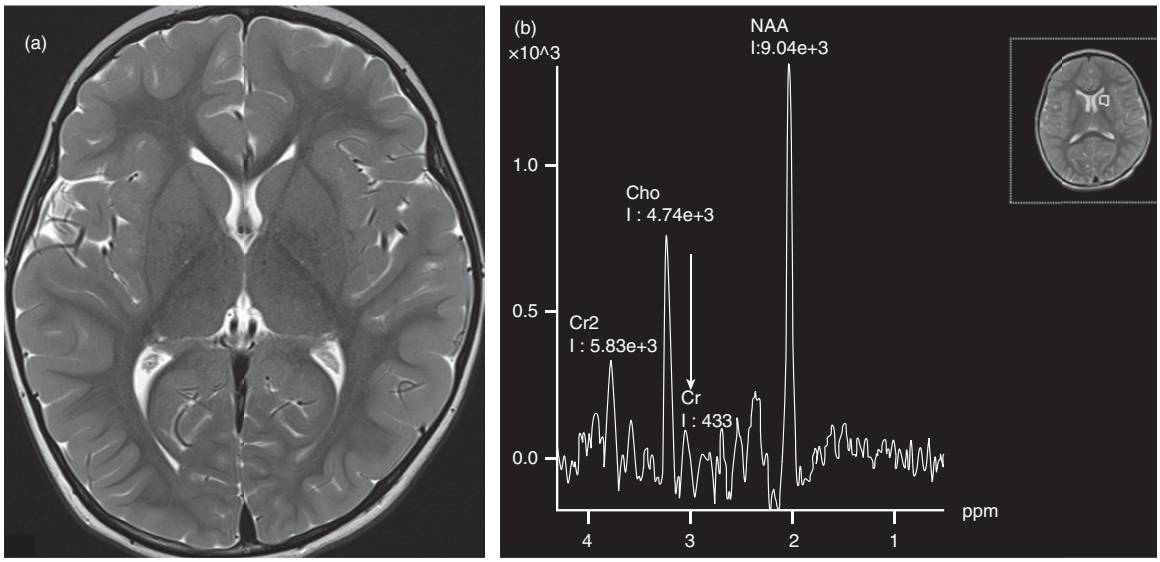

Figure 4.13 A 4-year-old male with developmental delay, hypotonia, and X-linked creatine deficiency secondary to SLC6A8. (a) Axial T2 image at the level of the basal ganglia demonstrates no discrete signal abnormality. (b) Intermediate echo time MRS of the left basal ganglia demonstrates the absence of the normal creatine peak (arrow).

Mimics

While several of the disorders described above have specific imaging findings, it should be emphasized that many non-metabolic genetic and acquired disorders can have similar imaging findings. These mimics can usually be excluded by clinical history and/or biochemical evaluation.

Metabolic/Toxic (Non-Genetic)

Kernicterus in the chronic phase can present with atrophy and T2 hyperintensity in the globus pallidi, subthalamic nuclei, dentate nuclei, and hippocampi, which could be mistaken for an IEM-absent clinical context (Figure 4.14) [33]. Likewise, profound nutritional deprivation can result in Wernicke encephalopathy, typically with signal abnormality along the margins of the third ventricle (thalami, periaqueductal gray matter) as well as the mammillary bodies (Figure 4.15) [34]. Non-ketotic hyperglycemia occurs in individuals with uncontrolled diabetes and presents with movement disorders; on imaging,

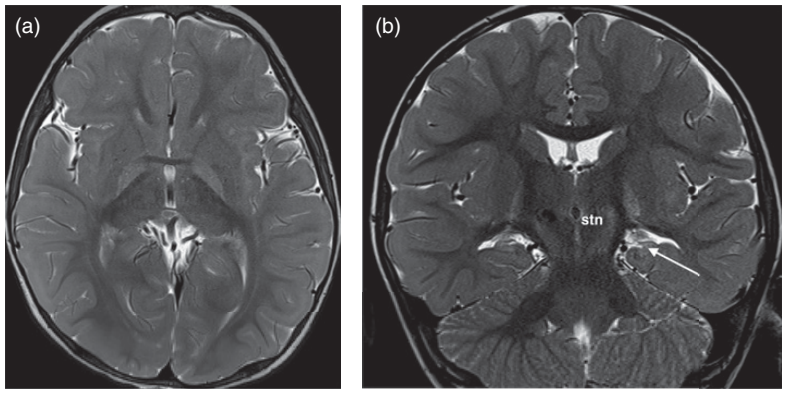

Figure 4.14 Kernicterus evaluated at 16 months for generalized dystonia, global developmental delay, hearing loss, and cortical visual impairment. (a) An axial T2 image at the level of the basal ganglia demonstrates abnormal T2 hyperintensity of the globus pallidi. (b) Coronal T2 imaging additionally demonstrates T2 hyperintensity of the subthalamic nuclei ("stn" on the left) and hippocampi (arrow on the left), the latter with volume loss.

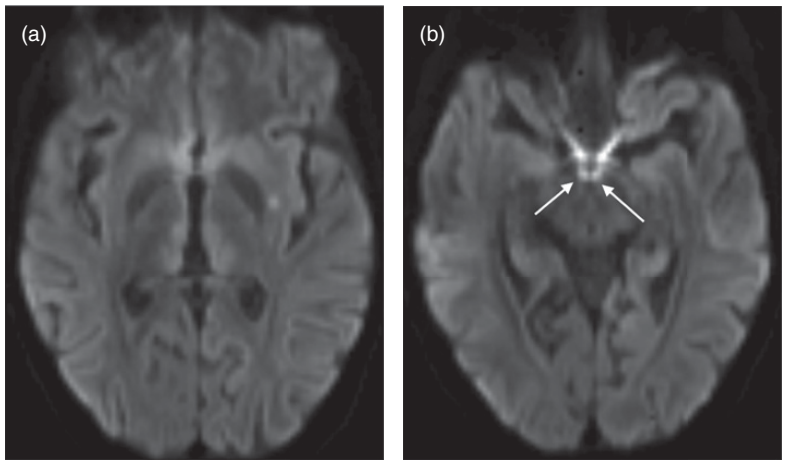

Figure 4.15 Wernicke syndrome in an 11-year-old cancer patient receiving chemotherapy and presenting with diffuse weakness and short-term memory loss. Diffusion-weighted imaging demonstrates abnormal signals in the medial thalami and left basal ganglia (a) as well as the mammillary bodies (arrows, b). Involvement of the thalami, periaqueductal gray matter, and mammillary bodies is typical for Wernicke syndrome.

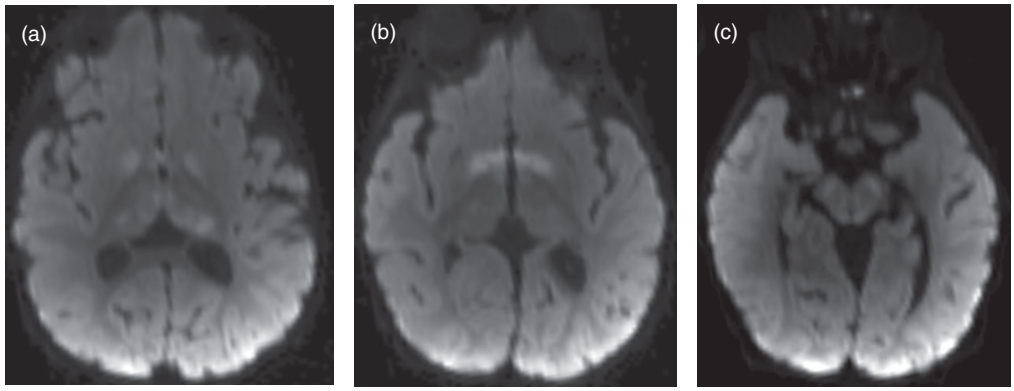

Figure 4.16 A 9-month-old infant with tuberous sclerosis and infantile spasms treated with vigabatrin. Axial diffusion-weighted images demonstrate abnormal signals in: (a) the globus pallidus and thalami; (b) the innominate substance and genu of the internal capsule; and (c) the cerebral peduncles.

affected patients typically have unilateral or asymmetrical basal ganglia hyperdensity on CT or T2 hyperintensity on MRI [35]. Drug toxicity can also involve the deep gray matter structures (e.g. methadone or vigabatrin) [36] (Figure 4.16).

Ischemic

Dystonic cerebral palsy due to in utero or perinatal insult can be indistinguishable from end-stage metabolic disease with profound volume loss that encompasses the deep gray matter (Figure 4.17) [37, 38].

Likewise, hypoxic ischemic injury later in life can present with deep gray matter signal abnormality and other abnormalities that depend on the severity of the insult (Figure 4.18).

Genetic (Not Metabolic)

Juvenile Huntington disease is unique for frequent T2 hyperintensity in the corpus striatum in addition to the caudate-predominant atrophy seen in older patients (Figure 4.19) [39]. Bilateral infantile striatal necrosis caused by defects in the *NUP62* gene can have a similar appearance to mitochondrial disorders but are distinguishable by lack of lactate [40].

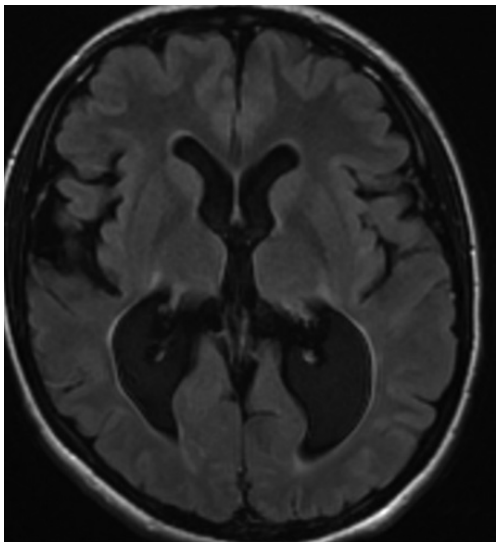

Figure 4.17 19-year-old patient, former premature infant, with athetosis, dystonia, and spastic quadraparesis. The axial FLAIR image demonstrates marked thinning of the posterior periventricular white matter, minimal periventricular gliosis, and the small size of the thalami. These are typical findings of white matter of prematurity.

Infectious/Inflammatory

Finally, inflammatory and infectious conditions can cause deep gray matter signal abnormality (e.g. viral encephalitis, acute disseminated encephalomyelitis, acute necrotizing encephalopathy) [41] (Figure 4.20).

Metabolic Movement Disorders Associated with Basal Ganglia Mineralization on MRI

In addition to being a site of physiological mineralization, the deep gray matter and functionally connected brainstem/dentate nuclei undergo pathological mineralization in several metabolic disorders presenting with movement disorders.

Neurodegeneration with Brain Iron Accumulation

The NBIA disorders are a group of progressive neurodegenerative disorders which share excessive accumulation of iron in deep gray matter nuclei, most conspicuously on SWI sequences [42, 43]. There are currently as many as 12 conditions under the NBIA rubric [43]. The NBIA disorders typically present with dystonia, occasionally with parkinsonism or ataxia. Most of the NBIA disorders present in childhood, whereas aceruloplasminemia and neuroferritinopathy present in adulthood and beta-propeller protein-associated neurodegeneration (BPAN; also known as SENDA) has a biphasic course with static developmental delay in childhood, followed by progressive neurodegeneration in young adulthood [41].

All NBIA disorders share a predisposition to iron accumulation in the globus pallidus and substantia nigra; however, specific imaging features are recognized for several NBIA disorders (see Table 4.2). For the single most common NBIA disorder, pantothenate kinase-associated neurodegeneration (PKAN), susceptibility of the globus pallidus is accompanied

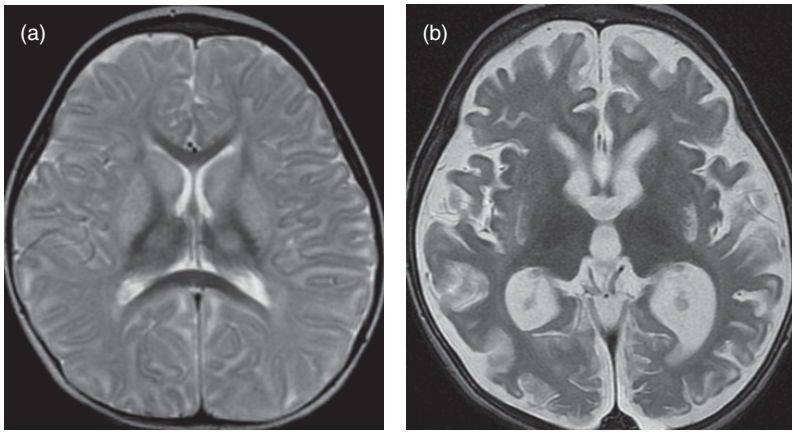

Figure 4.18 Hypoxic ischemic injury in an 11-month-old infant with carbon monoxide poisoning and cardiac arrest. (a) Axial T2 image from the admission MRI demonstrates extensive deep gray matter and diffuse hemispheric signal T2 prolongation. (b) At a six-month follow up, there is evolution to extensive deep and cortical gray matter encephalomalacia.

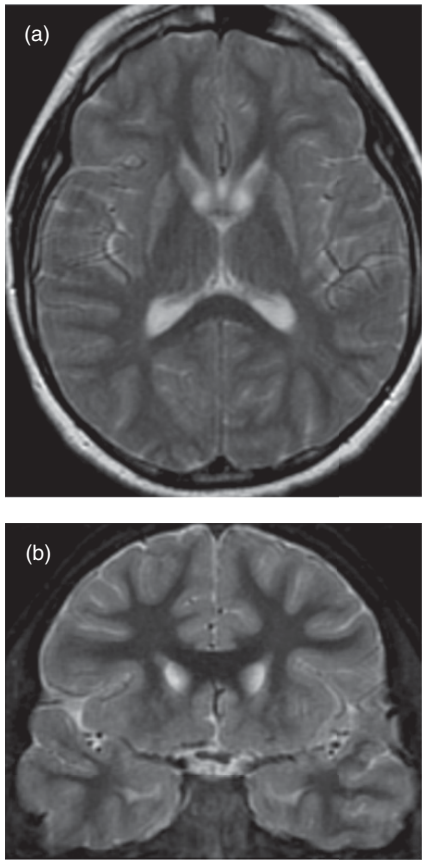

Figure 4.19 Juvenile Huntington disease in a 10-year-old child with dysarthria, chorea, and mild ataxia. (a) Axial T2 and (b) coronal T2 images demonstrate marked volume loss and T2 hyperintensity in the corpus striatum (caudate and putamen).

by central T2 hyperintensity dubbed the "eye of the tiger" sign, a feature not generally seen in other NBIA disorders (Figure 4.21). Early PKAN also lacks significant substantia nigra mineralization, based on historical literature [45, 46]. The second most common NBIA disorder, phospholipase A2 group VI (PLA2G6) deficiency, has three major phenotypes. The infantile neuroaxonal dystrophy (INAD) and juvenile *PLA2G6*-associated neurodegeneration phenotypes are notable for cerebellar atrophy and gliosis, though only a subset of INAD patients have been reported to have deep gray matter (dentate, substantia nigra, globus pallidus) susceptibility (Figure 4.22) [47]. Neuroferritinopathy and aceruloplasminemia forms of NBIA are distinct for abnormal T2 hyperintensity of the thalami and putamen [48]. WDR45-associated BPAN is unique for a halo of T1 hyperintensity surrounding substantia nigra mineralization [49] (Figure 4.23), and C19orf12 NBIA is associated with signal abnormality between the internal/external nuclei of the globus pallidus [42].

Disorders of Manganese Metabolism

Manganese may abnormally accumulate in the deep gray matter, brainstem, and dentate nuclei due to disorders of heavy-metal transport. Because manganese has magnetic properties, it acts as a natural MRI contrast agent and causes sites of deposition to appear intrinsically T1 hyperintense on brain MRI. To date, two disorders of manganese transport resulting in manganese neurotoxicity have been described,

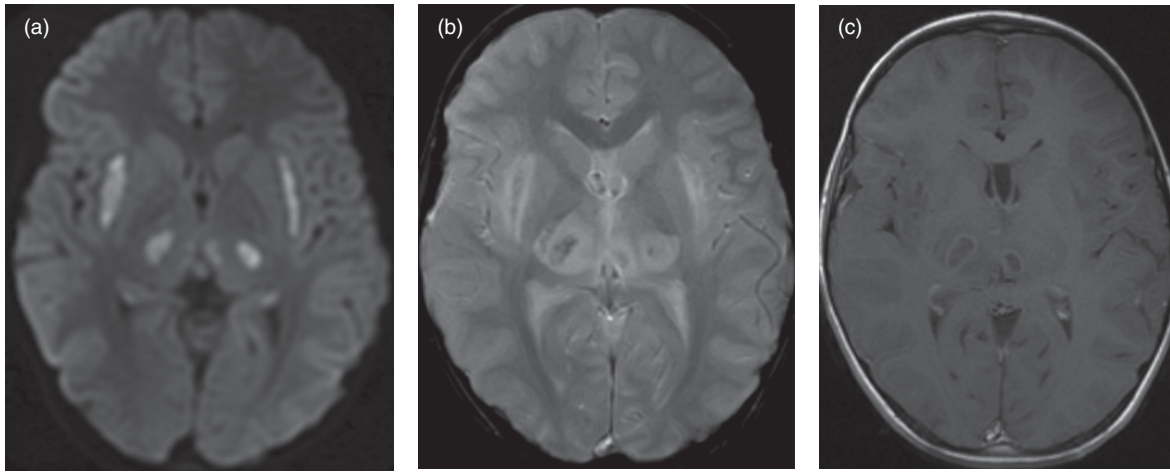

Figure 4.20 Acute necrotizing encephalitis in a patient with febrile illness, encephalopathy, and gait changes. (a) Axial diffusion imaging demonstrates cytotoxic edema in the claustrum and thalami, accompanied by petechial hemorrhage (hypointensity) on (b) the axial T2 * gradient echo sequence, sensitive to magnetic field disturbances. (c) MRI T1 axial image with contrast. The thalamic lesions demonstrate rim enhancement, consistent with necrosis.

Table 4.2 NBIA disorders (adapted from [42–44])

NBIA disorder	Gene/locus	Sites of susceptibility	Other imaging features
Pantothenate kinase-associated neurodegeneration (PKAN)	Pantothenate kinase 2 (*PANK2*)	Globus pallidus	Central T2 hyperintensity of globus pallidus ("eye of the tiger")
PLA2G6-associated neurodegeneration (PLAN), infantile neuroaxonal dystrophy 1 (INAD1)	Phospholipase A2 group VI (*PLA2G6*)	Globus pallidus, dentate nuclei, substantia nigra	Cerebellar atrophy and gliosis
Aceruloplasminemia	Ceruloplasmin	Basal ganglia and thalami	White matter hyperintensity, Visceral organ iron deposition
Hereditary neuroferritinopathy	Ferritin light chain 1 (*FTL1*)	Globus pallidus, putamen, dentate	Cavitation of lentiform nuclei, cerebellar atrophy
COASY protein-associated neurodegeneration (CoPAN)	Coenzyme A synthetase (COASY)	Globus pallidus	
Mitochondrial membrane protein-associated neurodegeneration (MPAN)	C19orf12	Globus pallidus, substantia nigra	Cortical, cerebellar atrophy, GPe/GPi T2 hyperintensity reported in some individuals
Fatty acid hydroxylase associated neurodegeneration	Fatty acid 2-hydroxylase (FA2H)	Globus pallidus, substantia nigra	White matter signal abnormality, brainstem atrophy
Beta-propeller protein–associated neurodegeneration (BPAN)	WD repeat domain 45 (WDR45)	Globus pallidus, substantia nigra	Substantia nigra T1 hyperintensity
Kufor–Rakeb syndrome	ATPase cation transporting 13A2 (ATP13A2)	Inconsistent basal ganglia mineralization	Cerebral atrophy
Woodhouse–Sakati syndrome	DDB1 and CUL4 associated factor 17 (DCAF17)	Inconsistent globus pallidus and substantia nigra	White matter signal abnormality
Leukoencephalopathy with dystonia and motor neuropathy	Sterol carrier protein 2 (SCP2)	Globus pallidus, dentate, substantia nigra, red nucleus	T2 hyperintensity of thalami, brainstem
Possible new NBIA syndrome	GTP binding protein 2 (GTPBP2)	Globus pallidus, substantia nigra	Cerebellar atrophy

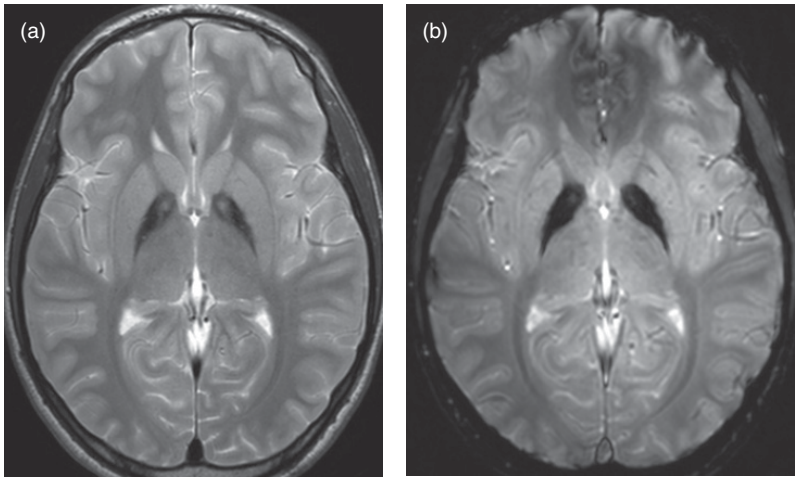

Figure 4.21 PKAN in a 15-year-old youth with disabling dystonia. (a) Axial T2-weighted imaging at the level of the basal ganglia demonstrates central globus pallidus T2 hyperintensity surrounded by T2 hypointensity. (b) On the axial T2* gradient echo sequence, there is intensification of the T2 hypointensity, typical for magnetic substances like iron.

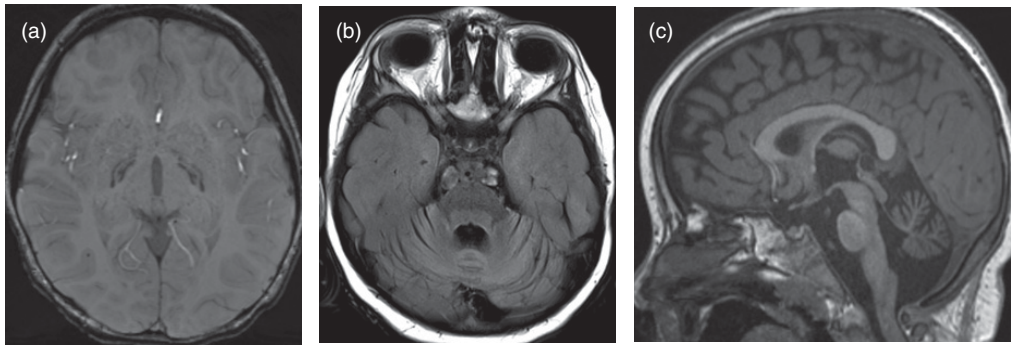

Figure 4.22 Suspected infantile neuroaxonal dystrophy, presenting as hypotonia and developmental regression at 14 months of age. (a) Axial SWI at the level of the basal ganglia demonstrates an unusual degree of susceptibility in the globus pallidus for a patient of 4 years. (b) Axial FLAIR and (c) sagittal T1 images demonstrate atrophy of the cerebellum with associated folia FLAIR hyperintensity.

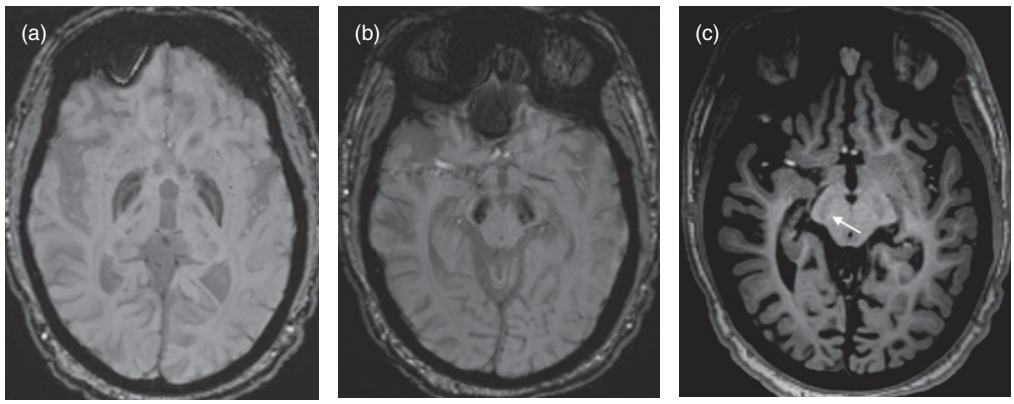

Figure 4.23 Adult with developmental delay, intellectual disability, and spastic quadriparesis with regression as a teenager. Ultimately found to have a *WDR45* mutation on exome sequencing. Axial SWI demonstrates abnormal iron deposition in (a) the globus pallidus and (b) the substantia nigra. (c) On axial T1-weighted imaging, there is subtle T1 hyperintensity surrounding the substantia nigra (arrow), which is a unique feature of BPAN.

SLC30A10 and *SLC39A14* gene-related disorders [50–52], both of which lead to conspicuous T1 hyperintensity of the deep-gray nuclei and their related brainstem/cerebellar nuclei (Figure 4.24). Both disorders present with childhood to adult-onset dystonia and parkinsonism. The *SLC30A10* gene-related disorder also involves liver disease and polycythemia.

IEMs Associated with Brain Calcification

Primary familial brain calcification (previously called Fahr disease) results in extensive dystrophic calcification of the basal ganglia and, to a lesser extent, the thalamus and dentate nuclei [53, 54]. This is typically an adult-onset disease, although adolescent cases have been reported. The movement disorder in Fahr syndrome includes parkinsonism, tremor, ataxia, dystonia, and choreoathetosis. At least five genetic causes of familial brain calcification are known at the present time, but reportedly half of the suspected causes do not have an identified etiology. Signal abnormalities have been reported in familial brain calcification, presumed to represent gliosis. However, the most striking feature of this group of disorders is the extensive calcification that far exceeds senescent calcification seen in older adults. Since calcification can be underestimated on MRI (even SWI), there may be a role for CT if calcification is suspected.

Additional IEMs associated with calcifications include mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, dihydropteridine dehydrogenase (DHPR) deficiency, and, rarely, cerebral folate deficiency.

Mimics

An important simulant of abnormal deep gray matter mineralization is deep gray matter T2 hypointensity

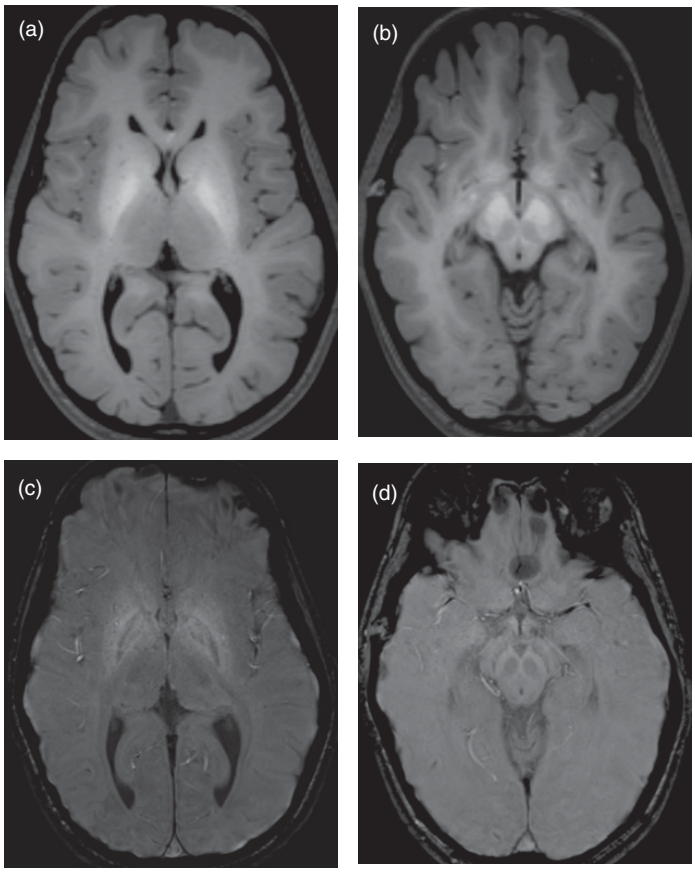

Figure 4.24 A 7-year-old child with SLC39A14 deficiency and dystonia. Axial T1 images (a, b) demonstrate abnormal T1 hyperintensity of the basal ganglia (especially the globus pallidus) and substantia nigra with no convincing pathological iron deposition on SWI (c, d).

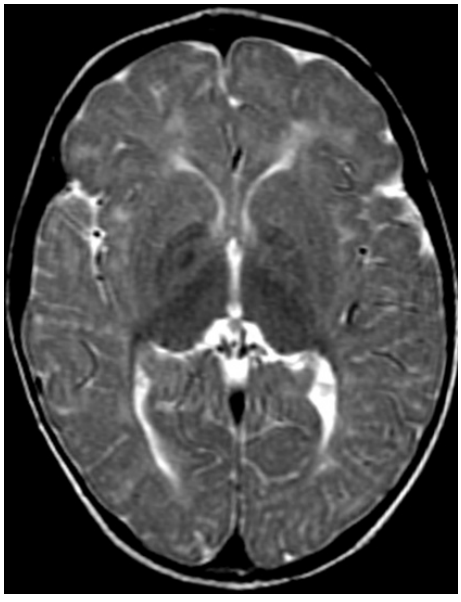

Figure 4.25 Fucosidosis at 32 months of age. On this axial T2-weighted image, there is diffuse hypomyelination. There is also relative T2 hypointensity of the globus pallidus and thalamus. There was no calcification on follow-up CT imaging.

seen in fucosidosis. In this disorder, the deep gray matter is relatively well myelinated in the background of otherwise poor brain myelination, leading to relative T2 hypointensity [6, 55] (Figure 4.25). Movement disorders, particularly dystonia, are not infrequent in fucosidosis, making this entity an important differential diagnostic consideration for a patient with deep gray matter T2 hypointensity, abnormal myelination, and movement disorder.

The juvenile form of GM1 gangliosidosis may also mimic deep gray matter mineralization. Presentation typically involves chronically progressive generalized dystonia. MRI may demonstrate bilateral T1 hyperintensity/T2 hypointensity of the globus pallidi [56].

An important differential diagnosis for imaging suggestive of manganese accumulation includes total parenteral nutrition (Figure 4.26) or environmental manganese exposure (well water, mining, etc.). The differential diagnosis for cerebral calcification is myriad, including disorders of calcium homeostasis, congenital cytomegalovirus

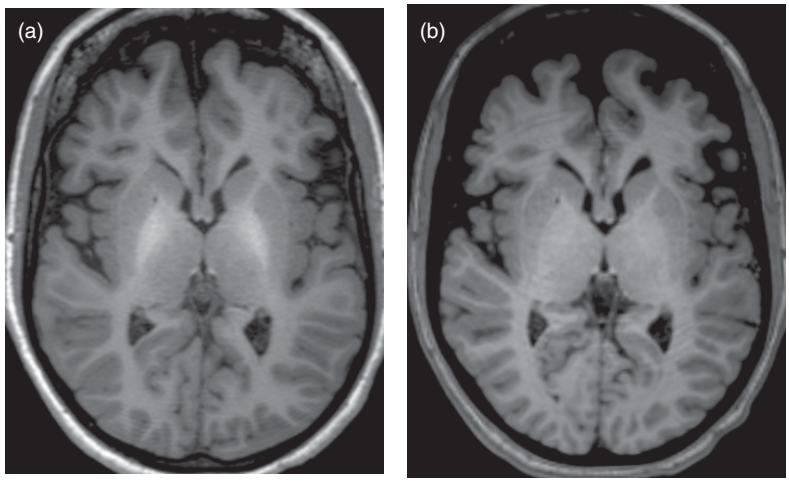

Figure 4.26 Iatrogenic manganese deposition in an adult requiring chronic total parenteral nutrition. (a) During evaluation for poor seizure control, intrinsic T1 hyperintensity was noted in the globus pallidus and supranormal manganese levels were recorded from blood. (b) Follow-up axial T1 imaging 18 months after adjusting the total parenteral nutrition to a lower manganese concentration, the basal ganglia had normalized in intensity.

(CMV), prior intracranial hemorrhage, cerebral vascular disorders, Aicardi–Goutières syndrome, Cockayne syndrome, telomeropathies, and many others. The reader is referred to a number of reviews on the approach to intracranial calcification [57].

Metabolic Movement Disorders Associated with White Matter-Predominant Signal Abnormality

White matter-predominant signal abnormalities are seen in a variety of metabolic movement disorders, typically in disease-specific patterns.

Galactosemia

Classic galactosemia results from deficiency of the galactose-1-phosphate uridyltransferase (GALT) enzyme that converts galactose-1-phosphate to uridine diphosphate galactose. Individuals with galactosemia accumulate galactose and galactitol in body fluids. If a galactose-free diet is not instituted in early infancy, children develop progressive cataracts, liver disease, renal tubulopathy, and potentially cerebral edema [58]. Spectroscopy in an untreated child may demonstrate elevated galactitol [59]. Even with dietary management, there are diet-independent long-term sequelae in some individuals, including premature ovarian failure in females, cognitive abnormalities, and a complex movement disorder that includes tremor, ataxia, dystonia, and choreoathetosis. Neuroimaging may demonstrate delayed myelination in the subcortical white matter that is notable for its patchy appearance (Figure 4.27) [16].

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) refers to genetic defects in the branched-chain alpha ketoacid dehydrogenase enzyme complex, which catalyzes the second step of branched-chain amino acid catabolism. If untreated, this disorder results in highly elevated levels of the branched-chain amino acids leucine, isoleucine, and valine as well as their corresponding ketoacids in the blood and cerebrospinal fluid (CSF). Leucine in particular is neurotoxic. Competition from branched-chain amino acids with tryptophan and tyrosine across a shared central nervous system transporter also result in potential central nervous system deficiencies of biogenic amines. MSUD typically presents clinically with episodes of encephalopathy and ataxia provoked by protein load or metabolic stressors [60]. Patients may also develop acute-onset dystonia. Older children and adults with MSUD may manifest movement disorders, including tremor, dystonia, and parkinsonism [61]. Neuroimaging in MSUD during a metabolic decompensation may demonstrate cerebral edema and diffusion restriction in the actively myelinating areas of the brain and cerebellum (Figure 4.28) [62]. MRS may demonstrate a branched-chain ketoacid peak at 0.9 ppm.

Glycine Encephalopathy

Glycine encephalopathy, also known as non-ketotic hyperglycinemia, is a disorder of the glycine cleavage system that converts the amino acid glycine into ammonia and carbon dioxide. Glycine is excitatory in the cortex and inhibitory in the brainstem and spinal cord. Glycine encephalopathy typically presents prenatally with fetal hiccups/excess fetal movement, and then in the early infantile period with

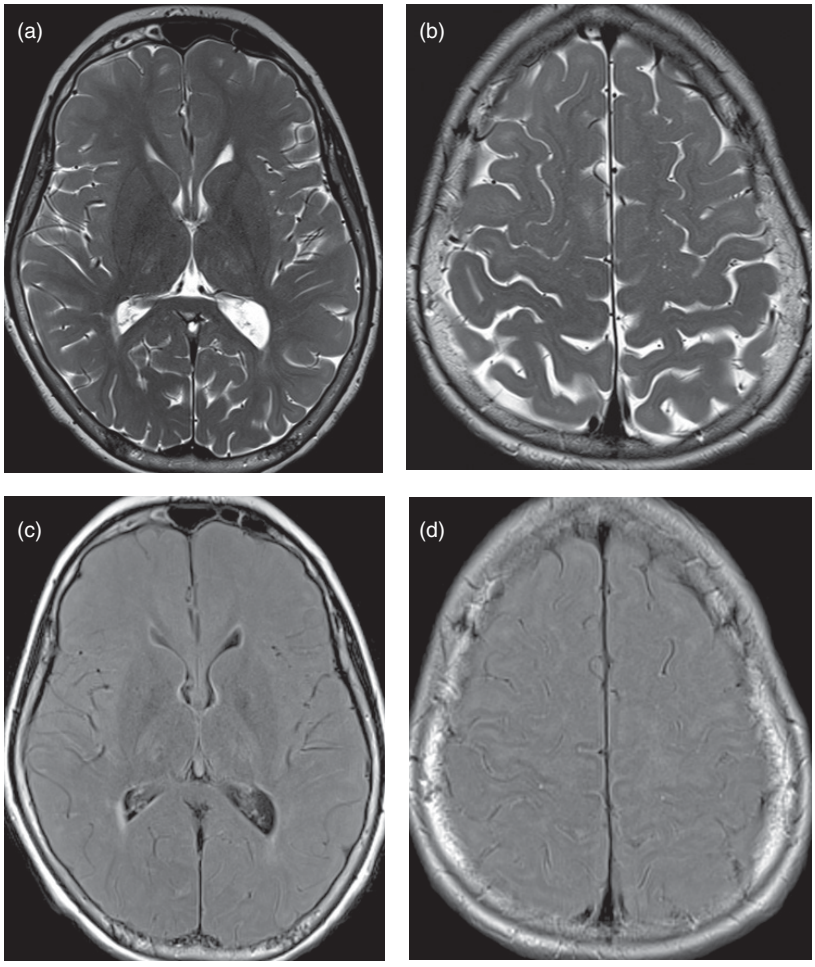

Figure 4.27 12-year-old female with classic galactosemia, severe tremor, and premature ovarian failure. Axial T2 images at the level of (a) the basal ganglia and (b) superior frontoparietal lobes demonstrate somewhat attenuated grey-white matter differentiation. (c, d) On same level FLAIR images, there is a patchy high signal, suggestive of hypomyelination.

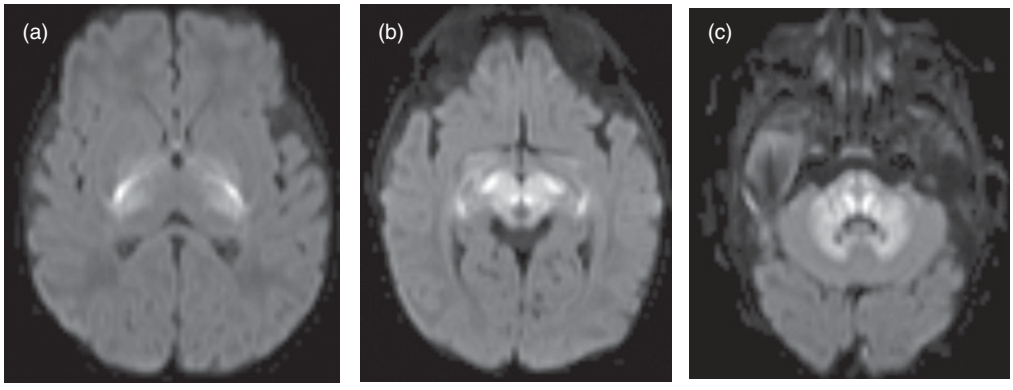

Figure 4.28 MSUD detected on an abnormal newborn screening exam, imaged at 13 days old. Axial diffusion-weighted images demonstrate abnormal signals in (a) the deep gray matter and internal capsule, (b) the midbrain, and (c) the pons as well as the cerebellar white matter.

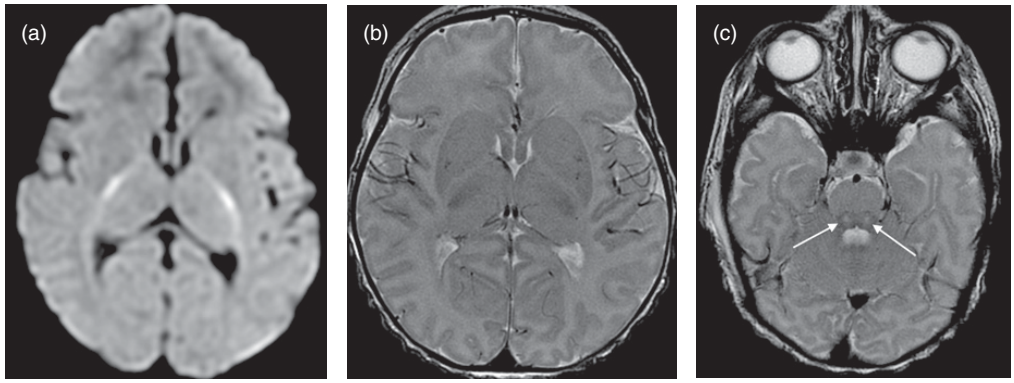

Figure 4.29 Non-ketotic hyperglycinemia in a newborn presenting with cardiomyopathy, hypotonia, myoclonic jerks, and burst suppression on EEG. (a) Axial diffusion-weighted imaging demonstrates diffusion restriction in the internal capsule and optic radiations. On T2-weighted imaging, there is (b) a corresponding lack of myelination of the posterior limb of the internal capsule and (c) an abnormal signal in the central tegmental tracts (arrows).

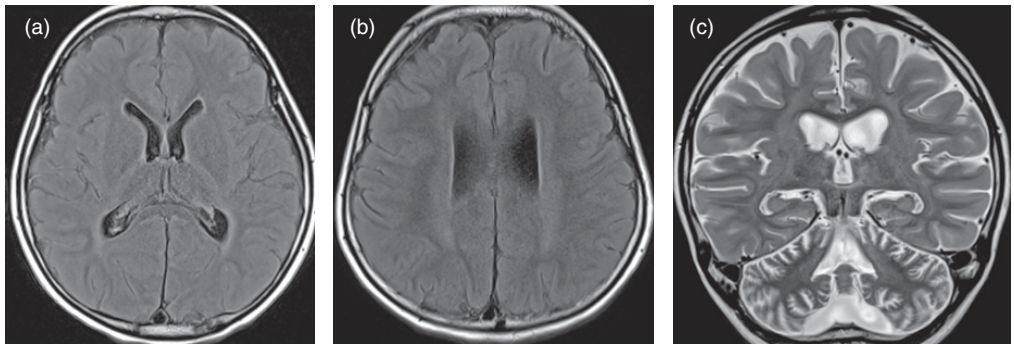

Figure 4.30 Neuronal ceroid lipofuscinosis type 6 (Batten disease) presenting as developmental regression, deteriorating gait, dysarthria, and tremor at 4 years of age. (a, b) Axial FLAIR and (c) coronal T2-weighted images demonstrate diffuse central white matter T2 hyperintensity, consistent with dysmyelination, accompanied by mild generalized volume loss.

hiccups, myoclonus, seizures, low tone, bulbar symptoms, and respiratory failure [16]. Although generalized delay in myelination or normal brain imaging may be present, affected patients frequently will have diffusion restriction in early myelinating structures (e.g. dorsal brainstem and internal capsule) (Figure 4.29). There may be dysgenesis of the corpus callosum. Additionally, MRS in severely affected cases will have detectable glycine accumulation [5, 63].

Neuronal Ceroid Lipofuscinoses

The neuronal ceroid lipofuscinoses are a group of chronically progressive neurodegenerative disorders frequently associated with epilepsy, myoclonus, ataxia, progressive dementia, and retinopathy. Parkinsonism has also been reported in the juvenile form [16]. Many of these disorders constitute lysosomal defects or disorders of autophagy. On neuroimaging, findings are often non-specific, reflecting varying degrees of cerebral and cerebellar volume loss. However, associated dysmyelination in the central white matter is frequently present, particularly for later-onset neuronal ceroid lipofuscinosis variants (Figure 4.30). There may also be T2 hypointensity of the thalami [64].

MCT8 Thyroid Hormone Cell-Membrane Transporter Defect

Pathogenic variants in the SLC6A8 thyroid hormone transporter result in a neurodevelopmental disorder called Allan–Herndon–Dudley syndrome, which presents with severe developmental delay, hypotonia, muscle weakness, progressive spasticity, dystonia, athetosis, and paroxysmal dyskinesia. Biochemical evaluation is remarkable for elevated T3 and reduced reverse T3 [65]. Neuroimaging is notable for delayed

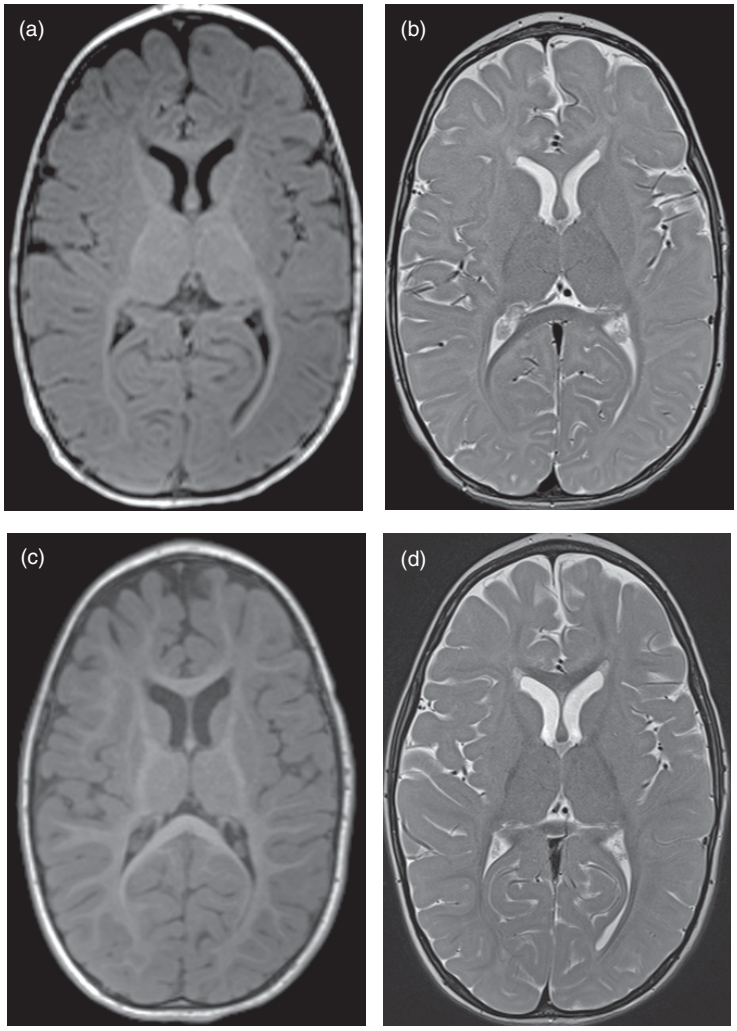

Figure 4.31 MCT8 deficient male at (a, b) 9 months and (c, d) 28 months. Initial imaging at 9 months demonstrates a profoundly delayed myelination pattern on axial T1-weighted imaging (a) though the myelination pattern is less severely delayed on axial T2-weighted imaging (b). By 28 months, myelination has progressed on (c) axial T1 and (d) axial T2 imaging. Though still abnormal the interval progress in myelination is a clue that this case does not represent a typical hypomyelinating leukodystrophy, which are generally static.

myelination that may normalize by age 4 years (Figure 4.31) [66].

Metabolic Movement Disorders with Normal or Non-specific Imaging Findings

In contrast to the disorders discussed above, several metabolic movement disorders lack recognizable or specific findings on structural MRI. For example, glucose transporter type 1 (GLUT1) deficiency syndromes may have a wide array of imaging manifestations from global atrophy to completely normal imaging (Figure 4.32) [67]. Lesch–Nyhan disease and Niemann–Pick disease type C both manifest non-specific volume loss (Figures 4.33 and 4.34) [68, 69]. Adenylosuccinate lyase deficiency may demonstrate non-specific cerebral or cerebellar atrophy (Figure 4.35); spectroscopy may demonstrate an elevation of succinyladenosine [70]. Disorders of biogenic amine metabolism are typically associated with normal or non-specific imaging patterns, although DHPR deficiency (mentioned earlier), a disorder of biopterin metabolism, is associated with white matter T2 hyperintensity and basal ganglia calcification.

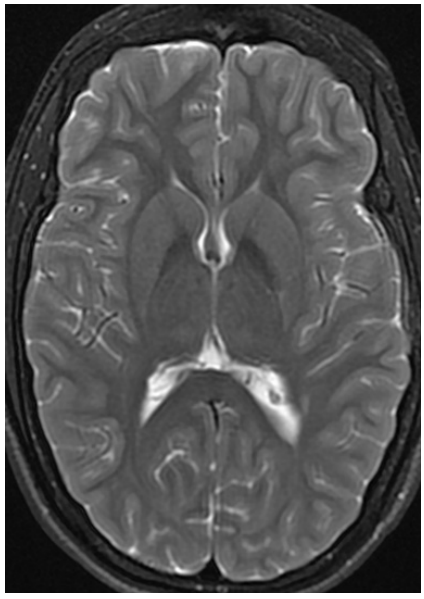

Figure 4.32 15-year-old male with GLUT1 deficiency syndrome and absence epilepsy. Although GLUT1 deficiency can be associated with cerebral atrophy, this patient's MRI is structurally normal.

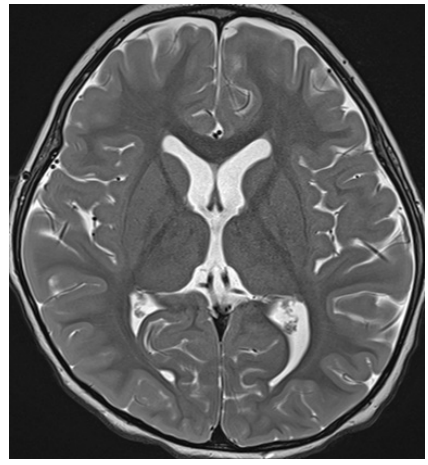

Figure 4.33 A 3-year-old male Lesch–Nyhan patient with global developmental delay, hypotonia, self injurious behavior, and upper extremity dystonia. On this axial T2 image at the level of the basal ganglia, there is mild non-specific prominence of the lateral ventricles for a patient this age, but there is no discernible signal abnormality.

Conclusions

IEMs associated with movement disorders have a number of common neuroimaging patterns, including symmetrical basal ganglia T2 hyperintensity, basal ganglia mineralization, or, less often, cerebral white matter abnormalities. A number of IEMs have normal structural neuroimaging, or non-specific cerebral atrophy. Spectroscopy can also indicate a metabolic disorder in select cases. The reader should also be cognizant of acquired disorders and non-metabolic genetic disorders that can mimic these patterns.

Standard MRS has limited resolution to detect metabolites. Further resolution may be possible with the application of two-dimensional correlation (COSY) spectroscopy. This may have both diagnostic and management applications. This technology has already been used to quantify cerebral phenylalanine and tyrosine levels in vivo in patients with phenylketonuria [71]. In addition, facial recognition technology using artificial intelligence has recently been applied to the study of dysmorphology in the field of clinical genetics [72]. Similar technology could also be applied to the systematic study of the neuroimaging patterns in various metabolic and other neurodegenerative disorders to improve diagnostic rates. Work is already underway examining structure-based computational analysis in adult neurodegenerative disorders [73].

Key Points and Clinical Pearls

- MRI brain is an important component in the evaluation for an inborn error of metabolism (IEM) associated with a movement disorder.
- In addition to standard sequences, susceptibility-weighted imaging (SWI) should be included to evaluate for mineralization, and spectroscopy should be considered.
- Bilateral, symmetrical T2 hyperintensity of the basal ganglia may suggest an organic acid disorder, a mitochondrial disorder, infantile-onset GM1 or GM2 gangliosidosis, Wilson's disease, or guanidinoacetate N-methyltransferase deficiency.
- Susceptibility on SWI or T1 hyperintensity of basal ganglia may suggest cerebral mineralization.
- If there is evidence of cerebral mineralization, the clinician should attempt to ascertain the type of mineralization (iron, calcium, or manganese).
- The differential diagnosis of basal ganglia mineralization includes various forms of neurodegeneration with brain iron accumulation, disorders of manganese transport, and disorders associated with dystrophic cerebral calcification.

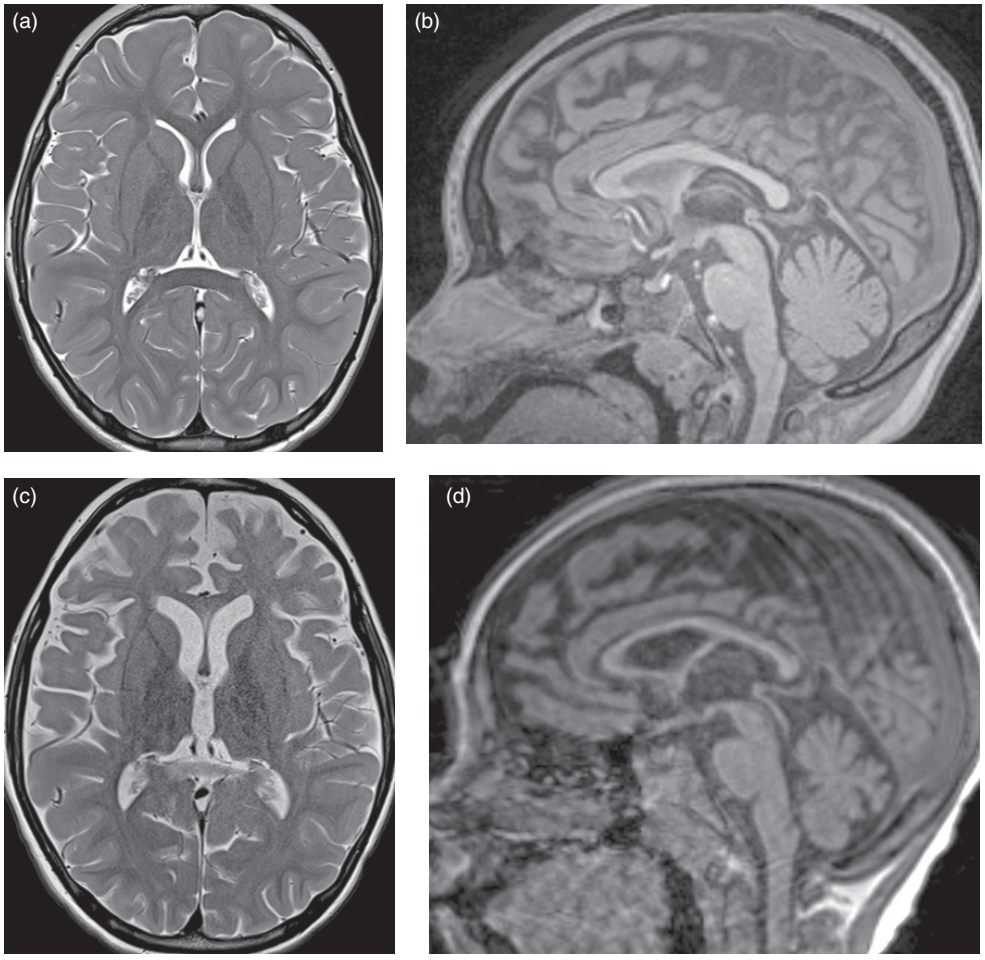

Figure 4.34 Niemann–Pick disease type C with hepatomegaly in the first year of life, intractable seizures, oculomotor apraxia, and hypotonia. (a) Axial T2 and (b) sagittal T1 images obtained at 6 years of life demonstrate normal volume and no specific pattern of signal abnormality. After neurological deterioration 2 years later, (c) axial T2 and (d) sagittal T1 images demonstrate the onset of generalized parenchymal atrophy.

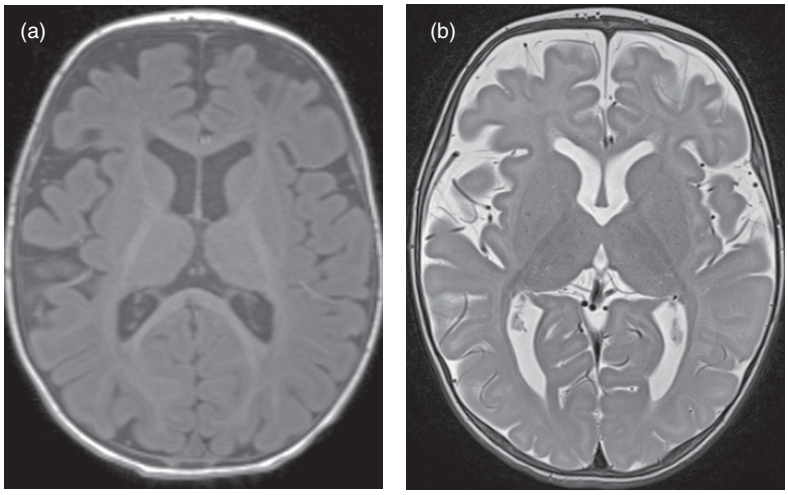

Figure 4.35 A 6-month-old infant with choreiform movements, developmental delay, elevated CSF succinyladenosine, and pathogenic mutations in adenylosuccinate lyase. (a) Axial T1 and (b) axial T2 images demonstrate a moderate prominence of the subarachnoid spaces and a mild prominence of the ventricles, consistent with low volume. Myelination was within range for age. There were no patterns of signal abnormality to suggest a specific diagnosis radiographically.

- Predominant cerebral white matter abnormalities can be seen in maple syrup urine disease, glycine encephalopathy, classic galactosemia, MCT8 gene-related disorder, and the neuronal ceroid lipofuscinoses.
- MRS can be useful in the diagnosis of mitochondrial disorders, cerebral creatine deficiency syndromes, glycine encephalopathy, and maple syrup urine disease.
- A number of IEMs that present with significant movement disorders are associated with normal or non-specific neuroimaging patterns, including glucose transporter type 1 deficiency, disorders of biogenic amine metabolism, Lesch–Nyhan disease and other purine or pyrimidine disorders, and Niemann–Pick disease type C.

Directions for Future Research

- Two-dimensional COSY (correlation spectroscopy), for both diagnostic and management applications.
- Facial recognition technology using artificial intelligence, as recently applied to the study of dysmorphology in the field of clinical genetics.
- Application of similar technology for the systematic study of neuroimaging patterns in various metabolic and other neurodegenerative disorders.
- Structure-based computational analysis in adult neurodegenerative disorders.

References

1. Parikh S, Bernard G, Leventer RJ, et al. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephelopathies. Mol Genet Metab. 2015;**114**(4):501–15.
2. Sedel F, Saudubray JM, Roze E, Agid Y, Vidailhet M. Movement disorders and inborn errors of metabolism in adults: A diagnostic approach. J Inherit Metab Dis. 2008;**31**(3):308–18.
3. van der Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology. 1999;**213**(1):121–33.
4. van der Knaap MS, Valk J. Magnetic Resonance of Myelination and Myelin Disorders. 3rd edn. Berlin: Springer; 2005.
5. Barkovich AJ, Patay Z. Metabolic, Toxic, and autoimmune/inflammatory brain disorders. In Barkovich AJ, Raybaud C, editors. Pediatric Neuroimaging. Philadelphia, PA: Wolters Kluwer; 2019, pp. 405–632.
6. Yang E, Prabhu SP. Imaging manifestations of the leukodystrophies, inherited disorders of white matter. Radiol Clin North Am. 2014;**52**(2):279–319.
7. Barkovich MJ, Barkovich AJ. Normal development of the fetal, neonatal, and infant brain, skull, and spine. In Barkovich AJ, Raybaud C, editors. Pediatric Neuroimaging. Philadelphia: Wolters Kluwer; 2019, pp. 18–80.
8. Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng YC. Susceptibility-weighted imaging: Technical aspects and clinical applications, part 1. AJNR Am J Neuroradiol. 2009;**30**(1):19–30.
9. Mittal S, Wu Z, Neelavalli J, Haacke EM. Susceptibility-weighted imaging: Technical aspects and clinical applications, part 2. AJNR Am J Neuroradiol. 2009;**30**(2):232–52.
10. Aoki S, Okada Y, Nishimura K, et al. Normal deposition of brain iron in childhood and adolescence: MR imaging at 1.5 T. Radiology. 1989;**172**(2):381–5.
11. Aquino D, Bizzi A, Grisoli M, et al. Age-related iron deposition in the basal ganglia: Quantitative analysis in healthy subjects. Radiology. 2009;**252**(1):165–72.
12. Harder SL, Hopp KM, Ward H, et al. Mineralization of the deep gray matter with age: A retrospective review with susceptibility-weighted MR imaging. AJNR Am J Neuroradiol. 2008;**29**(1):176–83.
13. Legido A, Zimmerman RA, Packer RJ, et al. Significance of basal ganglia calcification on computed tomography in children. Pediatr Neurosci. 1988;**14**(2):64–70.
14. McKinney AM. Basal ganglia: Physiologic calcification. In McKinney AM, editor. Atlas of Normal Imaging Variation of the Brain, Skull, and Craniocervical Vasculature. Berlin: Springer; 2017, pp. 427–40.
15. Chen W, Zhu W, Kovanlikaya I, et al. Intracranial calcifications and hemorrhages: Characterization with quantitative susceptibility mapping. Radiology. 2014;**270**(2):496–505.
16. Saudubray JM, van den Bergh G, Walter JH. Inborn Metabolic Diseases: Diagnosis and Treatment, 5th edn. Berlin: Springer; 2012.
17. Brismar J, Ozand PT. CT and MR of the brain in the diagnosis of organic acidemias. Experiences from 107 patients. Brain Dev. 1994;**16** Suppl:104–24.

18. Harting I, Neumaier-Probst E, Seitz A, et al. Dynamic changes of striatal and extrastriatal abnormalities in glutaric aciduria type I. Brain. 2009;**132**(Pt 7):1764–82.
19. Harting I, Seitz A, Geb S, et al. Looking beyond the basal ganglia: The spectrum of MRI changes in methylmalonic acidaemia. J Inherit Metab Dis. 2008;**31**(3):368–78.
20. Radmanesh A, Zaman T, Ghanaati H, et al. Methylmalonic acidemia: Brain imaging findings in 52 children and a review of the literature. Pediatr Radiol. 2008;**38**(10):1054–61.
21. Schreiber J, Chapman KA, Summar ML, et al. Neurologic considerations in propionic acidemia. Mol Genet Metab. 2012;**105**(1):10–5.
22. Strauss KA, Lazovic J, Wintermark M, Morton DH. Multimodal imaging of striatal degeneration in Amish patients with glutaryl-CoA dehydrogenase deficiency. Brain. 2007;**130**(Pt 7):1905–20.
23. Bonfante E, Koenig MK, Adejumo RB, Perinjelil V, Riascos RF. The neuroimaging of Leigh syndrome: Case series and review of the literature. Pediatr Radiol. 2016;**46**(4):443–51.
24. Bricout M, Grevent D, Lebre AS, et al. Brain imaging in mitochondrial respiratory chain deficiency: Combination of brain MRI features as a useful tool for genotype/phenotype correlations. J Med Genet. 2014;**51**(7):429–35.
25. Morava E, van den Heuvel L, Hol F, et al. Mitochondrial disease criteria: Diagnostic applications in children. Neurology. 2006;**67**(10):1823–6.
26. Tabarki B, Al-Shafi S, Al-Shahwan S, et al. Biotin-responsive basal ganglia disease revisited: Clinical, radiologic, and genetic findings. Neurology. 2013;**80**(3):261–7.
27. Kobayashi O, Takashima S. Thalamic hyperdensity on CT in infantile GM1-gangliosidosis. Brain Dev. 1994;**16**(6):472–4.
28. Muthane U, Chickabasaviah Y, Kaneski C, et al. Clinical features of adult GM1 gangliosidosis: Report of three Indian patients and review of 40 cases. Mov Disord. 2004;**19**(11):1334–41.
29. van Wassenaer-van Hall HN, van den Heuvel AG, Algra A, Hoogenraad TU, Mali WP. Wilson disease: Findings at MR imaging and CT of the brain with clinical correlation. Radiology. 1996;**198**(2):531–6.
30. Prashanth LK, Sinha S, Taly AB, Vasudev MK. Do MRI features distinguish Wilson's disease from other early onset extrapyramidal disorders? An analysis of 100 cases. Mov Disord. 2010;**25**(6):672–8.
31. Skowronska M, Litwin T, Dziezyc K, Wierzchowska A, Czlonkowska A. Does brain degeneration in Wilson disease involve not only copper but also iron accumulation? Neurol Neurochir Pol. 2013;**47**(6):542–6.
32. Mercimek-Mahmutoglu S, Stoeckler-Ipsiroglu S, Adami A, et al. GAMT deficiency: Features, treatment, and outcome in an inborn error of creatine synthesis. Neurology. 2006;**67**(3):480–4.
33. van Toorn R, Brink P, Smith J, Ackermann C, Solomons R. Bilirubin-induced neurological dysfunction: A clinico-radiological-neurophysiological correlation in 30 consecutive children. J Child Neurol. 2016;**31**(14):1579–83.
34. Zuccoli G, Santa Cruz D, Bertolini M, et al. MR imaging findings in 56 patients with Wernicke encephalopathy: Nonalcoholics may differ from alcoholics. AJNR Am J Neuroradiol. 2009;**30**(1):171–6.
35. Lai PH, Tien RD, Chang MH, et al. Chorea-ballismus with nonketotic hyperglycemia in primary diabetes mellitus. AJNR Am J Neuroradiol. 1996;**17**(6):1057–64.
36. Pearl PL, Vezina LG, Saneto RP, et al. Cerebral MRI abnormalities associated with vigabatrin therapy. Epilepsia. 2009;**50**(2):184–94.
37. Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: A systematic review. Dev Med Child Neurol. 2007;**49**(2):144–51.
38. Schwartz ES, Barkovich AJ. Brain and spine injuries in infancy and childhood. In Barkovich AJ, Raybaud C, editors. Pediatric Neuroimaging. Philadelphia, PA: Wolters Kluwer; 2019, pp. 405–632.
39. Gonzalez-Alegre P, Afifi AK. Clinical characteristics of childhood-onset (juvenile) Huntington disease: Report of 12 patients and review of the literature. J Child Neurol. 2006;**21**(3):223–9.
40. Basel-Vanagaite L, Muncher L, Straussberg R, et al. Mutated *NUP62* causes autosomal recessive infantile bilateral striatal necrosis. Ann Neurol. 2006;**60**(2):214–22.
41. Neilson DE. The interplay of infection and genetics in acute necrotizing encephalopathy. Curr Opin Pediatr. 2010;**22**(6):751–7.
42. Gregory A, Hayflick S. Neurodegeneration with brain iron accumulation. GeneReviews®. 2013;Feb 28 (updated Oct 21, 2019).
43. Di Meo I, Tiranti V. Classification and molecular pathogenesis of NBIA syndromes. Eur J Paediatr Neurol. 2018;**22**(2):272–84.
44. Kruer MC, Boddaert N, Schneider SA, et al. Neuroimaging features of neurodegeneration with brain iron accumulation. AJNR Am J Neuroradiol. 2012;**33**(3):407–14.
45. Hayflick SJ, Hartman M, Coryell J, Gitschier J, Rowley H. Brain MRI in neurodegeneration with brain iron accumulation with and without *PANK2* mutations. AJNR Am J Neuroradiol. 2006;**27**(6):1230–3.

46. Hayflick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden–Spatz syndrome. N Engl J Med. 2003;**348**(1):33–40.
47. Iodice A, Spagnoli C, Salerno GG, et al. Infantile neuroaxonal dystrophy and *PLA2G6*-associated neurodegeneration: An update for the diagnosis. Brain Dev. 2017;**39**(2):93–100.
48. McNeill A, Birchall D, Hayflick SJ, et al. T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. Neurology. 2008;**70** (18):1614–9.
49. Wynn DP, Pulst SM. A novel *WDR45* mutation in a patient with beta-propeller protein-associated neurodegeneration. Neurol Genet. 2017;**3**(1):e124.
50. Quadri M, Federico A, Zhao T, et al. Mutations in *SLC30A10* cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet. 2012;**90**(3):467–77.
51. Tuschl K, Meyer E, Valdivia LE, et al. Mutations in *SLC39A14* disrupt manganese homeostasis and cause childhood-onset parkinsonism–dystonia. Nat Commun. 2016;**7**:11601.
52. Rodan LH, Hauptman M, D'Gama AM, et al. Novel founder intronic variant in *SLC39A14* in two families causing manganism and potential treatment strategies. Mol Genet Metab. 2018;**124**(2):161–7.
53. Ramos EM, Carecchio M, Lemos R, et al. Primary brain calcification: An international study reporting novel variants and associated phenotypes. Eur J Hum Genet. 2018;**26**(10):1462–77.
54. Yao XP, Cheng X, Wang C, et al. Mutations in *MYORG* cause autosomal recessive primary familial brain calcification. Neuron. 2018;**98**(6):1116–23 e5.
55. Steenweg ME, Vanderver A, Blaser S, et al. Magnetic resonance imaging pattern recognition in hypomyelinating disorders. Brain. 2010;**133** (10):2971–82.
56. De Grandis E, Di Rocco M, Pessagno A, Veneselli E, Rossi A. MR imaging findings in 2 cases of late infantile GM1 gangliosidosis. AJNR Am J Neuroradiol. 2009;**30** (7):1325–7.
57. Livingston JH, Stivaros S, van der Knaap MS, Crow YJ. Recognizable phenotypes associated with intracranial calcification. Dev Med Child Neurol. 2013;**55**(1):46–57.
58. Nelson MD, Jr., Wolff JA, Cross CA, Donnell GN, Kaufman FR. Galactosemia: Evaluation with MR imaging. Radiology. 1992;**184**(1):255–61.
59. Berry GT, Hunter JV, Wang Z, et al. In vivo evidence of brain galactitol accumulation in an infant with galactosemia and encephalopathy. J Pediatr. 2001;**138** (2):260–2.
60. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: A study of 36 patients. Pediatrics. 2002;**109** (6):999–1008.
61. Carecchio M, Schneider SA, Chan H, et al. Movement disorders in adult surviving patients with maple syrup urine disease. Mov Disord. 2011;**26**(7):1324–8.
62. Cavalleri F, Berardi A, Burlina AB, Ferrari F, Mavilla L. Diffusion-weighted MRI of maple syrup urine disease encephalopathy. Neuroradiology. 2002;**44**(6):499–502.
63. Khong PL, Lam BC, Chung BH, Wong KY, Ooi GC. Diffusion-weighted MR imaging in neonatal nonketotic hyperglycinemia. AJNR Am J Neuroradiol. 2003;**24**(6):1181–3.
64. Santavuori P, Vanhanen SL, Autti T. Clinical and neuroradiological diagnostic aspects of neuronal ceroid lipofuscinoses disorders. Eur J Paediatr Neurol. 2001;**5** Suppl A:157–61.
65. Fu J, Dumitrescu AM. Inherited defects in thyroid hormone cell-membrane transport and metabolism. Best Pract Res Clin Endocrinol Metab. 2014;**28** (2):189–201.
66. Vaurs-Barriere C, Deville M, Sarret C, et al. Pelizaeus–Merzbacher-like disease presentation of *MCT8* mutated male subjects. Ann Neurol. 2009;**65**(1):114–8.
67. Hao J, Kelly DI, Su J, Pascual JM. Clinical aspects of glucose transporter type 1 deficiency: Information from a global registry. JAMA Neurol. 2017;**74**(6):727–32.
68. Group N-CGW, Wraith JE, Baumgartner MR, et al. Recommendations on the diagnosis and management of Niemann–Pick disease type C. Mol Genet Metab. 2009;**98**(1–2):152–65.
69. Harris JC, Lee RR, Jinnah HA, et al. Craniocerebral magnetic resonance imaging measurement and findings in Lesch–Nyhan syndrome. Arch Neurol. 1998;**55**(4):547–53.
70. Jurecka A, Zikanova M, Kmoch S, Tylki-Szymanska A. Adenylosuccinate lyase deficiency. J Inherit Metab Dis. 2015;**38**(2):231–42.
71. Waisbren SE, Prabhu SP, Greenstein P, et al. Improved measurement of brain phenylalanine and tyrosine related to neuropsychological functioning in phenylketonuria. JIMD Rep. 2017;**34**:77–86.
72. Jang D-H. AB052. Application of facial dysmorphology analysis technology (Face2gene) in Korean rare genetic diseases. Ann Transl Med. 2017; **Sep 5**(Suppl 2):AB052.
73. Faria AV, Liang Z, Miller MI, Mori S. Brain MRI pattern recognition translated to clinical scenarios. Front Neurosci. 2017;**11**:578.

Chapter 5

Biochemical Testing for Metabolic Movement Disorders

Nenad Blau and Georg F. Hoffmann

Introduction

Strategies in the biochemical testing for movement disorders depend on the available laboratory test panels and clinical description of the patient. Clinical signs and symptoms may already provide a hint for the selection of biochemical investigations. Therefore, a precise clinical definition of the movement disorder is of great importance [1–4]. The term "movement disorders" refers to a group of neurological conditions that cause abnormally decreased or increased movements, which may be voluntary or involuntary. For example, ataxia often results from dysfunction of the part of the brain that controls coordinated movement, the cerebellum. Cerebellar dysfunction may cause uncoordinated or clumsy balance, speech, or limb movements, among other symptoms. Chorea is characterized by repetitive, brief, irregular, somewhat rapid, involuntary movements that typically involve the face, mouth, trunk, and limbs. Dystonia involves sustained involuntary muscle contractions with twisting, repetitive movements. It may affect the entire body (generalized dystonia) or one part of the body (focal dystonia). Myoclonus causes lightning-quick jerks of a muscle or a group of muscles. Parkinsonism describes a group of conditions that has symptoms similar to those of Parkinson disease, characterized by dystonia, tremor, stiffness (rigidity), slow decreased movement (bradykinesia), or imbalance. Spasticity is characterized by increased muscle contractions causing stiffness or tightness of the muscles that may interfere with movement, speech, and walking. Tremor causes involuntary rhythmic shaking of the hands, head, or other parts of the body. Further signs and symptoms of movement disorders may include reduced muscle tone, repetitive hand movements, disturbed eye movements, irregular breathing, and gait abnormalities. Movement disorders in children are mainly divided into three subgroups: ataxia, hyperkinetic/dyskinetic movement disorders (which include dystonia, chorea, athetosis, myoclonus, tremors, tics, and stereotypies), and hypokinetic movement disorders, which include parkinsonism.

Our ability to unravel and diagnose movement disorders due to metabolic diseases is still hampered by the fact that neurological symptoms and disease courses greatly overlap with non-metabolic diseases and that not all diseases presenting with abnormal movements fit the description of classic movement disorders.

Clinical and Biochemical Background

We used the large database approach, to select inborn errors of metabolism (IEMs) with signs and symptoms associated with movement disorders. IEMbase (www.iembase.org) [5] is a knowledgebase tabulating 1,441 IEMs (as of February 2020), categorized according to the recently proposed nosology [6]. IEMbase lists age-matched biochemical and clinical phenotypes for each of the diseases and generates a list of matching diagnoses. With the resulting list, users can generate differential diagnosis charts, suggested biochemical test panels, and targeted gene panels in order to pursue concurrent biochemical and genetic/genomic investigations for a rapid diagnosis.

Signs and symptoms associated with movement disorders listed in the IEMbase are summarized in Box 5.1. They are assigned to 7 groups: (1) ataxia, (2) dystonia, (3) chorea/athetosis, (4) myoclonus, (5) tremor, (6) hypokinetic–rigid syndrome, and (7) other signs and symptoms. The most common symptoms in the 208 selected IEMs were ataxia (73%), dystonia (47%), chorea/athetosis (24%), hypokinetic–rigid syndrome (17%), tremor (15%), and myoclonus (14%) [7].

Box 5.1 Signs and symptoms of disturbed movements associated with 208 IEMs. Data source: IEMbase (www.iembase.org).

1. Ataxia
   - Truncal ataxia
   - Cerebellar ataxia
   - Spasticity (diplegia, tetraplegia, paraplegia, paresis, paraparesis)
2. Dystonia
   - Oculogyric crises
3. Chorea/athetosis
4. Myoclonus
5. Tremor
6. Hypokinetic–rigid syndrome
   - Akinesia
   - Bradykinesia
   - Hypokinesia
7. Other signs and symptoms
   - Hyperekplexia
   - Stereotyped fencing and/or bicycling movements
   - Paroxysmal exercise-induced dyskinesia
   - Midline hand movements
   - Myokymia

A total of 208 inherited metabolic diseases were identified to present with the above-mentioned signs and symptoms of movement disorders (Box 5.2). This list is by far not complete, due to a continuously rising number of newly described diseases and better phenomenological delineation of diseases.

Diagnostic biomarkers described in these 208 IEMs include basic laboratory investigations, e.g. blood gases, lactate, glucose, ammonia, blood counts, liver enzymes or creatine kinase (some in addition to blood or plasma also in the cerebrospinal fluid [CSF]), profiles of amino acids in plasma and organic acids in urine, as well as acylcarnitines in dried blood spots or plasma, and purines and pyrimidines in urine. Further specific laboratory investigations include cholesterol, sterols, phytanic acid, sialotransferrins, amino acids, pterins and biogenic amines in the CSF, glutathione, homocysteine, vitamins E and B, coenzyme Q10 (CoQ10), iron, manganese, and copper. A more detailed list of biochemical tests is summarized in Table 5.1.

Laboratory Diagnosis of Movement Disorders

Laboratory diagnosis of typical movement disorders can be straightforward, e.g., in a child with progressive dystonia and diurnal fluctuation of symptoms and no cognitive impairment, there is a strong suspicion for Segawa disease (autosomal-dominant GTP cyclohydrolase 1 (GTPCH1 deficiency). Direct analysis of CSF biogenic amines and pterins (neopterin and biopterin) is highly diagnostic. The diagnosis can be strengthened by an oral phenylalanine loading test and confirmed by *GCH1* sequencing. Another relatively straightforward approach is the diagnosis of disorders initially detected by newborn screening, e.g. hyperphenylalaninemias due to tetrahydrobiopterin (BH_4) deficiencies, requiring amino acids, pterins, and dihydropteridine reductase measurements, or glutaric aciduria type 1 (GA-1) with elevated specific acylcarnitines (glutarylcarnitine) and a characteristic organic acid profile. For the majority of other movement disorders a combination of basic laboratory investigations (see above), amino and organic acid profiles, and a number of tests with specific biomarkers are necessary for diagnosis [8]. Some of these tests can be abnormal, but not necessarily diagnostic, and with a combination of six metabolic profiles (including routine tests) about 60% of movement disorders can be detected (Figure 5.1). Unfortunately, for many disorders presenting with movement symptoms (14%) there are no specific biomarker tests (e.g. glutamate aspartate transporter deficiency, hyperekplexia due to glycine transporter 2 defect, Birk–Landau–Perez syndrome, as well as a number of mitochondrial, lipid metabolism, storage, or glycosylation disorders), and DNA testing is the only way to obtain the diagnosis.

Nosology Groups, Signs and Symptoms, and Laboratory Investigation

Beside the routine chemistry and hematology investigations, which are, with the exception of porphyrias and storage disorders, important for all groups, amino acids in plasma, organic acids in urine, and acylcarnitines in plasma or dried blood spots are highly diagnostic for disorders of nitrogen-containing compounds (e.g. amino acid

Box 5.2 Inherited metabolic diseases presenting with movement disorders and their classification in corresponding metabolic pathways. Diseases with movement disorder as a primary or prominent feature are highlighted in bold.

1. **Disorders of nitrogen-containing compounds**
   - (a) **Disorders of pyrimidine metabolism:**
     - CAD trifunctional protein deficiency
   - (b) **Disorders of purine metabolism:**
     - Phosphoribosyl pyrophosphate synthetase 1 superactivity
     - Phosphoribosyl pyrophosphate synthetase 1 deficiency
     - Purine nucleoside phosphorylase deficiency
     - Adenylosuccinate lyase deficiency
     - Hypoxanthine–guanine phosphoribosyltransferase deficiency
   - (c) **Disorders of creatine metabolism:**
     - **Guanidinoacetate N-methyltransferase (GAMT) deficiency**
     - **Creatine transporter deficiency**
   - (d) **Disorders of glutathione metabolism:**
     - Gamma-glutamylcysteine synthetase deficiency
     - Glutathione synthetase deficiency, severe
   - (e) **Disorders of ammonia detoxification:**
     - Ornithine transcarbamylase deficiency
     - Argininosuccinate synthetase deficiency
     - Argininosuccinate lyase deficiency
     - Arginase deficiency
     - Hyperornithinemia–hyperammonemia–homocitrullinuria (HHH) syndrome
     - Mitochondrial ornithine transporter deficiency
   - (f) **Disorders of amino acid transport:**
     - Hartnup disease
   - (g) **Disorders of monoamine metabolism**
     - **Tyrosine hydroxylase deficiency**
     - **Aromatic L-amino acid decarboxylase deficiency**
     - **Dopamine transporter deficiency**
     - **Dopamine–serotonin vesicular transport defect**
   - (h) **Disorders of phenylalanine and tetrahydrobiopterin metabolism:**
     - Phenylalanine hydroxylase deficiency (classic PKU)
     - **Autosomal-recessive GTPCH1 deficiency**
     - **Autosomal-dominant GTPCH1 deficiency (Segawa disease)**
     - **6-Pyruvoyl-tetrahydropterin synthase deficiency**
     - **Sepiapterin reductase deficiency**
     - Dihydropteridine reductase deficiency
     - **DNAJC12-deficient hyperphenylalaninemia**
   - (i) **Disorders of sulfur amino acid and sulfide metabolism**
     - Methionine adenosyltransferase I/III deficiency
     - Classic homocystinuria
     - Sulfite oxidase deficiency
     - Ethylmalonic encephalopathy
   - (j) **Disorders of branched-chain amino acid metabolism**
     - Maple syrup urine disease type 1a
     - Maple syrup urine disease type 1b
     - Maple syrup urine disease type 2
     - Dihydrolipoamide dehydrogenase deficiency

Box 5.2 (cont.)

- Isovaleric acidemia
- Methylglutaconic aciduria type 1
- Mitochondrial short-chain enoyl-CoA hydratase deficiency
- 3-Hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency
- **2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency**
- Propionic acidemia PCCA
- Propionic acidemia PCCB
- Methylmalonyl-CoA epimerase deficiency
- Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency
- Combined malonic and methylmalonic aciduria
- Malonic aciduria

(k) Disorders of lysine metabolism:

- **Glutaric aciduria type 1 (GA-1)**

(l) Disorders of proline and ornithine metabolism:

- Pyrroline-5-carboxylate synthase deficiency

(m) Disorders of beta- and gamma-amino acids:

- Beta-ureidopropionase deficiency
- Gamma-aminobutyric acid (GABA) transaminase deficiency
- Succinic semialdehyde dehydrogenase deficiency

(n) Disorders of glutamate metabolism:

- Glutamate aspartate transporter deficiency

(o) Disorders of serine metabolism:

- Phosphoglycerate dehydrogenase deficiency

(p) Disorders of glycine metabolism:

- Glycine encephalopathy due to glycine decarboxylase deficiency
- Glycine encephalopathy due to aminomethyltransferase deficiency
- **Hyperekplexia due to glycine transporter 2 defect**

(q) Disorder of asparagine metabolism:

- Asparaginase deficiency

2. Disorders of vitamins, cofactors, metals, and minerals

(a) Disorders of cobalamin metabolism:

- Imerslund–Gräsbeck syndrome
- cblC disease
- Methylcobalamin synthesis defect – cblD variant 1
- Methionine synthase deficiency – cblG
- cblX disease

(b) Disorders of folate metabolism:

- Hereditary folate malabsorption
- **Folate receptor alpha deficiency**
- Methylenetetrahydrofolate reductase deficiency
- Dihydrofolate reductase deficiency

(c) Disorders of biotin metabolism:

- Biotinidase deficiency
- Holocarboxylase synthetase deficiency

(d) Disorders of thiamine metabolism:

- Thiamine pyrophosphokinase deficiency
- **Mitochondrial thiamine pyrophosphate transporter deficiency**

Box 5.2 (cont.)

(e) Disorders of nicotinamide adenine dinucleotide (NAD) metabolism:
Mitochondrial NAD kinase 2 deficiency
NAXE deficiency

(f) Disorders of pantothenate metabolism:
- **Pantothenate kinase-associated neurodegeneration (PKAN)**
- Coenzyme A synthase deficiency

(g) Disorder of pyridoxine metabolism:
- Pyridoxine-dependent epilepsy
- Pyridox(am)ine phosphate oxidase deficiency

(h) Disorder of vitamin E metabolism:
- Alpha-tocopherol transfer protein deficiency

(i) Disorders of molybdenum metabolism:
- Molybdenum cofactor deficiency

(j) Disorders of copper metabolism:
- **Wilson disease**
- Menkes disease

(k) Disorders of iron metabolism:
- **Neuroferritinopathy**
- **Aceruloplasminemia**

(l) Disorders of manganese metabolism:
- **SLC30A10 deficiency**
- **SLC39A14 deficiency**
- SLC39A8 deficiency

(m) Disorders of zinc metabolism:
- Birk–Landau–Perez syndrome

(n) Disorders of selenium metabolism:
- Selenocysteine synthase deficiency

3. Disorders of carbohydrates

(a) Disorders of carbohydrate transport and absorption:
- **Glucose transporter 1 (GLUT1) deficiency**

(b) Disorders of galactose metabolism:
- Classic galactosemia

(c) Disorders of the pentose phosphate pathway and polyol metabolism:
- Ribose-5-phosphate isomerase deficiency

(d) Disorders of gluconeogenesis:
- **Pyruvate carboxylase deficiency**

(e) Disorders of glycolysis:
- Triosephosphate isomerase deficiency

4. Mitochondrial disorders of energy metabolism

(a) Disorders of pyruvate metabolism:
- **Pyruvate dehydrogenase (PDH) deficiency**

(b) Disorders of the Krebs cycle:
- Mitochondrial aconitase deficiency
- **Succinyl-CoA ligase beta subunit (SUCLA2) deficiency**
- **Succinyl-CoA ligase alpha subunit (SUCLG1) deficiency**
- Fumarase deficiency
- Mitochondrial malate dehydrogenase deficiency
- Plasma membrane citrate transporter deficiency

(c) Disorders of metabolite repair:
- **L-2-hydroxyglutaric aciduria**

Box 5.2 (cont.)

(d) Disorders of mitochondrial carriers:
- Aspartate–glutamate carrier 1 deficiency

(e) Disorders of mitochondrial complex subunits and assembly:
- **Leigh syndrome (various genes)**
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (various genes)
- **Myoclonic epilepsy with ragged red fibers (MERRF; various genes)**
- **Neuropathy, ataxia, and retinitis pigmentosa (NARP)**

(f) Disorders of mitochondrial DNA depletion:
- POLG deficiency
- MPV17 deficiency
- Twinkle mitochondrial DNA helicase deficiency
- FBXL4 deficiency

(g) Disorders of mitochondrial translation factors:
- C12orf65 release factor deficiency

(h) Disorders of mitochondrial tRNA incorporation and recycling:
- Mitochondrial aspartyl-tRNA synthetase deficiency
- Mitochondrial methionyl-tRNA synthetase deficiency
- Mitochondrial tryptophanyl-tRNA synthetase deficiency

(i) Disorders of mitochondrial fusion:
- OPA1 deficiency
- Costeff syndrome
- MSTO1 deficiency

(j) Disorders of mitochondrial phospholipid metabolism:
- **MEGDEL syndrome**

(k) Disorders of mitochondrial protein import:
- **DNAJC19 deficiency**
- **Mohr–Tranebjaerg syndrome**

(l) Disorders of mitochondrial protein quality control:
- Mitochondrial processing peptidase alpha deficiency
- **Caseinolytic peptidase B (CLPB) deficiency**
- **Sacsin deficiency**
- AFG3L2 deficiency
- **Parkin deficiency**

(m) Primary coenzyme Q10 deficiencies:
- COQ2 deficiency
- COQ6 deficiency
- COQ8A deficiency

5. Disorders of lipids

(a) Disorders of ketone body metabolism:
- Beta-ketothiolase deficiency

(b) Disorders of fatty acid synthesis and elongation:
- **Mitochondrial enoyl-CoA reductase deficiency**
- **ELOVL4 deficiency**
- **ELOVL5 deficiency**

(c) Disorders of the fatty alcohol cycle:
- Sjögren–Larsson syndrome

(d) Disorders of intracellular triglyceride metabolism:
- Chanarin–Dorfman syndrome
- Celia's encephalopathy

Box 5.2 (cont.)

- **(e) Disorders of non-mitochondrial phospholipid metabolism:**
  - Phosphatidylserine flippase ATP8A2 deficiency
  - ***PLA2G6*-associated neurodegeneration (PLAN)**
  - PNPLA6 deficiency
  - **PHARC syndrome**
- **(f) Disorders of non-lysosomal sphingolipid metabolism:**
  - **Fatty acid hydroxylase-associated neurodegeneration**
  - GBA2 deficiency
- **(g) Disorders of palmitoylation:**
  - CLN1 disease
- **(h) Disorders of lipoprotein metabolism:**
  - Apolipoprotein B deficiency (familial hypobetalipoproteinemia)
  - Abetalipoproteinemia
- **(i) Disorders of cholesterol biosynthesis:**
  - Mevalonate kinase deficiency
- **(j) Disorders of bile acid synthesis:**
  - Oxysterol 7α-hydroxylase deficiency
  - Cerebrotendinous xanthomatosis
  - Alpha-methylacyl-CoA racemase deficiency
  - Peroxisomal branched-chain acyl-CoA oxidase deficiency

6. Disorders of tetrapyrroles

- **(a) Disorders of heme metabolism:**
  - Recessive porphobilinogen deaminase deficiency
  - Coproporphyrinogen oxidase deficiency
  - Congenital methemoglobinemia due to CYB5R3 deficiency

7. Storage disorders

- **(a) Disorders of autophagy:**
  - **Beta-propeller protein-associated neurodegeneration (BPAN)**
  - SNX14 deficiency
- **(b) Neuronal ceroid lipofuscinoses:**
  - CLN2 disease
  - CLN4 disease
  - CLN5 disease
  - CLN7 disease
  - CLN8 disease
  - CLN10 disease
  - CLN11 disease
  - ATP13A2 deficiency
  - CLN13 disease
  - CLN14 disease
- **(c) Sphingolipidoses:**
  - Gaucher disease
  - Gaucher disease-like disorder due to saposin C deficiency
  - GM1 gangliosidosis
  - Beta-hexosaminidase alpha subunit deficiency (Tay–Sachs disease)
  - Beta-hexosaminidase beta subunit deficiency (Sandhoff disease)
  - Krabbe disease
  - Metachromatic leukodystrophy
  - Multiple sulfatase deficiency
  - Combined saposin deficiency

Box 5.2 (cont.)

(d) Oligosaccharidoses:
- **Sialidosis**
- **Galactosialidosis**
- Alpha-mannosidosis
- Beta-mannosidosis
- Fucosidosis

(e) Disorders of lysosomal cholesterol metabolism:
- **Niemann–Pick disease type C (NPC)**

(f) Disorders of lysosomal transport or sorting:
- Salla disease
- **Action myoclonus–renal failure syndrome**

8. Disorders of peroxisomes

(a) Disorders of peroxisomal fatty acid oxidation:
- X-linked adrenoleukodystrophy (X-ALD)
- Peroxisomal acyl-CoA oxidase deficiency
- D-Bifunctional protein deficiency
- **Sterol carrier protein-2 deficiency**
- **Refsum disease (classic, adult)**

(b) Disorders of peroxisomal biogenesis:
- Zellweger spectrum disorders – peroxin deficiencies

9. Congenital disorders of glycosylation

(a) **Disorders of N-linked glycosylation:**
- Phosphomannomutase 2 deficiency
- DPAGT1-CDG
- ALG1-CDG
- RFT1-CDG
- ALG6-CDG
- ALG13-CDG

(b) Disorders of glycosylphosphatidylinositol biosynthesis:
- PIGG-CDG
- PIGN-CDG
- PGAP1-CDG
- PGAP3-CDG

(c) Disorders of glycolipid glycosylation:
- **ST3GAL5-CDG**
- B4GALNT1-CDG

(d) Disorders of dolichol metabolism:
- DPM1-CDG
- MPDU1-CDG
- **Steroid 5 alpha-reductase 3 deficiency**

(e) Glycosylation disorders of vesicular trafficking:
- TRAPPC11-CDG
- COG4-CDG
- COG5-CDG
- COG8-CDG
- **GOSR2-CDG**

(f) Disorder of deglycosylation:
- **N-glycanase 1 deficiency**

Table 5.1 Laboratory test used in the diagnosis of metabolic movement disorders

Routine test	Special test(s)	Profiles
Blood count	Guanidino compounds	Amino acids including homocysteine
Hemoglobin	Glutathione	Organic acids including methylmalonic acid
Coagulation factors	Orotic acid	Acylcarnitines
Ammonia	SAH/SAM	Purines and pyrimidines
Urea	Sulfite/thiosulfate	Sialotransferrines
Uric acid	Pipecolic acid	Biogenic amines
ASAT/ALAT	GABA/beta-alanine/homocarnosine	Pterins
CK	Vitamins B_{12}, A, E	Folates
ALP	CoQ10	Oligosaccharides
Creatinine	Thiamine/thiamine phosphate	Lysosomal enzymes
Glucose	Cyclic NADHX	DNA panels
Lactate/pyruvate	Iron (brain)	
3-Hydroxybutyrate	Manganese	
Copper	PLP/AASA	
Ceruloplasmin	Polyols	
Iron	Dihydroacetone phosphate	
Protein	Citrate/isocitrate/cis-aconitate *N*-Acetylaspartate (brain) Arachidonic acid/docosahexaenoic acid Lipids panel/Apo-B Apo-CIII Leukotrienes Sterols Bile acids Porphyrins Cathepsin Sulfatides Sialic acid VLCFA including phytanic/pristanic acids Plasmalogenes GPI-anchored proteins	

Abbreviations: Apo, apolipoprotein; ASAT/ALAT, aspartate aminotransferase to alanine aminotransferase ratio; GPI, glycosylphosphatidylinositol; PLP/AASA, pyridoxalphosphate to α-amino adipic semialdehyde ratio; SAM/SAH, S-adenosylmethionine to S-adenosylhomocysteine ratio; VLCFA, very long chain fatty acid.

metabolism defects, hyperammonemias), as well as for disorders of vitamins and mitochondrial disorders of energy metabolism (e.g. Krebs cycle disorders). Biogenic amines, pterins, folates, and amino acids in the CSF are highly diagnostic in some disorders of nitrogen-containing compounds (e.g. primary and secondary biogenic amine deficiencies or defects in folate metabolism or transport), sialotransferrins in plasma for some congenital disorders of glycosylation, and lysosomal enzymes for storage disorders (Figure 5.2).

When calculated for the six most common signs and symptoms associated with abnormal movement (ataxia, dystonia, chorea/athetosis, myoclonus, tremor. and hypokinetic rigidity), routine chemistry and hematology, amino acids in plasma, organic acids in urine, acylcarnitines in plasma or dried blood spots, lysosomal enzymes in plasma, and CSF amino acids, biogenic amines, pterins, and folates seem to be the most important tests (Figure 5.3).

Table 5.2 summarizes biochemical and genetic investigations in 56 inherited metabolic diseases classified as typical movement disorders.

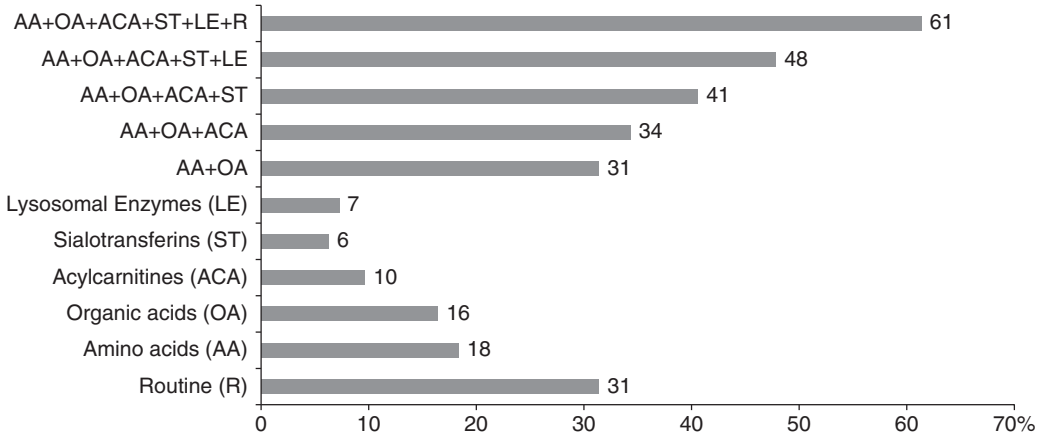

Figure 5.1 Percentage of movement disorders (n = 208) with a series of pathological laboratory tests.

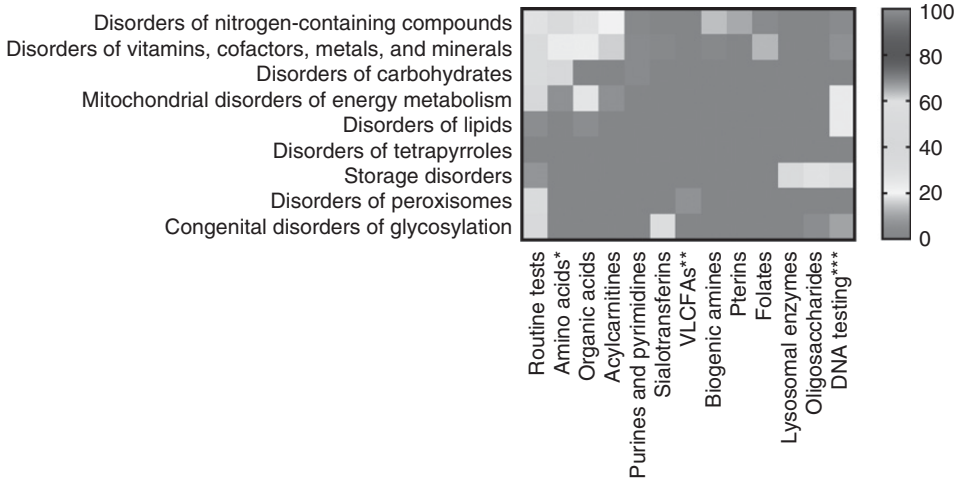

Figure 5.2 Power of laboratory tests in the diagnosis of movement disorders for nine groups of inherited metabolic diseases. Heat map: red (0) match no diagnostic importance, blue–violet match in 80–100% of disorders (within the group) as highly diagnostic. *Amino acids analysis including homocysteine. ** VLCFAs including phytanic and pristanic acids. ***DNA analysis in diseases with no laboratory biomarkers.

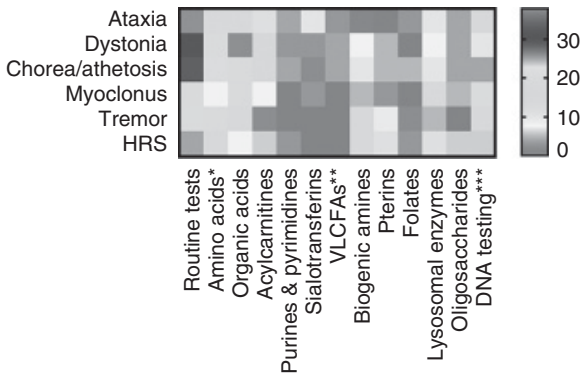

Figure 5.3 Power of laboratory tests in the diagnosis of 208 inherited metabolic movement disorders presenting with six major signs and symptoms. Heat map: red (0) match no diagnostic importance, blue–violet match in 30–40% of disorders (within the symptom group) as highly diagnostic. *Amino acids analysis including homocysteine. ** VLCFAs including phytanic and pristanic acids. ***DNA analysis in diseases with no laboratory biomarkers.

Table 5.2 Summary of biochemical and genetic investigations in 56 inherited metabolic diseases classified as typical movement disorders.

Name	Routine	AAs	OAs	AC	SI	NT	Pterins	Folates	LyE	OS	VLCFAs	GAA	Fe	Mn	VitE	VitB6	DNA
Guanidinoacetate methyltransferase deficiency	X											X					
Creatine transporter deficiency	X											X					
Tyrosine hydroxylase deficiency						X											
Aromatic L-amino acid decarboxylase deficiency						X											
Dopamine transporter deficiency						X											
Dopamine-serotonin vesicular transport defect						X											
Autosomal recessive GTPCH1 deficiency		X				X	X										
Autosomal dominant GTPCH1 deficiency						X	X										
Sepiapterin reductase deficiency							X										
DNAJC12-deficient hyperphenylalaninemia		X					X										
Methylglutaconic aciduria type I			X	X													
2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency		X	X	X													
Glutaric aciduria type 1 (GA-1)			X	X													
Hyperekplexia due to glycine transporter 2 defect																	X
Folate receptor alpha deficiency								X									

Table 5.2 (cont.)

Name	Routine	AAs	OAs	AC	SI	NT	Pterins	Folates	LyE	OS	VLCFAs	GAA	Fe	Mn	VitE	VitB6	DNA
Biotin–thiamine-responsive basal ganglia disease	X															X	
Pantothenate kinase-associated neurodegeneration (PKAN)													X				
Alpha-tocopherol transfer protein deficiency															X		
Wilson disease	X																
Neuroferritinopathy													X				
Aceruloplasminemia	X																
SLC30A10 deficiency	X													X			
SLC39A14 deficiency														X			
Glucose transporter 1 (GLUT1) deficiency	X																
Pyruvate carboxylase deficiency	X	X															
Pyruvate dehydrogenase (PDH) deficiency	X																
Succinyl-CoA ligase beta subunit (SUCLA2) deficiency	X		X	X													
Succinyl-CoA ligase alpha subunit (SUCLG1) deficiency	X		X	X													
L-2-hydroxyglutaric aciduria		X	X														
Leigh syndrome (various genes)	X																
Myoclonic epilepsy with ragged red fibers (MERRF; various genes)	X																

Neuropathy, ataxia and retinitis pigmentosa (NARP)	X	X						
MEGDEL syndrome	X		X					
DNAJC19 deficiency	X		X					
Mohr–Tranebjaerg syndrome								X
CLPB deficiency	X		X					
Sacsin deficiency								X
Parkin deficiency								X
Mitochondrial enoyl-CoA reductase deficiency	X							
ELOVL4 deficiency								X
ELOVL5 deficiency								X
PLA2G6-associated neurodegeneration							X	
PHARC syndrome								X
Fatty acid hydroxylase-associated neurodegeneration							X	
Beta-propeller protein-associated neurodegeneration (BPAN)							X	
Sialidosis				X	X			
Galactosialidosis				X	X			
Niemann–Pick disease type C (NPC)				X				
Action myoclonus-renal failure syndrome								X
Sterol carrier protein-2 deficiency						X		

Table 5.2 (cont.)

Name	Routine	AAs	OAs	AC	SI	NT	Pterins	Folates	LyE	OS	VLCFAs	GAA	Fe	Mn	VitE	VitB6	DNA
Refsum disease (classic, adult)	X										X						
Phosphomannomutase 2 deficiency	X				X												
ST3GAL5-CDG																	X
Steroid 5 alpha-reductase 3 deficiency					X												
GOSR2-CDG	X																
N-glycanase 1 deficiency										X							

AA, amino acids; AC, acylcarnitines; Fe, iron; GAA, guanidinoacetate; Mn, manganese; LyE, lysosomal enzymes; NT, neurotransmitters; OA, organic acids; OS, oligosaccharides; ST, sialotransferrins; VitB6, vitamin B6; VitE, vitamin E; VLCFA; very long chain fatty acids.

Conclusions and Further Directions

Traditionally, the laboratory diagnosis of inherited metabolic diseases largely relies on targeted hypothesis-driven measurements of metabolites in body fluids [9]. In the rapidly developing field of biochemical genetics within the era of omics, new methods including targeted and untargeted metabolomics, NMR spectroscopy in combination with omics approaches, and especially genomics, can enable quicker and better diagnoses as well as the discovery of additional inherited metabolic diseases associated with movement disorders. For the affected patients as well as the caregivers, correct and more efficient diagnoses are of utmost importance. Now and in the future, these possibilities require standardized and optimized collaborations between all caring physicians (neurologists and neuroradiologists as well as genetic and metabolic specialists) and an interactive personalized diagnostic path and evaluation of clinical, genetic, radiological, and metabolic data. This complexity is unfortunately often not sufficiently addressed in neurometabolic disorders including those associated with movement disorders, especially when only the primary genetic path is followed without a corresponding metabolic work-up. For the metabolic part the centerpiece is well-established laboratory methods listed in Box 5.2 and high standards of good laboratory practice in specialized metabolic laboratories.

Key Points and Clinical Pearls

- Clinical signs and symptoms may already provide a hint for the selection of biochemical investigations.
- More than 200 inherited metabolic diseases present with signs and symptoms of movement disorders.
- Diagnostic biomarkers described in inherited metabolic movement diseases include basic laboratory chemistry, profiles of amino acids in plasma and organic acids in urine, as well as acylcarnitines in dried blood spots or plasma, and purines and pyrimidines in urine.
- Additional specific laboratory investigations include cholesterol, sterols, phytanic acid, sialotransferrins, amino acids, pterins and biogenic amines in the CSF, glutathione, homocysteine, vitamins E and B, CoQ10, iron, manganese, and copper.

Directions for Future Research

- Targeted and untargeted metabolomics, NMR spectroscopy in combination with omics approaches, especially genomics will enable quicker and better diagnoses, as well as the discovery of additional inherited metabolic diseases associated with movement disorders.

References

1. Garcia-Cazorla A, Wolf NI, Mochel F, Hoffmann GF. Neurological disease. In Hoffmann GF, editor. Inherited Metabolic Diseases. Berlin: Springer-Verlag; 2017, pp. 251–92.
2. Ebrahimi-Fakhari D, Van Karnebeek C, Munchau A. Movement disorders in treatable inborn errors of metabolism. Mov Disord. 2019;**34**:598–613.
3. Christensen CK, Walsh L. Movement disorders and neurometabolic diseases. Semin Pediatr Neurol. 2018;**25**:82–91.
4. Jinnah HA, Albanese A, Bhatia KP, et al. Treatable inherited rare movement disorders. Mov Disord. 2018;**33**(1):21–35.
5. Lee JJY, Wasserman WW, Hoffmann GF, van Karnebeek CDM, Blau N. Knowledge base and mini-expert platform for the diagnosis of inborn errors of metabolism. Genet Med. 2018;**20**(1):151–8.
6. Ferreira CR, van Karnebeek CDM, Vockley J, Blau N. A proposed nosology of inborn errors of metabolism. Genet Med. 2019;**21**(1):102–6.
7. Ferreira CR, Hoffmann GF, Blau N. Clinical and biochemical footprints of inherited metabolic diseases. I. Movement disorders. Mol Genet Metab. 2019;**127**(1):28–30.
8. Hoffmann FG, Blau N. Signs and symptoms of neurotransmitter disorders: Approach to diagnosis. In Hoffmann FG, Blau N, editors. Congenital Neurotransmitter Disorders: A Clinical Approach. Huppauge, NY: Nova Publishers Inc; 2014.
9. Wevers RA, Blau N. Think big: Think omics. J Inherit Metab Dis. 2018;**41**(3):281–3.

Chapter 6

Genetic Testing for Metabolic Movement Disorders

Tom J. de Koning

Introduction

Diagnosing inborn errors of metabolism (IEMs) and particularly those complicated by movement disorders means working in a fascinating and overlapping area between neurology, child neurology, metabolic disease, and genetics. At this crossroad between different medical specialties, it is not uncommon that patients enter a long diagnostic journey. Patients can present to a movement disorder specialist, a metabolic specialist, or a clinical geneticist. It is interesting to note that the approach to a diagnosis can be quite different in any of these medical specialties. Neurologists and clinical geneticists often find it difficult to start their diagnostic process in a patient with a suspected IEM with biochemical or enzymatic testing as they are more familiar with molecular testing. On the other hand, specialists for IEMs will often consider biochemical testing their usual starting point to diagnose an IEM. Because biochemical analytical techniques evolved earlier than the techniques to analyze DNA, historically IEMs were diagnosed by detecting abnormal metabolites or enzyme function. It is important to realize that IEMs are genetic disorders with the majority being autosomal-recessive disorders. Other patterns of Mendelian inheritance, including autosomal-dominant, X-linked, and maternal inheritance, can all occur in IEMs. Moreover, the latter inheritance pattern is specific for IEMs due to mutations in mitochondrial DNA (mtDNA). So in most patients with a suspected IEM, molecular genetic testing can be considered a first-tier test, identical to DNA testing routines in other genetic diseases. However, what makes metabolic movement disorders somewhat different from other genetic movement disorders is that a number of metabolic movement disorders are treatable disorders, and these treatable disorders should be prioritized in the diagnostic approach.

In recent years, the availability of next-generation sequencing (NGS) has changed the landscape of diagnosing inherited diseases, including metabolic movement disorders. One of the reasons for the success of NGS is that it allows a one-step laboratory routine with which can target almost all genetic diseases, not only IEMs, enabling clinicians to cover a wide range of genetic diseases in a single run. The application of NGS in neurology has not only unraveled many novel disease-associated genes, but also has shown that in many metabolic movement disorders a single gene defect can cause a whole spectrum of symptoms. Clinicians using NGS need to have a set of skills to determine how and when to use data, and how to interpret genetic variants in the clinical context. Clinicians need to be aware of the pitfalls and limitations of molecular testing and what to do when NGS does yield a molecular diagnosis. NGS techniques, variant interpretation, potential pitfalls, and a diagnostic strategy that incorporates NGS are discussed.

Sequencing Techniques

Sanger Sequencing

Until a decade ago, Sanger sequencing was the gold standard for detecting mutations in disease-associated genes. This method revolutionized DNA analysis, in particular after automated sequencers became available, facilitating multiple samples to be analyzed simultaneously and delivering test results within a short period of time. In principle, Sanger sequencing consists of determining the sequence of a single gene including intron–exon boundaries and introns, depending on the size of the gene. Rather long reads of DNA can be analyzed, circumventing problems of analyzing genomic regions with great homology, such as pseudogenes. However, when multiple different genes need to be analyzed, multiple single gene tests need to be performed, making this technique time-consuming and hence costly.

Sanger sequencing has not disappeared from diagnostic laboratories as this technique is still the gold standard for disorders of tandem repeats or polyglutamine repeats such as the autosomal-dominant spinocerebellar ataxias, Huntington disease, and fragile X. When just a single gene needs to be analyzed, Sanger sequencing can still be the method of choice. Sanger sequencing is also employed for verification of NGS results.

Next-Generation Sequencing

Next-generation sequencing (NGS) is sometimes referred to as massive parallel sequencing, because this is what the technique does. Small fragments of DNA, usually about 150 base pairs, are multiplied many times and these reads of DNA are aligned by software programs to a standard or reference genomic sequence. For details about NGS, the reader is referred to some excellent recent reviews on this topic [1]. Clinicians need to have an understanding of the NGS techniques offered, including limitations and potential diagnostic pitfalls.

NGS Methods

In diagnostic laboratories, different NGS techniques are used and can include sequencing the patient's entire genome (whole-genome sequencing, WGS) or the exons of every protein-coding gene (whole-exome sequencing, WES) or targeting specific disease-causing genes (targeted resequencing, TRS or "gene panels").

Whole-Genome Sequencing

WGS can be used to determine the complete nucleotide sequence of an entire DNA sample, including all the coding and non-coding sequences. The major advantage of this approach is that the complete genomic information will be available and the actual sequencing is relatively fast, since only a short time is required for sample preparation. In contrast to WES discussed below, information from protein-coding sequences does not need to be captured in additional procedures. This is why WGS has been successfully applied for the rapid diagnostic sequencing of critically ill newborns in intensive care units [2], among which of course IEMs are potential diagnoses. WGS is a fast technique, but a major disadvantage of sequencing the whole genome is that it yields a large amount of data that require extensive filtering to provide meaningful information with regard to (known) disease-causing mutations. Therefore, laboratories usually only include and analyze data from the protein-coding sequences, similar to what is done in WES. In addition, WGS as a diagnostic technique is still expensive and there may be problems regarding incidental findings, that is, the identification of potential or definite pathogenic mutations unrelated to the disease for which the genetic test was originally requested. Incidental findings can be encountered in both WGS and WES and raise ethical issues that are discussed later.

Whole-Exome Sequencing

In contrast to WGS, which basically analyzes every single nucleotide of the genome, WES focuses only on the protein coding regions (exons) of the genome. This allows the simultaneous analysis of all the coding regions of known IEM disease genes as well as of novel, potentially disease-causing, genes. To perform WES, first all the coding exons in a DNA sample need to be enriched before the sequence can be analyzed. A major advantage of WES is that all the potential disease-causing genes are included in the analysis: both all the known disease genes associated with movement disorders as well as genes not yet related to a disease. In particular, WES can reveal new disease genes or mutations in genes that have not yet been associated with a certain clinical phenotype. The advantage of WES over WGS is that considerably higher read depths can be achieved at lower cost; furthermore, WES data sets are easier to handle. However, some major concerns for WES include its incomplete representation, in most cases because of low coverage of base-pair reads in certain exons, most often related to insufficient capturing of GC-rich sequences. In the past, incomplete representation and low coverage have led to clinically relevant mutations being missed when WES was used in clinical diagnostics, and therefore these still represent serious quality issues that need to be addressed.

The advantage of being able to test large numbers of genes is sometimes challenged by an incomplete sequence depth. Although capturing techniques have improved, the issues of coverage and sequence depth must still be carefully considered when WES is offered in diagnostic testing. In practice, this means that when a specific disease is suspected and WES did not result in a molecular diagnosis, looking back at the coverage of genes of interest may be advisable.

When a large number of potential disease-associated genes are involved, as is the case in IEMs with more than 800 potential genes, a considerable

number of sequence variants needs to be interpreted by laboratory staff. For this reason, most laboratories will apply subpanels of groups of disorders or parent–child trio analysis to reduce the number of sequence variants for interpretation. Trio analysis also facilitates the identification of de novo mutations, which are quite common in neurological disorders, but have not yet been systematically investigated in IEMs.

Despite some of the limitations of WES, it is used in most diagnostic laboratories since it can be applied for the majority of monogenic disorders. The advantage is that all exons are captured and laboratory staff only need adjust filter strategies for different indications. An additional advantage is that new disease-associated genes can be added relatively simply to the gene lists used to filter the data and that new disease-associated genes can be discovered in WES data sets. As with WGS, incidental findings are an issue, as discussed below.

Targeted Resequencing

This third and widely used NGS strategy is to enrich only the coding regions of genes of interest for a specific disease or diagnostic category, for instance all genes for movement disorders associated with dystonia. For TRS, a disease and gene-specific capturing kit needs to be designed and produced. There are some major advantages to restricting the mutation analysis to a limited set of genes: targeted enrichment provides a superior quality of representation and a much higher read depth than that which is usually obtained with WGS or WES. Because the focus is on specific genes, known intronic mutations in these genes can be included in the capture and panel design. For known repeat sequences or structural rearrangements, specific bioinformatics tools can be applied, overcoming some of the major limitations of WES. In addition, as the focus is on known disease genes associated with a certain clinical phenotype, the laboratory staff face fewer challenges in analyzing the data sets and interpreting variants. This leads to shorter turn-around times for test results. Moreover, TRS minimizes the problem of incidental findings. Depending on the platform and the enrichment strategy used, several hundred target genes can be analyzed for multiple patients in a single run. One of the drawbacks of the technique is that gene-specific capturing kits need to be ordered, and adding new disease-associated genes requires a new customized capturing kit requiring new validation of capturing and coverage. TRS can still be a cost-effective alternative to WES, yielding very high-quality sequencing results for movement disorder diagnostics [3].

Variant Interpretation

The basis of all NGS procedures is that extensive filtering algorithms are used to discard sequence variants that are not (or unlikely) associated with disease. This allows selection of a relatively small subset of variants that potentially could explain the clinical phenotype. It is important that clinicians requesting NGS must have some understanding of how these variants are reported and how likely they explain the clinical phenotype. Variants are called **pathogenic** when the probability that the variant is causing pathogenicity is more than 99%. A variant is called **likely pathogenic** when the probability is between 90% and 99%, and finally the variant is called a **variant of unknown significance** (VUS) when the probability of pathogenicity is less than 90% or when no reliable prediction can be made that the variant is indeed benign [4].

Biesecker et al. [5] published an excellent guide for clinicians to apply the data produced by genetic laboratories. They underscore the fact that there is a common misconception that a genetic finding is a deterministic, infallible predictive tool. Clinicians should realize that this is frequently not the case. Pathogenic variants are easy to interpret, but in many cases variants are found that are not predictive of the phenotype, yet can still be useful in making a diagnosis or altering treatment management. The appropriate integration of genetic testing results in comprehensive diagnostic assessments, and neither overestimating nor underestimating the predictive power of genetic analyses is needed to arrive at an accurate diagnosis. So despite the fact that NGS revolutionized our diagnostic procedures, a diagnosis still requires integration and assessment of all available information.

In order to arrive at the correct diagnosis, a knowledge of the clinical phenotypes related to the genes tested is crucial. Therefore, we prefer a multidisciplinary setting where clinicians and laboratory staff discuss the NGS results and interpret variants in relation to the patient's phenotype. It is important that clinical specialists are involved who have expertise in the disorders tested. A multidisciplinary setting to discuss laboratory results within a team of physicians and laboratory staff is quite common in metabolic laboratories, but this setting is infrequent in laboratories offering NGS diagnostics [6].

Other Molecular Techniques Used in Clinic

Array-CGH and SNP Analysis

Other molecular techniques can contribute to a molecular diagnosis, and this is particularly true for techniques that detect larger structural rearrangements in DNA, such as deletions of genes or even of multiple genes. These techniques, such as array comparative genome hybridization (array-CGH) and single nucleotide polymorphism (SNP) analysis, are quite commonly used in children with developmental delay and intellectual disability. However, although not very often reported in relation to IEMs, complex phenotypes with deletions of (multiple) genes are not uncommon in patients with movement disorders and this is particularly true when developmental or behavioral problems are also part of the phenotype. Dale [7] reported quite a significant diagnostic yield of microdeletions in a group of 7/25 (28%) children with a suspected genetic cause of their movement disorder. Multiple disease-associated genes involved in microdeletions sometimes lead to a contiguous gene syndrome. Well-known examples of these are deletions involving *SGCE*, causing a syndrome of myoclonus–dystonia, deafness, and split hand malformation [8]. Other examples of such complex phenotypes with involvement of a known movement disorder gene are deletions with congenital mirror movements and deletions involving *TOR1A* [9, 10].

Interestingly, deletions in the region of a known movement disorder gene can cause the movement disorder phenotype, even when the deletion does not include the gene itself. Adjacent deletions can disrupt gene function, and this has been repeatedly reported for instance in benign hereditary chorea associated with deletions nearby *NKX2-1* [11]. Thus, when there is a clear suspicion for a specific gene defect based on the clinical phenotype, it is worthwhile pursuing an array-CGH in search of structural genomic abnormalities.

In many laboratories, SNP analysis will be the technique used to diagnose structural genomic rearrangements. In contrast to array-CGH, SNP analysis is often combined with WES, for instance as a quality-control test. In addition to testing for structural abnormalities, SNP analysis can also be used to test for consanguinity and to identify homozygous regions in search for recessive disorders. Yet another application is to detect uniparental disomy (UPD), which is relevant for imprinted genes such as *SGCE*.

RNA Sequencing

Sequencing of transcripts or RNA sequencing has been used in DNA diagnostics for many years as a test to find out whether changes/variants in genomic DNA lead to detectable changes in RNA transcripts and hence protein function. When there is no functional test available, i.e. an enzyme assay or transporter assay, RNA sequencing can be used to test the functional relevance of a given DNA change. Massive parallel RNA sequencing allows large-scale transcriptome analysis. Although this technique is not yet available in many diagnostic laboratories, RNA sequencing can be of additional value in a diagnostic setting [12]. Particularly in patients with a suspected mitochondrial disease, a 10% increase in diagnostic yield can be established by performing transcriptome analysis demonstrating intronic loss of functions variants. The diagnostic yield of RNA sequencing may be even higher when the affected tissue is tested. Cummings et al. [13] showed that RNA sequencing on muscle biopsy material significantly increased diagnostic yield as it demonstrated specific splice-altering variants in both exonic and intronic regions that were not detected by preceding WES analyses. It is very likely that RNA sequencing will become available on a large scale in the near future and this will help establish risk scores for more complex genetic disorders.

Diagnostic Yield of NGS Techniques

Depending on the group of disorders and selection of patients, the diagnostic yield of WES or other NGS strategies varies between 15% and 50%, but can be higher in selected patient populations. Bergant et al. [14] investigated, in a large cohort of patients (n = 1059), whether or not additional and extensive analyses on exome data sets could contribute to a higher diagnostic yield. The authors reported that a 4% increase in the number of diagnoses could be established. This was mainly achieved by the addition of a copy number variant analysis and better splice site prediction.

WES only covers about 2% of our DNA. Sequence variants in non-coding (introns) and regulatory domains of the genes of interest are not analyzed and hence not reported. Cordeiro et al. [15] showed that in a pediatric movement disorder clinic the diagnostic yield of NGS techniques could be as high as 50%, with many metabolic movement disorders among these diagnoses. For comparison,

the diagnostic yield of cerebrospinal fluid (CSF) diagnostic procedures in about the same population of patients was considerably lower, at about 13% [16]. Reid et al. [17] showed that in 13% of their highly selected cases of undiagnosed neurometabolic disorders more than one gene defect was found to be present, a proportion of patients not to be ignored, and a finding that can only be established by comprehensive genetic testing.

Finally, several groups have shown that NGS as a first-line diagnostic approach can be cost effective. Of note, in a study by van Egmond et al. [18] on the cost-effectiveness of NGS, a patient with glutaric aciduria type 1 and a patient with Niemann–Pick disease type C were diagnosed at ages 44 and 62 respectively, ages at which an IEM as the cause of movement disorders is rarely considered. Adults with metabolic movement disorders are more likely to be detected by NGS.

Pitfalls in the Molecular Diagnosis of IEMs

Despite the fact that NGS offers a powerful technique, there are several scenarios that warrant consideration.

Mutations in Promoter and Intronic Regions

As discussed above, WES will miss mutations in promoter regions and intronic regions. Although these are infrequent causes of IEMs, they certainly exist. In some disorders, for instance in dopa-responsive dystonia and tyrosine hydroxylase deficiency, mutations in the promoter region are well described [19, 20]. This means that in a patient with a clinical suspicion but negative WES, CSF analysis can be very important to arrive at the correct diagnosis. In cases of metabolic movement disorders when one suspects a specific IEM, it can be worthwhile to contact a research group working on this disorder.

Not only mutations in promotor regions but intronic mutations are also well-known, albeit less frequent, causes of IEM and are seen in patients with common IEMs such as phenylketonuria and Wilson disease [21]. We know these intronic mutations exist, again because there is a very good and easy-to-obtain biomarker in blood that allows a diagnosis even if the first-pass genetic test is negative. Therefore, a clinical suspicion for a specific disorder or group of disorders should not be discarded based on negative NGS results. Other ways of confirming the suspected clinical diagnosis should be considered, such as looking for a biomarker or an enzymatic assay, considering a separate analysis for promotor and intronic mutations, or testing for larger intragenic abnormalities as discussed below. In many cases, contacting laboratories that can perform these kinds of additional tests, often in a research setting, can be a way to obtain a molecular diagnosis.

Larger Structural Abnormalities

Another pitfall one should be aware of is the fact that larger structural rearrangements, such as deletions of a number of nucleotides (more than three or four) or even a whole exon, are not necessarily reported when NGS data sets are analyzed. A technique to test for these somewhat larger rearrangements in genes is multiplex ligation-dependent probe amplification (MLPA). Array-CGH or SNP analysis is applied to diagnose large rearrangements (whole genes or multiple genes), but MLPA is the technique used to test for rearrangements within a single gene. For each single gene, an MLPA test needs to be designed and ordered, and therefore MLPA is usually only available in laboratories with a research interest. Intragenic deletions are also rare causes of disease but, interestingly, specific deletions may be associated with certain clinical phenotypes, as observed in *CACNA1A* where deletions are associated with migraine [22].

Mutations in Mitochondrial DNA

When NGS is performed, the majority of laboratories will report only variants in nuclear genes, and genes encoded by mtDNA are not covered. A separate analysis of mtDNA needs to be requested when a mitochondrial disease is suspected. An issue related to testing mtDNA is the fact that varying heteroplasmy in different tissues can complicate diagnostic testing. The diagnostic yield from DNA obtained from blood may be lower than that of DNA obtained from muscle or a urine sample [23]. This issue applies even more to adults with neurological symptoms, because mutations in mtDNA are more prevalent in adults than in children. It is estimated that less than 20% of the pediatric patients with a suspected mitochondrial disease have a mutation in mtDNA whereas, in contrast, 70–75% of the adult patients with suspected mitochondrial disease have mutations in mtDNA [24]. Given the difficulty of determining heteroplasmy, the complexity of dedicated quantified

polymerase chain reactions for large mitochondrial DNA deletions, and the issue of quantifying mtDNA depletion, diagnostic samples are preferably tested by a reference laboratory for mitochondrial diseases.

Heterozygote Mutations in Recessive IEMs

In recent years it has been shown that patients carrying just one mutated allele can present with a phenotype of recessive disorders. This has been shown for instance in disorders of proline synthesis, a group of IEMs associated with movement disorders, particularly in adults with spastic paraparesis. Coutelier et al. [25] showed that de novo heterozygote mutations in *ALDH18A1*, the gene that encodes delta-1-pyrroline-5-carboxylate synthase, could in fact cause disease. The mechanism by which these mutations reduce enzymatic function is via a loss of dimerization/tetramerization of protein complexes. Another mechanism by which only one mutation will lead to a disease phenotype is allelic expression imbalance, a mechanism that has been demonstrated for *PEX6* causing a Zellweger syndrome spectrum disorder [26]. Many of the enzymes involved in biochemical pathways are indeed dimers or tetramers, so a dominant negative effect on protein complex formation may be more common than suspected, and the same may be true for allelic expression imbalance.

The occurrence of these specific heterozygous mutations causing dominant-negative effects or allelic expression imbalance is easily discarded as the cause of the patient's phenotype, simply because disorders are labeled as a recessive disease. Segregation studies in parents and family members might help to interpret findings, because when the heterozygous mutation is a de novo mutation this might be a hint to the mechanisms discussed.

Repeat Disorders Are Not Reported by NGS Strategies

Although nucleotide repeat disorders, such as polyglutamine repeats in autosomal-dominant ataxias, are usually not associated with IEMs, they are common causes of movement disorders. Moreover, these repeat disorders can occur in children as well, usually with a more severe clinical phenotype and caused by genetic anticipation, resulting in increases of repeat length. These tandem repeats are not reported by WES analysis software because they are discarded as errors. Therefore when one is considering a movement disorder that may be caused by nucleotide repeats, dedicated testing for this group of repeat disorders must be considered. Most laboratories still use Sanger sequencing for this purpose.

Recently, specific pentanucleotide intronic repeats in two genes were also shown to be associated with a movement disorder, in this case familial cortical tremor [27]. It is very likely that these intronic repeats will be observed in other movement disorders. Again, this molecular mechanism has not yet been shown in IEMs, but one should be aware of the fact that these intronic repeats can be missed by NGS.

Another recently emphasized and rather unique cause of recessive disease is intronic repeat sequences that affect methylation and thereby protein expression [28]. This mechanism of inappropriate methylation has been shown for a recessive disorder causing developmental delay, but could potentially affect enzymatic activity through inappropriate methylation as well.

These examples show that we need to advance our bioinformatics techniques to cover intronic variants and variants in regulatory regions.

Incidental Findings

It is outside the scope of this chapter to discuss all details related to incidental findings. Guidelines are available from several professional organizations regarding reporting incidental findings [29, 30]. Clinicians ordering an NGS test should inform patients and families about the possibility of incidental findings and obtain proper informed consent before the test is performed.

There are several potential strategies to minimize incidental findings. Late-onset neurodegenerative diseases, i.e. genetic forms of Parkinson disease or early-onset Alzheimer disease, do not necessarily need to be included in diagnostic tests for children. Therefore, different WES filter sets are used depending on the age of the patient. However, even when different gene lists for different age categories are used, potential incidental findings need to be discussed with patients or parents. Examples include heterozygous mutations in *GBA*, the gene for Gaucher disease, which are associated with a higher risk for Parkinson disease, or the fact that carriers of a mutation in the ataxia–telangiectasia gene *ATM* might carry a higher risk for developing breast cancer.

Strategies to minimize incidental findings include different filter strategies for children and adults and a stepwise approach. First, according to the movement disorder phenotype observed, specific lists of

gene are tested. When this does not result in a diagnosis, in a second step WES may be offered and the patient or parents will receive detailed counseling regarding potential incidental findings.

Biochemical Testing Versus Molecular Testing

Specific biochemical testing for IEMs should not be confused with routine chemistry tests such as whole blood cell count, sedimentation rate, C-reactive protein, lactate, transaminases, copper, ceruloplasmin, and creatine kinase. These first-line tests remain important in the initial diagnostic testing of all patients with movement disorders and not only in those with a suspected IEM.

When discussing the two approaches for diagnostic testing, biochemical and NGS, in patients suspected to have an IEM, one should realize that in many clinics NGS is already used as a confirmatory test for abnormal biochemical findings. Ghosh et al. [31] showed that this could be a successful strategy in the diagnostic process for IEMs and an approach with which one potentially can avoid burdensome follow-up diagnostic procedures. NGS is not used only in follow-up of biochemical testing; biochemical testing is of course used to interpret DNA variants observed in genes associated with IEMs. Variants classified as likely pathogenic or variants of unknown significance can be functionally assessed and confirmed with biochemical testing.

In some areas, testing has shifted completely from biochemical testing toward molecular testing. An important example is suspected mitochondrial disease. Until recently, the use of muscle biopsies and testing of respiratory chain complexes was believed to be the cornerstone of diagnostic testing. But as indicated by a statement from the American Mitochondrial Society, muscle and other biopsies are no longer the primary route for obtaining a diagnosis. The diagnosis of a suspected mitochondrial disease should first be attempted through extensive molecular testing [32]. Previously identified deficiencies of oxidative phosphorylation were often secondary to another disorder or even immobility due to severe neurological disease. While the presence of specific metabolites in plasma or urine, such as ethylmalonic, methylmalonic, or 3-methylglutaconic acid, will facilitate NGS strategies, an NGS-first strategy can also be applied.

Yet another area where molecular testing is preferred over biochemical testing is in IEMs where there are no consistent alterations in metabolite concentrations in body fluids and enzymatic assays are not available. This is for instance the case in disorders of proline and asparagine synthesis, conditions often associated with movement disorders and encephalopathy. In these synthesis defects, surprisingly the concentrations of amino acids in plasma, urine, and CSF can be completely normal, and these IEMs will be missed when one solely relies on metabolite analysis [33].

Some metabolic movement disorders are treatable, and these need to be prioritized. There is one area in movement disorder diagnostics where NGS is inferior to biochemical testing, and this is in acute-onset movement disorders. The speed with which biochemical testing produces test results cannot be met by NGS, not even by rapid WGS. It is unlikely that in the coming years NGS results will become available within a few hours, which is the case with biochemical testing. Therefore, in case of a movement disorder emergency, biochemical testing, such as organic acid analysis, amino acid analysis, or acylcarnitine profiling, remains important and is certainly preferred over NGS. NGS can be used to confirm a suspected IEM or can be used simultaneously to diagnose disorders that can resemble an IEM. As an example, mutations in *ATP1A3* can give rise to an acute encephalopathy with movement disorders in the setting of an intercurrent illness, similar to what is observed in mitochondrial disorders [34].

Diagnostic Strategy

The starting point of every diagnostic strategy remains meticulous phenotyping and defining the movement disorder phenomenology. In acute-onset movement disorders, acquired disorders need to be discriminated from genetic disorders such as IEMs. In many acute situations, testing for both acquired disorders and metabolic testing for an IEM, as well as testing for other genetic movement disorders, is appropriate.

For patients with an insidious onset of movement disorders, NGS can certainly be used as a first-line approach to test for all potential genetic disorders associated with the phenotype. A strategy for the clinical use of NGS in patient with movement disorders is presented in Box 6.1.

Box 6.1 Strategies for the clinical use of NGS in patients with movement disorders

1. Define the clinical phenotype: Is this an acute-onset movement disorder?
2. Is the phenotype likely caused by an acquired disorder, for instance infection, autoimmune, or autoantibody? Aim to do immediate testing for these treatable disorders.
3. Could the acute presentation be caused by an IEM? Aim to obtain metabolic testing, such acylcarnitines and amino acids in blood combined with organic acids in urine.
4. If a specific movement disorder is suspected, aim diagnostic procedures at this specific diagnosis. In some disorders, e.g. dopa-responsive dystonia or paroxysmal kinesigenic dyskinesia, a medication trial can add to diagnostic information.
5. When a specific disorder is not suspected, start NGS diagnostics for genetic movement disorders including IEMs.
6. If the NGS test result suggests a molecular diagnosis that fits the phenotype, this is the end of molecular diagnostics.
7. When there are likely pathogenic or variants of unknown significance reported in a gene that may explain the phenotype, pursue this potential diagnosis, e.g. utilize a biochemical or enzymatic test, if available.
8. In the case of heterozygous variants reported in a gene that could explain the phenotype, pursue ancillary studies including MLPA of the gene. Heterozygous mutations can explain the phenotype through a dominant-negative effect or allelic expression imbalance.
9. In the event that NGS does not result in a molecular diagnosis, but a genetic cause is highly suspected, consider whether a diagnosis can be missed due to any of the pitfalls of NGS. Evaluate the coverage for genes considered as potential candidates. Evaluate whether or not the phenotype may be explained by mutations in mtDNA or a repeat nucleotide disorder.
10. Re-evaluate the phenotype. New genetic bases for movement disorders are reported regularly, and reanalyzing data sets may yield a molecular diagnosis. Advances in bioinformatics and other omics may lead to a revised diagnostic strategy.

Recent Developments

For many years, biochemical analyses in dried blood spots have played an important role in newborn screening programs worldwide. Development of sensitive tandem mass spectrometry, combined with microvolume enzymatic assays, has revolutionized screening procedures. It is now also feasible to perform NGS diagnostics on DNA extracted from dried blood spots as shown by Boemer et al. [35]. NGS will certainly enter our screening programs at some point.

Not only will genomics be embedded in newborn screening programs, but multi-omic modalities are likely to be introduced, such as metabolomics, proteomics, glycomics, transcriptomics, and epigenomics. These techniques will shift from research laboratories to clinical applications [36]. Even with these advances, the clinician will establish a diagnosis for the patient's presentation and give advice about an individualized treatment plan. Multidisciplinary teams will be needed to weigh the diagnostic information and arrive at an optimal management plan. This may be expected to include multi-omics teams that will include bioinformaticians and mathematicians along with genetic–metabolic specialists and genetic counselors. Teaching the proper use of NGS to clinicians will be crucial.

Key Points and Clinical Pearls

- Next-generation sequencing (NGS) has revolutionized our diagnostic approach including that of metabolic movement disorders.
- Despite the fact that NGS is a very powerful technique, it is the clinician who must decide whether the results of NGS explain the clinical phenotype of a given patient.
- Clinicians must have a basic understanding of how sequence variants are interpreted and reported.
- When NGS does not result in a molecular diagnosis, clinicians must be aware of the potential pitfalls and limitations of NGS. When a specific clinical diagnosis is suspected, additional tests are warranted.

- Intronic mutations, promotor region mutations, intragenic deletions, mutations in mitochondrial DNA, nucleotide repeats, and larger structural rearrangements are usually not covered in diagnostic NGS. Other molecular testing strategies complementary to NGS may be indicated.

Directions for Future Research

- Bioinformatics strategies and variant prioritizing algorithms are needed to advance the diagnostic value of NGS.
- Development of large-scale transcriptome analyses can contribute to understanding the functional consequences of variants.
- Multi-omics platforms will shift from research laboratories to clinical diagnostics, but further research is needed to optimize the clinical utility.

References

1. Pareek CS, Smoczynski R, Tretyn A. Sequencing technologies and genome sequencing. J Appl Genet. 2011;**52**(4):413–35.
2. van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid targeted genomics in critically ill newborns. Pediatrics. 2017;**140**(4).
3. Montaut S, Tranchant C, Drouot N, et al. Assessment of a targeted gene panel for identification of genes associated with movement disorders. JAMA Neurol. 2018;**75**(10):1234–45.
4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;**17**(5):405–24.
5. Biesecker LG, Nussbaum RL, Rehm HL. Distinguishing variant pathogenicity from genetic diagnosis: How to know whether a variant causes a condition. JAMA. 2018;**320**(18):1929–30.
6. Zeiger WA, Jamal NI, Scheuner MT, et al. Probable diagnosis of a patient with Niemann–Pick disease type C: Managing pitfalls of exome sequencing. JIMD Rep. 2018;**41**:47–51.
7. Dale RC, Grattan-Smith P, Nicholson M, Peters GB. Microdeletions detected using chromosome microarray in children with suspected genetic movement disorders: A single-centre study. Dev Med Child Neurol. 2012;**54**(7):618–23.
8. Asmus F, Hjermind LE, Dupont E, et al. Genomic deletion size at the epsilon-sarcoglycan locus determines the clinical phenotype. Brain. 2007;**130**(Pt 10):2736–45.
9. Campbell IM, Yatsenko SA, Hixson P, et al. Novel 9q34.11 gene deletions encompassing combinations of four Mendelian disease genes: *STXBP1*, *SPTAN1*, *ENG*, and *TOR1A*. Genet Med. 2012;**14**(10):868–76.
10. Poisson A, Lesca G, Chatron N, et al. 12q13.12q13.13 microdeletion encompassing *ACVRL1* and *SCN8A* genes: Clinical report of a new contiguous gene syndrome. Eur J Med Genet. 2019;**62**(11):103565.
11. Kharbanda M, Hermanns P, Jones J, Pohlenz J, Horrocks I, Donaldson M. A further case of brain–lung–thyroid syndrome with deletion proximal to *NKX2-1*. Eur J Med Genet. 2017;**60**(5):257–60.
12. Kremer LS, Bader DM, Mertes C, et al. Genetic diagnosis of Mendelian disorders via RNA sequencing. Nat Commun. 2017;**8**:15824.
13. Cummings BB, Marshall JL, Tukiainen T, et al. Improving genetic diagnosis in Mendelian disease with transcriptome sequencing. Sci Transl Med. 2017;**9**(386): pii: eaal5209.
14. Bergant G, Maver A, Lovrecic L, Comprehensive use of extended exome analysis improves diagnostic yield in rare disease: A retrospective survey in 1,059 cases. Genet Med. 2018;**20**(3):303–12.
15. Cordeiro D, Bullivant G, Siriwardena K, et al. Genetic landscape of pediatric movement disorders and management implications. Neurol Genet. 2018;**4**(5): e265.
16. Mercimek-Mahmutoglu S, Sidky S, Hyland K, et al. Prevalence of inherited neurotransmitter disorders in patients with movement disorders and epilepsy: A retrospective cohort study. Orphanet J Rare Dis. 2015;**10**:12.
17. Reid ES, Papandreou A, Drury S, et al. Advantages and pitfalls of an extended gene panel for investigating complex neurometabolic phenotypes. Brain. 2016;**139**(11):2844–54.
18. van Egmond ME, Lugtenberg CHA, Brouwer OF, et al. A post hoc study on gene panel analysis for the diagnosis of dystonia. Mov Disord. 2017;**32**(4):569–75.
19. Bodzioch M, Lapicka-Bodzioch K, Rudzinska M, et al. Severe dystonic encephalopathy without hyperphenylalaninemia associated with an 18-bp

deletion within the proximal GCH1 promoter. Mov Disord. 2011;**26**(2):337–40.

20. Willemsen MA, Verbeek MM, Kamsteeg EJ, et al. Tyrosine hydroxylase deficiency: A treatable disorder of brain catecholamine biosynthesis. Brain. 2010;**133** (Pt 6):1810–22.
21. Mukherjee S, Dutta S, Majumdar S, et al. Genetic defects in Indian Wilson disease patients and genotype–phenotype correlation. Parkinsonism Relat Disord. 2014;**20**(1):75–81.
22. Grieco GS, Gagliardi S, Ricca I, et al. New *CACNA1A* deletions are associated to migraine phenotypes. J Headache Pain. 2018;**19**(1):75.
23. Koenig MK. Presentation and diagnosis of mitochondrial disorders in children. Pediatr Neurol. 2008;**38**(5):305–13.
24. Theunissen TEJ, Nguyen M, Kamps R, et al. Whole exome sequencing is the preferred strategy to identify the genetic defect in patients with a probable or possible mitochondrial cause. Front Genet. 2018;**9**:400.
25. Coutelier M, Goizet C, Durr A, et al. Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia. Brain. 2015;**138**(Pt 8):2191–205.
26. Falkenberg KD, Braverman NE, Moser AB, et al. Allelic expression imbalance promoting a mutant *PEX6* allele causes Zellweger spectrum disorder. Am J Hum Genet. 2017;**101**(6):965–76.
27. Cen Z, Jiang Z, Chen Y, et al. Intronic pentanucleotide TTTCA repeat insertion in the *SAMD12* gene causes familial cortical myoclonic tremor with epilepsy type 1. Brain. 2018;**141**(8):2280–8.
28. LaCroix AJ, Stabley D, Sahraoui R, et al. GGC repeat expansion and exon 1 methylation of *XYLT1* is a common pathogenic variant in Baratela–Scott syndrome. Am J Hum Genet. 2019;**104**(1):35–44.
29. Middleton A, Morley KI, Bragin E, et al. Attitudes of nearly 7000 health professionals, genomic researchers and publics toward the return of incidental results from sequencing research. Eur J Hum Genet. 2016;**24** (1):21–9.
30. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): A policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;**19**(2):249–55.
31. Ghosh A, Schlecht H, Heptinstall LE, et al. Diagnosing childhood-onset inborn errors of metabolism by next-generation sequencing. Arch Dis Child. 2017;**102** (11):1019–29.
32. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015;**17**(9):689–701.
33. de Koning TJ. Amino acid synthesis deficiencies. J Inherit Metab Dis. 2017;**40**(4):609–20.
34. Dard R, Mignot C, Durr A, et al. Relapsing encephalopathy with cerebellar ataxia related to an *ATP1A3* mutation. Dev Med Child Neurol. 2015;**57** (12):1183–6.
35. Boemer F, Fasquelle C, d'Otreppe S, et al. A next-generation newborn screening pilot study: NGS on dried blood spots detects causal mutations in patients with inherited metabolic diseases. Sci Rep. 2017;**7**(1):17641.
36. van Karnebeek CDM, Wortmann SB, Tarailo-Graovac M, et al. The role of the clinician in the multi-omics era: Are you ready? J Inherit Metab Dis. 2018;**41** (3):571–82.

Chapter 7

A Phenomenology-Based Approach to Inborn Errors of Metabolism with Ataxia

Bianca M. L. Stelten and Bart P. C. van de Warrenburg

Phenomenology

Ataxia means "lack of order," and is defined as a cerebellar disorder characterized by disturbances of coordinated muscle activity. Clinically, cerebellar dysfunction manifests as nystagmus, dysarthria, intention tremor, dysdiadochokinesia, dysmetria, and/or gait ataxia [1]. Ataxia can be seen in numerous genetic, degenerative, and acquired diseases. For a consistent terminology and suggested work-up in this chapter, ataxia is phenotypically classified as: intermittent ataxia, chronic (progressive) ataxia, and ataxia with myoclonic epilepsy [2].

Etiology of Ataxia

The diagnostic work-up in ataxia can be challenging due to etiological heterogeneity and overlapping phenotypes, which have become even more complex with the increase in the number of genes associated with ataxia. Inborn errors of metabolism (IEMs) represent a large class of rare genetic disorders, with a wide range of symptoms and phenotypes, including ataxia. The clinical phenotype ranges from pure cerebellar dysfunction to mixed patterns with additional or predominant extrapyramidal, pyramidal, or cognitive features. Many of the disorders discussed in this chapter classically present in children, but adult-onset cases are described. Ataxia in IEMs can have an intermittent as well as slowly progressive course. Early symptoms in the neonatal period; later-onset acute or recurrent attacks with symptoms such as coma, ataxia, vomiting, and acidosis; chronic and progressive symptoms (failure to thrive, developmental delay, but most importantly neurological deterioration and psychiatric signs); and specific systemic signs can be suggestive of an IEM [3]. Exacerbation or worsening of symptoms after high protein ingestion, a long period of fasting, concurrent febrile illness or other physical stressors are also suggestive. A positive family history can be an important diagnostic clue [4].

For developing a differential diagnosis, brain MRI is generally one of the initial steps to rule out structural lesions. The genetic episodic ataxias may be mistaken for metabolic disorders presenting with intermittent ataxia. Another important differential diagnosis is intermittent ataxia due to drugs or intoxication, both treatable causes of ataxia [5]. Intermittent ataxias can present, when occurring for the first time, as an acute or subacute ataxia. Especially in children, more common causes such as infectious diseases or post-infectious inflammatory conditions must be excluded.

Inborn Errors of Metabolism with Ataxia

IEMs form a large group of genetic disorders that are mostly due to a single gene defect resulting in dysfunction of production, regulation, or function of enzymes. Most IEMs are associated with other neurological and/or systemic symptoms, and ataxia may not be the dominant feature. Amino acid and organic acid disorders normally present during episodes of stress or fasting. Urea cycle defects often present with intermittent episodes of behavioral disturbances and even coma, associated with hyperammonemia. A slowly progressive course is more suggestive of a peroxisomal or lysosomal disorder. In addition to IEMs caused by mutations in nuclear genes, there are some that are caused by mutations in mitochondrial DNA (mtDNA). The finding of ataxia with hearing loss, and evidence of increased blood lactate, is suspicious of a mitochondrial disorder [6]. Other clinical clues for mitochondrial disorders are multi-organ involvement, ophthalmoplegia, and maternal inheritance. A significant proportion of IEMs are treatable. Most treatments consist of avoidance of certain triggers, dietary restriction/supplementation, vitamin supplementation, or treatment focused at reducing the amount of the substance that is toxic to the nervous system. In some disorders, hematopoietic stem-cell transplantation can be considered. Many treatments prevent or eliminate

symptoms when initiated at a young age, emphasizing the need for early diagnosis [6].

Diagnostic Algorithm

An overview of the most common IEMs with ataxia is given in Table 7.1. Treatable disorders are shown in bold, and are discussed in more detail in the text. To provide guidance for the identification of (treatable) IEMs that can manifest with ataxia, a diagnostic algorithm is proposed (Figure 7.1). In the diagnostic work-up, clinical clues (Table 7.2) can be highly suggestive of a certain diagnosis. Brain MRI can be helpful not only for excluding acquired causes of ataxia, but by showing imaging patterns that point to specific genetic causes of ataxia (Table 7.3), for example in Wilson disease and in aceruloplasminemia. Most IEMs are associated with some degree of white matter disease, and in those with ataxia cerebellar atrophy is common. Also the absence of MRI abnormalities, for example in glucose transporter type 1 (GLUT1) deficiency syndrome, holds a diagnostic value. If there are no clinical clues or characteristic brain MRI patterns suggestive for a specific IEM, the next step is metabolic testing, depending on the type of ataxia. Finally, next-generation sequencing (NGS) or further mitochondrial work-up may often be required to reach a final diagnosis.

Intermittent Ataxias

Intermittent ataxia refers to recurrent attacks of ataxia, with or without interictal symptoms. Intermittent ataxia due to an IEM is the result of decompensation of metabolic processes. Attacks are triggered by intercurrent illnesses or catabolic states [1, 2]. Ataxia can be a result of metabolic decompensation in amino and organic aciduria – Hartnup disease, maple syrup urine disease, glutaric aciduria type 1, urocanic aciduria [2, 7], and urea cycle disorders (ornithine transcarbamylase deficiency). It also can be seen in mitochondrial disorders (pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, Leigh syndrome), as well in biotinidase deficiency, biotin–thiamine-responsive basal ganglia disease, and glucose transporter type 1 (GLUT1) deficiency syndrome. Biochemical signatures of these disorders may only be present intermittently, so testing must be done ideally when patients are symptomatic [2]. **Hartnup disease** is caused by mutations in the *SLC6A19* gene, coding for the neutral amino acid transporter, resulting in defective transport of primarily tryptophan. Reduced availability of tryptophan leads to a secondary deficiency of niacin and neurotransmitters. There is a phenotypic heterogeneity, ranging from a photosensitive pellagra-like rash and intermittent ataxia, to intellectual deficiency and psychiatric signs. Treatment consists of a high-protein diet and supplementation of nicotinamide and tryptophan, usually with a good outcome [8].

There are three genes associated with **maple syrup urine disease** (**MSUD**): *BCKDHA* (type Ia), *BCKDHB* (type Ib), and *DBT* (type II), encoding for the catalytic components of the branched-chain alpha acid dehydrogenase complex (BCKDC), which plays a role in the catabolism of the branched-chain amino acids leucine, isoleucine, and valine [9]. The clinical picture depends on the level of residual enzyme activity. In the case of severe enzyme deficiency, patients present with failure to thrive, poor feeding, lethargy, alternating flaccidity and opisthotonus, and respiratory failure (classic MSUD). Intermittent MSUD occurs if there is greater residual enzyme activity and presents with episodic encephalopathy, vomiting, ataxia, and metabolic acidosis. Acute exacerbations are associated with coma during intercurrent illnesses. Associated neurological symptoms can be developmental delay, pyramidal syndrome, peripheral neuropathy, dystonia, and epilepsy [1, 4, 9, 10]. Maple syrup odor of the urine is a classic finding in MSUD [1]. Early diagnosis and treatment can prevent the development of irreversible neurological complications. Treatment consists of avoiding triggers, dietary restriction of branched amino-acids, thiamine supplementation, and, in acute situations, dialysis [4].

Glutaric aciduria type 1 (**GA-1**) is caused by mutations in the gene encoding glutaryl-coenzyme A dehydrogenase (*GCDH*), resulting in the accumulation of glutaric acid, glutaryl carnitines, and other secondary metabolites. Clinical presentations and course are variable. Hypotonia and developmental delay can be the first signs of GA-1. In childhood, during intercurrent illnesses, it can present as an acute encephalopathy, which usually resolves within days, but with dystonia as a persisting feature. In contrast to metabolic decompensation in other acidurias, systemic acidosis or hypoglycemia are rarely seen in GA-1. A small proportion of patients does not present with episodes of encephalopathy, but rather develops ataxia or dystonia, as stable or slowly progressive features. Associated symptoms often are intellectual disability and epilepsy. Treatment consists of oral

Table 7.1 Overview of IEMs that manifest with ataxia (treatable disorders are shown in boldface type)

Disorder/IEM	Gene[a]	Type of ataxia[b]	Neurological features	Other clinical features	Investigations[c]	Treatment
Hartnup disease (OMIM 234500)	***SLC6A19* (AR)**	**A**	**Intellectual disability, ataxia, psychiatric signs**	**Photosensitive pellagra-like rash**	**Elevated excretion of amino acids in urine**	**High-protein diet, nicotinamide to relieve skin manifestations, tryptophan to improve neurological deficits**
Maple syrup urine disease (MSUD) (OMIM 248600)	*BCKDHA* (type Ia, 45%), *BCKDHB* (type Ib, 35%) and *DBT* (type II, 20%) (AR)	A	Developmental delay, episodic encephalopathy, ataxia, pyramidal syndrome, peripheral neuropathy, dystonia, epilepsy	Failure to thrive, poor feeding, respiratory failure, vomiting, lethargy, metabolic acidosis, maple syrup odor of urine	Normal to elevated ammonia, normal to low glucose Elevated branched-chain amino acids (isoleucine, leucine and valine) in plasma Elevated branched-chain hydroxyacids and ketoacids in urine Enzyme testing: low BCKDC activity	Dietary restriction of branched-chain amino acids, avoid fasting Thiamine supplementation in thiamine-responsive individuals In acute situations dialysis Frequent monitoring of plasma amino acid concentrations throughout pregnancy
Glutaric aciduria type 1 (GA-1) (OMIM 231670)	***GCDH* (AR)**	**A, B**	**Hypotonia, developmental delay, intellectual disability, acute encephalopathy, dystonia, ataxia, athetosis, epilepsy**	**Macrocephaly**	**Normal to elevated levels of carnitine and acylcarnitines in plasma Normal to elevated glutaric acid in plasma and urine Enzyme testing: low glutamate dehydrogenase activity**	**Low lysine diet, carnitine supplementation, intensified emergency treatment during periods of catabolism**
Urocanic aciduria (OMIM 276880)	*UROC1* (AR)	A	Intellectual disability, dysarthria, ataxia	-	Elevated urocanic acid and urocanoylglycine in urine.	- (benign course)
Ornithine transcarbamylase (OTC) deficiency (OMIM 311250)	***OTC* (XLR)**	**A**	**Symptoms are similar to that of MSUD Recurrent coma of unknown cause Intermittent episodes of ataxia, headache, vomiting, lethargy, behavioral changes Developmental delay, epilepsy, psychiatric signs**	**Hyperammonemia, respiratory alkalosis**	**Elevated serum ammonia concentration during episodes of symptoms Amino acids: to differentiate from amino acid and organic acidemias**	**Dietary restrictions: low protein, high calorie diet Supplementation with sodium phenylbutyrate, arginine In acute crisis: hemodialysis Periodic blood test for detection of elevated levels of ammonia may allow treatment before clinical symptoms appear**
Pyruvate dehydrogenase E1-alpha deficiency (PDH deficiency) (OMIM 312170)	***PDHA1* (XLD)**	**A, B**	**Hypotonia, epilepsy, ataxia, pyramidal syndrome, peripheral neuropathy Carbohydrate- and fever-sensitive ataxia is suggestive for PHD deficiency**	**Failure to thrive, metabolic acidosis Facial dysmorphic features: microcephaly, frontal bossing, wide nasal bridge Bilateral optic neuropathy**	**Elevated lactate and pyruvate, and normal glucose in serum Elevated alanine in plasma Enzyme testing: low activity of the PDH complex**	**Thiamine supplementation may be effective in the thiamine-responsive form Ketogenic diet Treatment of lactic acidosis with dichloroacetate**

Pyruvate carboxylase deficiency, type C (OMIM 266510)	*PC* (AR)	A	Type A and B manifest in the neonatal period or early infancy as PDH deficiency Type C manifests with relatively benign intermittent ataxia, mild developmental delay, dysarthria, dystonia, epilepsy	Failure to thrive, metabolic acidosis	Mildly elevated lactate and pyruvate, and normal to low glucose in serum Elevated alanine and lysine in plasma and urine Enzyme testing: low PC activity	-
Leigh syndrome (OMIM 25600)	*BSL1L*, *COX 10*, *COX 15*, *FOXRED1*, *NDUFAF*, *NDUFS3*, *NDUFS4*, *NDUFAF6*, *NDUFS7*, *NDUFS8*, *NDUFA10*, *SDHA*, *SURF1* (AR/ maternal inheritance)	A,B	Relapsing-remitting course in early childhood, often triggered by concurrent illnesses Ataxia is most common in mitochondrial defects Also hypotonia, pyramidal syndrome, ophthalmoplegia, and epilepsy	Optic neuropathy Respiratory abnormalities: hyperventilation, apnea Cardiomyopathy and conduction defects	Elevated serum and CSF lactate and pyruvate levels.	-
Biotinidase deficiency (OMIM 253260)	***BTD* (AR)**	**A,B,C**	**Hypotonia, developmental delay, (myoclonic) epilepsy, ataxia, pyramidal syndrome** **In case of partial biotinidase deficiency: symptoms provoked by stress**	**Erythematous skin rash, alopecia** **Optic atrophy** **Deafness** **Respiratory problems: hyperventilation, stridor**	**Elevated lactate in plasma** **Elevated organic acids in urine** **Enzyme testing: low biotinidase activity in serum**	**Biotin supplementation**
Biotin–thiamine-responsive basal ganglia disease (OMIM 607483)	***SLC19A3* (AR)**	**A**	**Subacute episodes of encephalopathy, characterized by confusion, external ophthalmoplegia, dystonia, ataxia, pyramidal syndrome, coma**	**-**	**Normal to high lactate in serum**	**Avoiding triggers** **Treatment with biotin and thiamine**
Glucose transporter type 1 (GLUT1) deficiency syndrome (OMIM 606777)	***SLC2A1* (AR)**	**A, B**	**Cognitive impairment, exercise-induced paroxysmal dyskinesia, dystonia, pyramidal syndrome, epilepsy** **Ataxia can be the only finding, mimicking other episodic ataxias** **Ataxia worsens before meals**	**Microcephaly**	**Low CSF-to-blood glucose ratio** **Lumbar puncture in fasting state and determination of blood glucose before the lumbar puncture** **Low to normal lactate in CSF**	**Ketogenic or modified Atkins diet**
Cerebrotendinous xanthomatosis (CTX) (OMIM 213700)	***CYP27A1* (AR)**	**B**	**Intellectual disability, epilepsy, pyramidal syndrome, cerebellar syndrome, peripheral neuropathy, extrapyramidal signs** **Psychiatric manifestations**	**Chronic diarrhea, bilateral cataract, tendon xanthomas (Achilles tendons)** **Neonatal jaundice** **Osteoporosis** **Atherosclerotic vascular disease**	**Elevated serum cholestanol, elevated urinary bile alcohols**	**Chenodeoxycholic acid 750 mg/day (children 15mg/kg per day). HMG-CoA reductase inhibitors can be added.**

Table 7.1 (cont.)

Disorder/IEM	Gene[a]	Type of ataxia[b]	Neurological features	Other clinical features	Investigations[c]	Treatment
Abetalipoproteinemia (OMIM 200100)	*MTP* (AR)	B	Intellectual disability, peripheral neuropathy, myopathy, ataxia, pyramidal syndrome	Failure to thrive, chronic diarrhea, vomiting and steatorrhea in early childhood, intestinal bleeding, retinitis pigmentosa	Acanthocytes in peripheral blood smears Decreased serum, low-density lipoproteins (LDL) and very low-density lipoproteins, increased high-density lipoprotein (HDL) cholesterol levels, low triglyceride levels Low Vitamin A and E in plasma	Diet with reduced fat intake, especially fats that contain long-chain fatty acids Vitamin E supplementation (oral alpha-tocopherol acetate preparation) Vitamin A supplements, and sometimes Vitamin K supplements
Ataxia with isolated vitamin E deficiency (AVED) (OMIM 277460)	*TTPA* (AR)	B	Ataxia, peripheral neuropathy, pyramidal syndrome, dystonia	Retinitis pigmentosa, cardiomyopathy, pes cavus, scoliosis	High cholesterol and triglyceride levels Low/absent serum Vitamin E	Oral administration of high dose vitamin E
Wilson disease (OMIM 277900)	*ATP7B* (AR)	B	Tremor, parkinsonism, dystonia, chorea, dysphagia, ataxia, epilepsy, and psychiatric symptoms Rare cases with cerebellar ataxia as presenting symptom have been described	Hepatic disease "Sunflower cataract" Kayser–Fleischer rings of the cornea	Elevated aspartate aminotransferase to alanine aminotransferase (ASAT/ALAT) ratio, low serum ceruloplasmin and copper levels Elevated urinary copper concentrations Increased copper on liver biopsy	Copper chelating agents (D-penicillamine, trientine and tetrathiomolybdate, and/or zinc salts)
Aceruloplasminemia (OMIM 604290)	*CP* (AR)	B	Ataxia, dystonia, chorea, parkinsonism, cognitive decline	Diabetes mellitus, anemia, iron accumulation in liver	Low hemoglobin, elevated plasma ferritin, low iron plasma, low transferrin, low copper, low ceruloplasmin	Treatment consists of iron chelating therapy and fresh-frozen plasma
Refsum disease (OMIM 266500)	*PHYH*, *PEX 7* (AR)	B	Ataxia, peripheral neuropathy	Anosmia, deafness, ichtyosis, short metacarpals and metatarsals, cardiac arrhythmias and cardiomyopathy Retinitis pigmentosa, subcapsular cataract, acute-angle closure glaucoma	Elevated phytanic acid levels in serum Enzyme testing	Dietary restriction of phytanic acid combined with a high-calorie diet No sudden weight loss Plasmapheresis or lipid apheresis can reduce the plasma concentration of phytanic acid in exacerbations
Niemann–Pick disease type C (NPC) (OMIM 257220)	*NPC1*, *NPC2* (AR)	B,C	Ataxia, vertical supranuclear gaze palsy, pyramidal syndrome, dystonia, loss of speech, (myoclonic) epilepsy, psychiatric signs, cognitive impairment	Neonatal jaundice and hepatosplenomegaly during infancy	Diagnosis is confirmed by biochemical testing of oxysterols and positive Filipin staining in cultured fibroblasts	Miglustat

Recessive ataxia with coenzyme Q10 deficiency (OMIM 612016 /208920 / 613728)	*ADCK3*, secondary in *APTX* and *ANO10* (AR)	B	Ataxia, peripheral neuropathy, epilepsy, intellectual disability, migraine, psychiatric signs, muscle weakness, hypotonia, upper motor neuron signs, dystonia, chorea, ptosis, ophthalmoplegia	Retinitis pigmentosa, optic atrophy, deafness	Muscle biopsy shows decreased levels of (coenzyme Q10) ubiquinone Plasma concentrations are influenced by dietary uptake and therefor not reliable Normal to elevated lactate	Treatment with ubiquinone (coenzyme Q10)
X-linked adrenoleukodystrophy (X-ALD) (OMIM 300100)	*ABCD1* (XLR)	B	Ataxia is not a common feature; typical characteristics: behavioral changes, pyramidal syndrome, peripheral neuropathy, cognitive impairment	Adrenal insufficiency/ Addison disease, with diffuse skin hyperpigmentation	High levels of VLCFAs in plasma Monitoring adrenal insufficiency	Dietary restriction of VLCFAs "Lorenzo's oil" Corticosteroid replacement therapy for patients with adrenal insufficiency Hematopoietic stem-cell transplantation
Metachromatic leukodystrophy (OMIM 250100)	*ARSA* (AR)	B	Ataxia is often not a presenting symptom; typical characteristics: epilepsy, tremor, peripheral neuropathy, pyramidal syndrome, cognitive impairment	Optic atrophy	Low activity of the enzyme acrylsulfatase Elevated protein in CSF Elevated sulfatides in urine Caution: "Pseudodeficiencies" due to polymorphism, diagnosis requires high urine excretion of sulfatides or molecular analysis of the *ARSA* gene	Hematopoietic stem-cell transplantation
Krabbe disease (OMIM 245200)	*CALC* (AR)	B	Ataxia, peripheral neuropathy, pyramidal syndrome, epilepsy Progressive ataxia is more prominent in adolescence	Optic atrophy	Low to absent functional activity of the enzyme beta-galactocerebrosidase Elevated protein in CSF	Hematopoietic stem-cell transplantation (at presymptomatic stage)
Alpha-mannosidosis (OMIM 248500)	*MAN2B1* (AR)	B	Intellectual disability, muscle weakness, ataxia, psychiatric signs	Facial abnormalities with macrocephaly, prominent forehead, rounded eyebrow, flattened nasal bridge, widely spaced teeth Skeletal abnormalities (scoliosis and deformation of the sternum) and deafness	Elevated mannose-oligosaccharides in urine Enzyme testing: alpha-mannosidase B	Hematopoietic stem-cell transplantation
Cerebral creatine deficiency syndromes (OMIM 612736/ 612718/ 300352)	*GAMT/GATM* (AR), *SLC6A8* (XLR)	B,(C)	Intellectual disability, (myoclonic)epilepsy, hypotonia, extrapyramidal signs, ataxia	Microcephaly, broad forehead, high palate, prominent nasal bridge, fifth-finger clinodactyly, failure to thrive, vomiting, constipation, hepatitis, mild cardiomyopathy	Guanidinoacetate (GAA), creatine, and creatinine in urine and plasma Molecular testing	Supplementation of creatine, ornithine and dietary restriction of arginine or protein

Table 7.1 (cont.)

Disorder/IEM	Gene[a]	Type of ataxia[b]	Neurological features	Other clinical features	Investigations[c]	Treatment
Cerebral folate deficiency (OMIM 613068)	***FOLR1* (AR)**	**B**	**Intellectual disability, ataxia, pyramidal syndrome, epilepsy**	**Hearing loss**	**Low CSF levels of 5-MTHF**	**Folinic acid**
POLG ataxia	*POLG* (nuclear gene)	B, C	Ataxia, external ophthalmoplegia, peripheral neuropathy, epilepsy, chorea, dystonia, myoclonus, cognitive impairment	-	Elevated lactate in plasma and CSF	–
L-2-hydroxyglutaric aciduria (OMIM 236792)	*L2HGDH* (AR)	B	Developmental delay, hypotonia, epilepsy, ataxia, pyramidal syndrome, extrapyramidal signs, behavioral disorders	Macrocephaly	Normal to elevated lysine in plasma and CSF Elevated levels of L-2-hydroxyglutaric acid in urine, plasma, and CSF	–
Congenital disorder of glycosylation, type 1a (CDG-1a, MGAT2-CDG) (OMIM 212065)	*PMM2* (AR)	B	Intellectual disability, hypotonia, cerebellar dysfunction, peripheral neuropathy, and extrapyramidal signs Acute neurological events: epilepsy, stroke-like episodes, impairment in consciousness	Failure to thrive, hepatic dysfunction, retinitis pigmentosa, subcutaneous lipodystrophy and inverted nipples	Isoelectric focusing of serum transferrin and enzyme analysis	–
GM2 gangliosidosis (Tay–Sachs/Sandoff disease) (OMIM 272800/268800)	*HEXA*/*HEXB* (AR)	B, C	Ataxia, dystonia, motor neuron disease, pyramidal syndrome, cognitive impairment/dementia, (myoclonic) epilepsy and psychiatric symptoms	Optical atrophy, cherry-red spot, macrocephaly	Elevated oligosaccharide in urine Enzyme testing: beta-hexosaminidase A and B activity	–
Neuropathy, ataxia, and retinitis pigmentosa (NARP) (OMIM 551500)	*MTATP6* (mitochondrial maternal inheritance)	A, B	Developmental delay and ataxia Muscle weakness and peripheral neuropathy develop later in the disease course Also epilepsy has been described	Retinitis pigmentosa, optic atrophy	Elevated lactate in plasma and CSF	–
PEX10-related peroxisomal biogenesis disorders (OMIM 602859)	*PEX10* (AR)	B	Intellectual disability, ataxia, peripheral neuropathy, pyramidal syndrome, extrapyramidal signs.	-	Elevated phytanic acid levels in serum.	–
Succinic semialdehyde dehydrogenase deficiency (OMIM 271980)	*ALDH5A1* (AR)	B,C	Developmental delay, hypotonia, encephalopathy, ataxia, (myoclonic) epilepsy, dystonia, myoclonus	-	Elevated 4-hydroxybutyric acid in urine	– (Vigabatrin has shown improvement in single case reports; treatment is mostly symptomatic)

Gaucher disease types 2 and 3 (OMIM 230900/ 231000)	*GBA* (AR)	(B),C	Ataxia, (myoclonic) epilepsy, pyramidal syndrome, peripheral neuropathy, dementia, ocular apraxia	Hepatosplenomegaly	Glucocerebrosidase enzyme activity	– (Hematopoietic stem-cell transplantation. Enzyme-replacement therapy. Effect on neurological disease remains to be established.)
Neuronal ceroid lipofuscinoses (OMIM 256731/ 601780)	*CLN5/CLN 6* (AR)	(B),C	Ataxia, (myoclonic) epilepsy, pyramidal syndrome, behavioral disturbances, Intellectual deficiency	Retinitis pigmentosa	Examination of lymphocytes or skin biopsy demonstrating "curvilinear bodies" Enzyme testing	–
Lafora disease (OMIM 254780)	*NHLRC1*, *EPM2A* (AR)	C	Epilepsy (varying from focal visual seizures, to tonic-clonic and myoclonic seizures), furthermore: myoclonus, psychosis, ataxia	-	Skin biopsy to detect "Lafora bodies"	–
Myoclonus epilepsy with ragged red fibers (MERRF) (OMIM 545000)	*MTTK*, *MTTL1*, *MTTH*, *MTTS1*, *MTTS2*, *MTTF*, *MTND5* (mitochondrial maternal inheritance)	C	Epilepsy (myoclonic), ataxia, pyramidal syndrome, dementia	Deafness, short stature, optic atrophy, cardiomyopathy with Wolff–Parkinson–White syndrome	Lactic acidosis Ragged red fibers in muscle biopsy	–
Sialidosis type 1 (OMIM 256550)	*NEU1* (AR)	C	Ataxia, (myoclonic) epilepsy	Bilateral macular cherry-red spot	Elevated excretion of sialyloligosaccharides in urine Enzyme testing: low neuraminidase activity	–

[a] AR, autosomal-recessive; XLR, X-linked recessive. [b] Type of ataxia: A: intermittent ataxia; B: chronic (progressive) ataxia; C: ataxia with myoclonic epilepsy. [c] Next generation sequencing (NGS) or mitochondrial work-up not included.

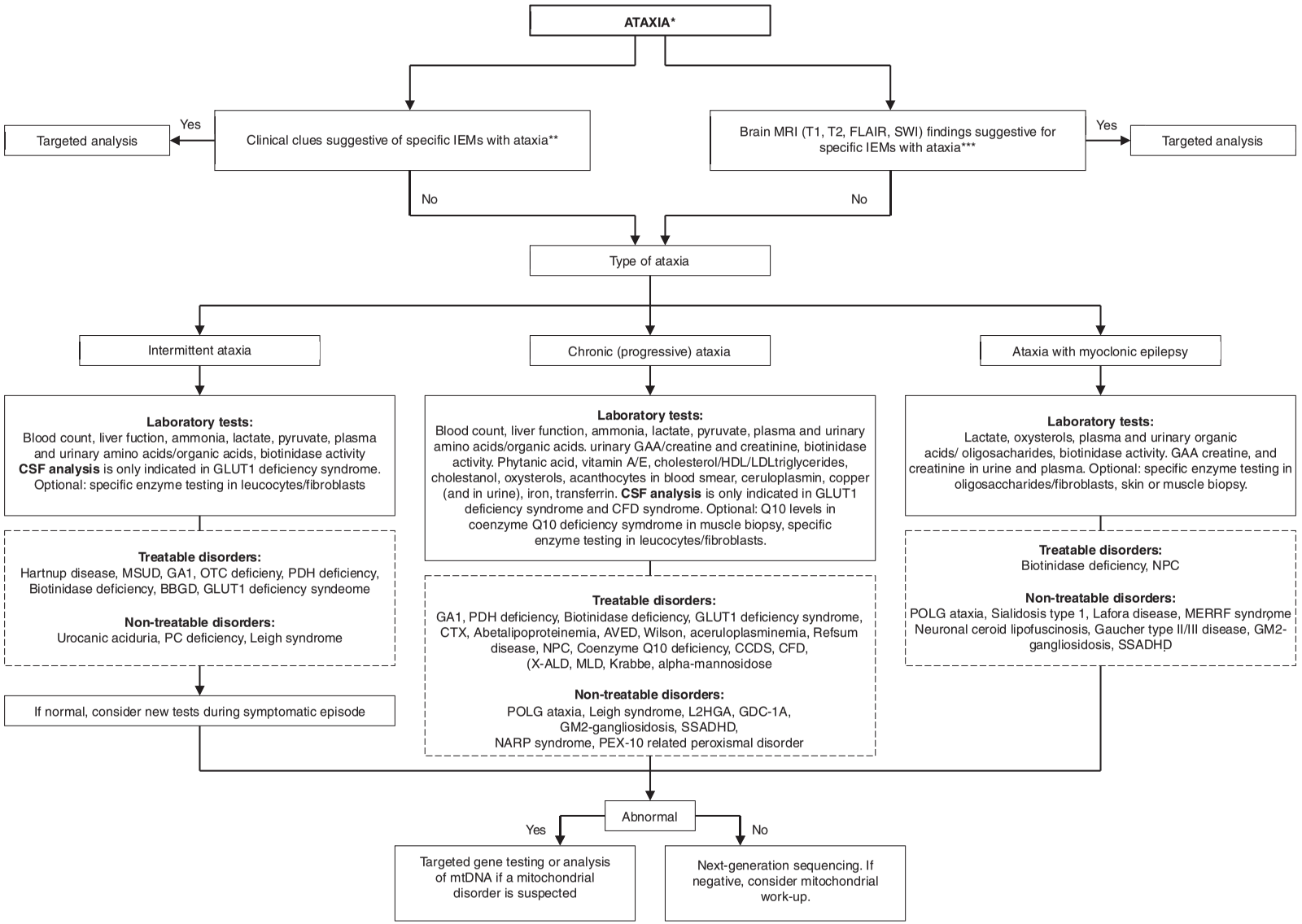

Figure 7.1 Diagnostic algorithm for ataxia. *Suggestive of IEM. **See Table 7.2. ***See Table 7.3.

Table 7.2 Clinical clues suggestive for specific IEMs with ataxia (treatable disorders are shown in bold)

Clinical clues	IEM
Neurological symptoms	
Macrocephaly	**GA-1**, L-2-hydroxyglutaric aciduria, GM2-gangliosidosis, **alpha-mannosidosis**
Microcephaly	**PDH deficiency**, **GLUT1 deficiency syndrome**, **cerebral creatine deficiency syndromes**
Recurrent coma	**OTC deficiency**, **MSUD**
Supranuclear palsy	**NPC**, Gaucher disease type 2 and 3
Exercise-induced paroxysmal dyskinesia	**GLUT1 deficiency syndrome**
Systemic symptoms	
Facial dysmorphic features	**PDH deficiency**, **alpha-mannosidosis**, **cerebral creatine deficiency syndromes**
Macula cherry-red spot	Sialidosis type 1, GM2 gangliosidosis
Cataract	**CTX, Refsum disease**, **Wilson disease**
Kayser–Fleischer rings	**Wilson disease**
Retinitis pigmentosa	CDG-1a, **abetalipoproteinemia**, **AVED, Refsum disease**, NARP syndrome, **recessive ataxia with coenzyme Q10 deficiency**, neuronal ceroid lipofuscinoses (i.e. CLN 5/6)
Optic nerve atrophy	**PDH deficiency**, Leigh syndrome, **biotinidase deficiency**, **recessive ataxia with coenzyme Q10 deficiency**, **MLD**, **Krabbe disease**, GM2 gangliosidosis, NARP, MERRF
Deafness	**Biotinidase deficiency**, **Refsum disease**, **recessive ataxia with coenzyme Q10 deficiency**, MERRF, **alpha-mannosidosis**, **cerebral folate deficiency**
Xanthomas	**CTX**
Ichtyosis	**Refsum disease**
Pellagra-like skin changes/photic dermatitis	**Hartnup disease**
Inverted nipples	GDC-1A
Chronic diarrhea	**CTX**, **abetalipoproteinemia**
Neonatal jaundice	**NPC**, **CTX**
Hepatosplenomegaly	**NPC**, Gaucher disease types 2 and 3
Maple syrup odor of the urine	**MSUD**
Adrenal insufficiency	**X-ALD**
Diabetes mellitus Anemia	**Aceruloplasminemia**, **mitochondrial diseases** **Aceruloplasminemia**
Cardiomyopathy	**AVED**, **Refsum disease**, Leigh syndrome, MERRF, **cerebral creatine deficiency syndromes**

carnitine supplementation and preventing metabolic crises and further neurological progression [11].

Ornithine transcarbamylase (**OTC**) deficiency is the most common disorder of the urea cycle, and caused by mutations in the gene encoding OTC, leading to hyperammonemia. The clinical symptoms are often similar to those of MSUD. In the neonatal period, it can present as a hyperammonemic coma with hypotonia, vomiting, and lethargy, particularly in affected males. Affected females have residual enzyme activity leading to an overall milder phenotype and better response to therapy [4, 12]. In adult-onset cases, intermittent episodes of ataxia, headache, vomiting, lethargy, and behavioral changes develop, for example following high protein intake. Also, developmental delay and epilepsy have been described [12]. If untreated, children with severe forms of OTC deficiency developed serious neurological sequelae and hyperammonemic coma, which may result in life-threatening complications. Treatment consists of dietary restriction and supplementation of arginine, sodium phenylbutyrate, or glycerol phenylglutarate.

Pyruvate dehydrogenase E1-alpha deficiency (**PDH deficiency**) is a mitochondrial disorder caused by mutations in the gene encoding the E1-alpha polypeptide (*PDHA1*) of the PDH complex. In the

Table 7.3 Characteristic brain MRI findings, other than white matter changes and cerebellar atrophy, suggestive for specific IEM with ataxia (treatable disorders are shown in bold)

IEM	Brain MRI findings
Maple syrup urine disease (MSUD)	Characteristic pattern of edema on diffusion-weighted imaging, involving cerebellar white matter, brainstem, globus pallidus, internal capsule and thalamus
Glutaric aciduria type 1 (GA-1)	Macrocephaly with expansion of subarachnoid convexity spaces Bilateral basal ganglia abnormalities: swelling, atrophy and necrosis
Pyruvate dehydrogenase E1-alpha (PDH) deficiency	Agenesis or hypoplasia of the corpus callosum Asymmetrical ventriculomegaly and intraventricular septations, with normal fourth ventricle.
Leigh syndrome	Symmetrical necrotic lesions in the basal ganglia and brainstem Involvement of cerebral or cerebellar white matter is unusual
Biotin-thiamine-responsive basal ganglia disease	Symmetrical and bilateral increased T2 signal intensity of the caudate and putamen during acute crisis, sometimes with involvement of the thalamus, brainstem nuclei, cortex, and vermis
L-2-hydroxyglutaric aciduria	Characteristic pattern of T2 hyperintensities of subcortical white matter, putamen, caudate, globus pallidus and dentate nucleus. Brainstem and cerebellar white matter are spared
Congenital disorder of glycosylation, type 1a (CDG-1a) (PMM2-CDG)	Cerebellar hypoplasia
Cerebrotendinous xanthomatosis	Hyperintense lesions on T2-weighted images in specifically the dentate nuclei, globus pallidus, substantia nigra, and inferior olive, extending to the adjacent cerebellar white matter
Wilson disease	Axial midbrain T2 can show a "face of the giant panda sign" Axial T2 at pons level may also show the "face of a miniature panda sign"
Aceruloplasminemia	Iron accumulation with uniform involvement of all basal ganglia and thalami
Recessive ataxia with coenzyme Q10 deficiency	Agenesis of corpus callosum
X-linked adrenoleukodystrophy (X-ALD)	T2-weighted lesions parieto-occipital involving the splenium, eventually spreading to the frontal lobes, with gadolinium enhancement
Metachromatic leukodystrophy	Symmetrical periventricular leukodystrophy with frontal predominance, sparing of subcortical U-fibres leading to a "butterfly pattern"

newborn, it presents with lactic acidosis, hypotonia, and epilepsy. Recurrent ataxia presents in childhood. Progressive ataxia, pyramidal symptoms, and peripheral neuropathy have also been described. Associated non-neurological symptoms include dysmorphic facial features, microcephaly, and optic neuropathy [1, 2, 13, 14]. Treatment consists of supplementation of thiamine, dichloroacetate, and the ketogenic diet [13]. Other non-treatable mitochondrial IEMs causing intermittent ataxia are **pyruvate carboxylase** (**PC**) deficiency [15] and **Leigh syndrome** [4, 16].

Biotinidase deficiency is a form of multiple carboxylase deficiency, caused by mutations in the *BTD* gene, leading to a neurocutaneous disorder. Biotinidase deficiency presents in childhood with hypotonia, (myoclonic) epilepsy, developmental delay, ataxia, and pyramidal syndrome. Ataxia can be intermittent, chronic (progressive), or combined with (myoclonic) epilepsy. Associated non-neurological symptoms are: eczematous skin rash, alopecia, optic atrophy, sensorineural deafness, and respiratory abnormalities. Intermittent symptoms are present in cases of partial biotinidase deficiency and triggered by stress. Biotinidase deficiency is treated by supplementation with oral biotin. Treatment is effective in preventing symptoms, but if optic atrophy and hearing loss have developed, these are usually irreversible [17, 18].

Biotin–thiamine-responsive basal ganglia disease (formerly known as biotin-responsive basal ganglia disease or BBGD, and also called thiamine-responsive encephalopathy) is caused by mutations in the *SLC19A3* gene, encoding a thiamine transporter (hTHTR2). It typically presents in childhood with subacute episodes of encephalopathy, triggered by illness or mild trauma. It is characterized by confusion, external ophthalmoplegia, dystonia, ataxia, pyramidal syndrome, seizures, and coma. Treatment with biotin

and thiamine early in the disease results in partial or complete improvement of clinical symptoms within days [19]. Avoiding triggers, i.e. states of catabolism, is important.

GLUT1 deficiency syndrome is caused by mutations in the gene encoding the GLUT1 transporter (*SLC2A1*), and results in impaired glucose transport into the brain. There are different phenotypes, ranging from the classic neonatal form with seizures, abnormal dyspractic head–eye movements, and acquired microcephaly to later forms of extrapyramidal syndromes, including dystonia and developmental impairment in children and a later-onset variant manifesting with exertional dyskinesias [20]. Ataxia can be the only symptom in GLUT1 deficiency, mimicking other episodic ataxias due to dominantly inherited channelopathies [2]. Extrapyramidal signs can be continuous or paroxysmal [20]. Ataxia may be more severe before meals [1]. In addition to testing for the gene, a lumbar puncture in a fasting state (four hours postprandial), to determine the cerebrospinal fluid (CSF)-to-blood glucose ratio, can confirm the diagnosis. GLUT1 deficiency syndrome is characterized by low glucose concentration in the CSF. A ketogenic diet markedly reduces seizures and the severity of movement disorders [20]. An effective alternative is the modified Atkins diet used for example in treating paroxysmal movement disorders in GLUT1 deficiency syndrome [21].

Chronic (Progressive) Ataxias

IEMs can present with chronic and in some cases progressive ataxia as the only symptom, but most IEMs show additional neurological and systemic features. In some cases, the clinical picture can remain relatively stable over time. For example, ataxia in coenzyme Q10 deficiency can present as chronic non-progressive ataxia. GLUT1 deficiency syndrome and Refsum disease can present with chronic ataxia with intermittent fluctuations. Progressive ataxia can be seen for example in cerebrotendinous xanthomatosis and Niemann–Pick disease type C, but other signs of progressive neurological dysfunction may become more prominent. GA-1, PDH deficiency, Leigh syndrome, biotinidase deficiency, and GLUT1 deficiency syndrome can present as both intermittent or chronic, progressive ataxia.

Cerebrotendinous xanthomatosis (**CTX**) is a lipid storage disease caused by mutations in the *CYP27A1* gene, encoding for sterol 27-hydroxylase, leading to accumulation of cholestanol in the central nervous system, eye lenses, and tendons. CTX may present as neonatal cholestatic jaundice. Typical clinical features in untreated CTX patients are infantile-onset intractable diarrhea, juvenile-onset bilateral cataracts, young-adult-onset tendon xanthomas, and progressive neurological and psychiatric disease. Neurological manifestations include intellectual disability, epilepsy, spasticity, peripheral neuropathy, ataxia, and other extrapyramidal movement disorders. Ataxia may be one of the presenting symptom in CTX [22]. Also, osteoporosis and cardiovascular disease have been reported. Treatment with chenodeoxycholic acid (CDCA) is effective in normalizing the biochemical abnormalities that underlie the pathogenesis in CTX, but is also effective in stabilizing, and even preventing neurological manifestations [23].

Abetalipoproteinemia is an inborn error of lipoprotein metabolism, caused by mutations in a gene coding for a subunit of the microsomal triglyceride transfer protein (MTTP). It is associated with clinical manifestations of malabsorption and a variety of progressive neurological symptoms related to vitamin E deficiency [4, 24]. Initial symptoms of the disease consist of failure to thrive and symptoms related to fat malabsorption (vomiting, chronic diarrhea, steatorrhea) in early childhood [24]. Late complications are neurological (peripheral neuropathy, myopathy, ataxia, spasticity, intellectual disability) and visual symptoms (retinitis pigmentosa). Early recognition is important because the neurodegenerative complications of abetalipoproteinemia are the result of vitamin E deficiency, which is amenable to treatment. Acanthocytes are found on peripheral blood smears [4]. Treatment consists of a diet with reduced fat intake and supplementing vitamin E, which inhibits the progression of the neurological disease and can prevent retinopathy. Also, concurrent supplementation of other fat-soluble vitamins such as vitamin A and K is recommended in case of deficiency [24].

In ataxia with isolated vitamin E deficiency (**AVED**), vitamin E deficiency results from mutations in the *TTPA* gene, coding for alpha-tocopherol transfer protein. The clinical picture mimics that of Friedreich ataxia, with progressive sensory and cerebellar ataxia as core clinical features. Associated features include head titubation, nystagmus, peripheral neuropathy, spasticity, dystonia, and also pes cavus, scoliosis, cardiomyopathy, and retinitis pigmentosa. Diagnosis is confirmed by low

serum vitamin E, though fat malabsorption must be excluded. Early treatment with high-dose vitamin E supplementation can stop the progression or even reverse neurological symptoms [24].

Wilson disease is a disorder of copper metabolism, caused by mutations in the *ATP7B* gene, leading to a deficiency of a copper-transport protein and build-up of copper. Hepatic disease is the common presentation early in life, whereas neurological manifestations usually develop later. The presenting neurological features are extrapyramidal signs, but ataxia as the initial manifestation has been described [4, 25]. Other symptoms consist of tremor, parkinsonism, dystonia, chorea, dysphagia, ataxia, and epilepsy. Psychiatric symptoms are also common. A characteristic finding is the presence of Kayser–Fleischer rings [25, 26]. Choice of therapy is copper chelating agents (penicillamine, trientine) and/or reduction of intestinal copper uptake with zinc. Treatment may reverse existing symptoms and can prevent the development of neurological sequelae [26].

Aceruloplasminemia is a form of neurodegeneration with brain iron accumulation (NBIA), caused by mutations in the gene encoding ceruloplasmin, leading to excessive and cytotoxic iron accumulation in the central nervous system and visceral organs. Progressive neurological manifestations, consisting of ataxia, dystonia, chorea, parkinsonism, and cognitive decline, are often preceded by diabetes mellitus and anemia [27]. Treatment consists of iron chelation therapy and fresh-frozen plasma treatment [28].

Refsum disease is an IEM of lipid metabolism caused by mutations in the gene encoding for phytanoyl-CoA hydroxylase (*PHYH*), resulting in the accumulation of phytanic acid, which is associated with neurotoxicity. Mutations in *PEX7* mimic Refsum disease. The presenting symptom is usually retinitis pigmentosa, between the ages of 10 years and 20 years. Also, posterior subcapsular cataracts and acute-angle closure glaucoma are common. Later, cerebellar ataxia and neuropathy, sometimes with muscle weakness, develop. Non-neurological symptoms suggestive of Refsum disease are anosmia, deafness, ichthyosis, short metacarpals and metatarsals, cardiac arrhythmias, and cardiomyopathy [29]. Neurological symptoms, cardiac disease, and ichthyosis correlate directly with the level of plasma phytanic acid. Refsum disease is characterized by sudden exacerbations due to intercurrent illnesses or fasting/weight loss [4]. The neurological signs and ichthyosis are very responsive to treatment, and early treatment can prevent the onset of neurological symptoms. Treatment consists of dietary restriction of phytanic acid and sometimes plasmapheresis or lipid apheresis in acute situations with arrhythmias or extreme weakness [29].

Niemann–Pick disease type C (**NPC**) is caused by mutations of the *NPC1* (95%) or *NPC2* (5%) gene, leading to a problem of intracellular cholesterol handling. There is a wide spectrum of clinical presentation with a range of systemic and neurological symptoms. Very early-onset patients are often diagnosed based on systemic manifestations. Ataxia is often an early sign, as well as learning problems. The typical course is that of a progressive development of ataxia, vertical supranuclear gaze palsy, spasticity, dystonia, epilepsy, psychiatric signs, and cognitive impairment. Paroxysmal hypotonia consistent with secondary cataplexy may be prominent. Associated systemic manifestations include neonatal jaundice and hepatosplenomegaly during infancy. A variety of treatments can alleviate neurological manifestations in NPC, but miglustat, an inhibitor of glucosylceramide synthase and thus glycosphingolipid synthesis, is the only currently approved disease-specific therapy for NPC [30].

Recessive ataxia with coenzyme Q10 deficiency is one of the five phenotypes of coenzyme Q10 deficiency, caused by mutations of *ADCK3*, and secondarily in mutations in the recessive ataxia genes *APTX* or *ANO10*. It can present as isolated ataxia with slow or minimal progression. Other reported manifestations include peripheral neuropathy, epilepsy, intellectual disability, migraine, psychiatric symptoms, muscle weakness, hypotonia, dystonia, chorea, ptosis, and ophthalmoplegia. Retinitis pigmentosa, optic atrophy, and deafness have been reported. Response to coenzyme Q10 supplementation in patients with cerebellar ataxia is variable [31, 32].

X-linked adrenoleukodystrophy (**X-ALD**) results from mutations in the *ABCD1* gene, causing impairment of degradation of very-long-chain fatty acids (VLCFAs) within the peroxisome, affecting the nervous system white matter. X-ALD can present with different clinical phenotypes: (1) the childhood cerebral form, (2) adrenomyeloneuropathy (AMN), and (3) Addison disease only. Ataxia or spastic ataxia as presenting signs have been described, particularly in AMN. X-ALD typically presents in childhood with behavioral changes, dysarthria, ataxia, pyramidal syndrome, peripheral neuropathy, visual loss, and cognitive impairment.

Associated features are adrenal insufficiency with diffuse skin hyperpigmentation. Treatment consists of dietary restriction of VLCFAs, "Lorenzo's oil," and corticosteroid replacement therapy for patients with adrenal insufficiency. Hematopoietic stem-cell transplantation is an option in early stages with evidence of brain involvement on MRI [33].

Metachromatic leukodystrophy is caused by mutations in the arylsulfatase A (*ARSA*) gene, leading to demyelination of the peripheral and central nervous system. Metachromatic leukodystrophy can present with different clinical phenotypes that include epilepsy, tremor, ataxia, peripheral neuropathy, and spasticity [34]. Ataxia is usually not a presenting or dominant symptom. In adults, this disease usually manifests with psychiatric symptoms and cognitive impairment [35]. An important associated feature is optic atrophy. Some patients with juvenile disease can benefit from hematopoietic stem-cell transplantation if performed early in the disease [35].

Krabbe disease is caused by mutations in the galactosylceramidase (*GALC*) gene, affecting the peripheral and central nervous system by the accumulation of galactosylceramide. Various presenting features have been described, most importantly ataxia, peripheral neuropathy, pyramidal syndrome, and epilepsy. Progressive ataxia is more prominent in adolescence. An associated feature is optic atrophy [35]. Patients with the infantile form of Krabbe disease can benefit from hematopoietic stem-cell transplantation at a presymptomatic stage, which improves survival and clinical outcome [36].

Alpha-mannosidosis is a lysosomal disorder caused by mutations in the *MAN2B1* gene. It is characterized by facial abnormalities with macrocephaly, prominent forehead, rounded eyebrows, flattened nasal ridge, and widely spaced teeth. Other associated features are skeletal abnormalities (scoliosis and deformation of the sternum), deafness, and recurrent infections. Neurological manifestations include developmental delay/intellectual disability, muscle weakness, ataxia, and psychiatric signs. There is a slow progression of neuromuscular and skeletal manifestations. Hematopoietic stem-cell transplantation can halt disease progression [37].

Cerebral creatine deficiency syndromes are inborn errors of creatine metabolism, involving deficiencies of the enzymes l-arginine:glycine amidinotransferase (AGAT) or guanidinoacetate N-methyltransferase (GAMT), or the creatine transporter (encoded by the gene *SLC6A8)*. Developmental delay/intellectual disability and epilepsy are common in all patients. Movement disorders include choreoathetosis, dystonia, and ataxia. Non-neurological features include microcephaly, broad forehead, high palate, prominent nasal bridge, fifth-finger clinodactyly, failure to thrive, vomiting, constipation, hepatitis, and mild cardiomyopathy. Treatment consists of creatine, ornithine supplementation in the case of GAMT deficiency, and dietary restriction of arginine [38].

Cerebral folate deficiency is caused by mutations in the *FOLR1* gene. Cerebral folate deficiency has a wide clinical presentation. The first symptoms are irritability and sleep disturbances, followed by developmental delay, ataxia, often refractory epilepsy, and hearing loss. Cerebral folate deficiency is associated with low CSF levels of 5-methyltetrahydrofolate (5-MTHF) in the presence of a normal plasma folate. Treatment consists of oral administration of folinic acid, which has blood–brain barrier penetrability. Administration of folic acid may exacerbate the deficiency [39].

Other non-treatable IEMs (summarized in Table 7.1) causing chronic, progressive ataxia are POLG-associated syndromes [40], L-2-hydroxyglutaric aciduria [4, 41], congenital disorder of glycosylation type 1A [42, 43], GM2 gangliosidosis [44], neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome [2, 45, 46], PEX10-related peroxisomal biogenesis disorders [47], and succinic semialdehyde dehydrogenase deficiency [48, 49].

Ataxias with Myoclonic Epilepsy

Features of progressive myoclonus ataxia (PMA) and progressive myoclonus epilepsy (PME) consist of variable combinations of myoclonus, ataxia, and epilepsy. It can be difficult to discriminate between PMA and PME. Therefore a refined definition for PMA requires the presence of myoclonus, ataxia, and no or infrequent (treatment-responsive) epilepsy [50]. Biotinidase deficiency and NPC are the only treatable IEMs that can cause ataxia with myoclonic epilepsy, and these have been described above. POLG-associated syndromes, GM2 gangliosidosis, succinic semialdehyde dehydrogenase deficiency, and also other non-treatable IEMs can cause ataxia with myoclonic epilepsy: sialidosis type 1 [51], Lafora disease [52], myoclonic epilepsy associated with ragged red fibers (MERRF) [53], different forms of neuronal ceroid lipofuscinosis (CLN5/CLN6) [54], and Gaucher disease types 2 and 3 [55].

Conclusions

A variety of IEMs, both treatable and untreatable, can present with ataxia. The exact IEM to consider depends on whether the ataxia is intermittent, chronic, or combined with myoclonus. In many IEMs, ataxia is part of a more complex phenotype, but can be the presenting or dominant disease feature. A diagnostic algorithm is presented to expedite diagnosis with the potential to initiate intervention early to prevent or partly reverse neurological complications.

Key Points and Clinical Pearls

- The diagnostic work-up of cerebellar ataxia is challenging due to etiological heterogeneity and overlapping phenotypes.
- Sometimes, clinical clues or certain brain MRI patterns can be highly suggestive of a specific inborn error of metabolism (IEM) as the cause of ataxia.
- An early diagnosis is important because treatment can often prevent the development of persistent (neurological) symptoms, especially in the case of treatable IEMs.

Directions for Future Research

- Exploring the phenotypic boundaries of genes associated with IEMs, with the emphasis on ataxia.
- Studying the optimal diagnostic strategies for IEMs, for example combinations of next-generation sequencing and metabolomics.
- Gaining more mechanistic insight into ataxia caused by IEMs to develop new and better therapies.
- Designing and testing new symptomatic treatments of ataxia, both pharmacological and non-pharmacological.

References

1. Poretti A, Benson JE, Huisman TA, Boltshauser E. Acute ataxia in children: Approach to clinical presentation and role of additional investigations. Neuropediatrics. 2013;**44**(3):127–41.
2. Garcia-Cazorla A, Wolf NI, Serrano M, et al. Inborn errors of metabolism and motor disturbances in children. J Inherit Metab Dis. 2009;**32**(5):618–29.
3. Saudubray JM, Sedel F, Walter JH. Clinical approach to treatable inborn metabolic diseases: An introduction. J Inherit Metab Dis. 2006;**29**(2–3):261–74.
4. Parker CC, Evans OB. Metabolic disorders causing childhood ataxia. Semin Pediatr Neurol. 2003;**10**(3):193–9.
5. van Gaalen J, Kerstens FG, Maas RP, Harmark L, van de Warrenburg BP. Drug-induced cerebellar ataxia: A systematic review. CNS Drugs. 2014;**28**(12):1139–53.
6. Gray RG, Preece MA, Green SH, et al. Inborn errors of metabolism as a cause of neurological disease in adults: An approach to investigation. J Neurol Neurosurg Psychiatry. 2000;**69**(1):5–12.
7. Espinos C, Pineda M, Martinez-Rubio D, et al. Mutations in the urocanase gene *UROC1* are associated with urocanic aciduria. J Med Genet. 2009;**46**(6):407–11.
8. Cheon CK, Lee BH, Ko JM, Kim HJ, Yoo HW. Novel mutation in *SLC6A19* causing late-onset seizures in Hartnup disorder. Pediatr Neurol. 2010;**42**(5):369–71.
9. Strauss KA, Puffenberger EG, Morton DH. Maple syrup urine disease. GeneReviews®. 2006;Jan 30 (updated May 9, 2013).
10. Simon E, Flaschker N, Schadewaldt P, Langenbeck U, Wendel U. Variant maple syrup urine disease (MSUD): The entire spectrum. J Inherit Metab Dis. 2006;**29**(6):716–24.
11. Superti-Furga A, Hoffmann GF. Glutaric aciduria type 1 (glutaryl-CoA-dehydrogenase deficiency): Advances and unanswered questions. Report from an international meeting. Eur J Pediatr. 1997;**156**(11):821–8.
12. Rowe PC, Newman SL, Brusilow SW. Natural history of symptomatic partial ornithine transcarbamylase deficiency. N Engl J Med. 1986;**314**(9):541–7.
13. Patel KP, O'Brien TW, Subramony SH, Shuster J, Stacpoole PW. The spectrum of pyruvate dehydrogenase complex deficiency: Clinical, biochemical and genetic features in 371 patients. Mol Genet Metab. 2012;**106**(3):385–94.
14. Debray FG, Lambert M, Gagne R, et al. Pyruvate dehydrogenase deficiency presenting as intermittent isolated acute ataxia. Neuropediatrics. 2008;**39**(1):20–3.
15. Marin-Valencia I, Roe CR, Pascual JM. Pyruvate carboxylase deficiency: Mechanisms, mimics and anaplerosis. Mol Genet Metab. 2010;**101**(1):9–17.

16. Sofou K, de Coo IFM, Ostergaard E, et al. Phenotype–genotype correlations in Leigh syndrome: New insights from a multicentre study of 96 patients. J Med Genet. 2018;**55**(1):21–7.

17. Wolf B. Biotinidase deficiency. GeneReviews®. 2000; Mar 24 (updated Jun 9, 2016).

18. Wolf B. "Think metabolic" in adults with diagnostic challenges: Biotinidase deficiency as a paradigm disorder. Neurol Clin Pract. 2017;**7**(6):518–22.

19. Tabarki B, Al-Shafi S, Al-Shahwan S, et al. Biotin-responsive basal ganglia disease revisited: Clinical, radiologic, and genetic findings. Neurology. 2013;**80**(3):261–7.

20. Leen WG, Klepper J, Verbeek MM, et al. Glucose transporter-1 deficiency syndrome: The expanding clinical and genetic spectrum of a treatable disorder. Brain. 2010;**133**(Pt 3):655–70.

21. Leen WG, Mewasingh L, Verbeek MM, et al. Movement disorders in GLUT1 deficiency syndrome respond to the modified Atkins diet. Mov Disord. 2013;**28**(10):1439–42.

22. Verrips A, van Engelen BG, Wevers RA, et al. Presence of diarrhea and absence of tendon xanthomas in patients with cerebrotendinous xanthomatosis. Arch Neurol. 2000;**57**(4):520–4.

23. Yahalom G, Tsabari R, Molshatzki N, et al. Neurological outcome in cerebrotendinous xanthomatosis treated with chenodeoxycholic acid: Early versus late diagnosis. Clin Neuropharmacol. 2013;**36**(3):78–83.

24. Hentati F, El-Euch G, Bouhlal Y, Amouri R. Ataxia with vitamin E deficiency and abetalipoproteinemia. Handb Clin Neurol. 2012;**103**:295–305.

25. Seo GH, Kim YM, Oh SH, et al. Biochemical and molecular characterisation of neurological Wilson disease. J Med Genet. 2018;**55**(9):587–93.

26. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol. 2015;**14**(1):103–13.

27. Vroegindeweij LHP, Langendonk JG, Langeveld M, et al. New insights in the neurological phenotype of aceruloplasminemia in Caucasian patients. Parkinsonism Relat Disord. 2017;**36**:33–40.

28. Poli L, Alberici A, Buzzi P, Marchina E, Lanari A, Arosio C, et al. Is aceruloplasminemia treatable? Combining iron chelation and fresh-frozen plasma treatment. Neurol Sci. 2017;**38**(2):357–60.

29. Wanders RJA, Waterham HR, Leroy BP. Refsum disease. GeneReviews®. 2006;Mar 20 (updated Jun 11, 2015).

30. Patterson MC, Mengel E, Wijburg FA, et al. Disease and patient characteristics in NP-C patients: Findings from an international disease registry. Orphanet J Rare Dis. 2013;**8**:12.

31. Emmanuele V, Lopez LC, Berardo A, et al. Heterogeneity of coenzyme Q10 deficiency: Patient study and literature review. Arch Neurol. 2012;**69**(8):978–83.

32. Balreira A, Boczonadi V, Barca E, et al. *ANO10* mutations cause ataxia and coenzyme Q(1)(0) deficiency. J Neurol. 2014;**261**(11):2192–8.

33. Raymond GV, Moser AB, Fatemi A. X-linked adrenoleukodystrophy. GeneReviews®. 1999;Mar 26 (updated Feb 15, 2018).

34. Mahmood A, Berry J, Wenger DA, et al. Metachromatic leukodystrophy: A case of triplets with the late infantile variant and a systematic review of the literature. J Child Neurol. 2010;**25**(5):572–80.

35. Sedel F, Tourbah A, Fontaine B, et al. Leukoencephalopathies associated with inborn errors of metabolism in adults. J Inherit Metab Dis. 2008;**31**(3):295–307.

36. Kwon JM, Matern D, Kurtzberg J, et al. Consensus guidelines for newborn screening, diagnosis and treatment of infantile Krabbe disease. Orphanet J Rare Dis. 2018;**13**:30.

37. Malm D, Nilssen O. Alpha-mannosidosis. Orphanet J Rare Dis. 2008;**3**:21.

38. Mercimek-Mahmutogly S, Salamons GS. Creatine deficiency syndromes. GeneReviews®. 2009;Jan 15 (updated Dec 10, 2015).

39. Hyland K, Shoffner J, Heales SJ. Cerebral folate deficiency. J Inherit Metab Dis. 2010;**33**(5):563–70.

40. Synofzik M, Srulijes K, Godau J, Berg D, Schols L. Characterizing POLG ataxia: Clinics, electrophysiology and imaging. Cerebellum. 2012;**11**(4):1002–11.

41. Steenweg ME, Jakobs C, Errami A, et al. An overview of L-2-hydroxyglutarate dehydrogenase gene (*L2HGDH*) variants: A genotype–phenotype study. Hum Mutat. 2010;**31**(4):380–90.

42. Miossec-Chauvet E, Mikaeloff Y, Heron D, et al. Neurological presentation in pediatric patients with congenital disorders of glycosylation type Ia. Neuropediatrics. 2003;**34**(1):1–6.

43. Drouin-Garraud V, Belgrand M, Grunewald S, et al. Neurological presentation of a congenital disorder of glycosylation CDG-Ia: Implications for diagnosis and genetic counseling. Am J Med Genet. 2001;**101**(1):46–9.

44. Maegawa GH, Stockley T, Tropak M, et al. The natural history of juvenile or subacute GM2 gangliosidosis: 21 new cases and literature review of 134 previously reported. Pediatrics. 2006;**118**(5):e1550-62.

45. Thorburn DR, Rahman J, Rahman S. Mitochondrial DNA-associated Leigh syndrome and NARP. GeneReviews®. 2003;Oct 30 (updated Sep 28, 2017).

46. Craig K, Elliott HR, Keers SM, et al. Episodic ataxia and hemiplegia caused by the 8993 T→C mitochondrial DNA mutation. J Med Genet. 2007;**44**(12):797–9.

47. Yamashita T, Mitsui J, Shimozawa N, et al. Ataxic form of autosomal recessive PEX10-related peroxisome biogenesis disorders with a novel compound heterozygous gene mutation and characteristic clinical phenotype. J Neurol Sci. 2017;**375**:424–9.

48. Lapalme-Remis S, Lewis EC, De Meulemeester C, et al. Natural history of succinic semialdehyde dehydrogenase deficiency through adulthood. Neurology. 2015;**85**(10):861–5.

49. Pearl PL, Wiwattanadittakul N, Roullet JB, Gibson KM. Succinic semialdehyde dehydrogenase deficiency. GeneReviews®. 2004;May 5 (updated Apr 28, 2016).

50. van der Veen S, Zutt R, Elting JWJ, et al. Progressive myoclonus ataxia: Time for a new definition? Mov Disord. 2018;**33**(8):1281–6.

51. Seyrantepe V, Poupetova H, Froissart R, et al. Molecular pathology of *NEU1* gene in sialidosis. Hum Mutat. 2003;**22**(5):343–52.

52. Turnbull J, Tiberia E, Striano P, et al. Lafora disease. Epileptic Disord. 2016;**18**(S2):38–62.

53. DiMauro S, Hirano M. MERRF. GeneReviews®. 2003; Jun 3 (updated Jan 29, 2015).

54. Mancini C, Nassani S, Guo Y, et al. Adult-onset autosomal recessive ataxia associated with neuronal ceroid lipofuscinosis type 5 gene (*CLN5*) mutations. J Neurol. 2015;**262**(1):173–8.

55. Roshan Lal T, Sidransky E. The spectrum of neurological manifestations associated with Gaucher disease. Diseases. 2017;**5**(1).

Chapter 8

A Phenomenology-Based Approach to Inborn Errors of Metabolism with Dystonia

Hendriekje Eggink, Anouk Kuiper, Tom J. de Koning, Martje E. van Egmond, and Marina A. J. Tijssen

Introduction

Historically, childhood-onset, isolated, generalized, and inherited forms of dystonia (such as DYT1 dystonia) and adult-onset, isolated, focal, mainly idiopathic dystonias have been emphasized. There is, however, growing awareness of neurometabolic disorders being etiological for both childhood-onset and adult-onset dystonia. The dystonia syndromes associated with inborn errors of metabolism (IEMs) usually have an early and (sub-) acute onset, progressive course, and generalized distribution [1]. In general, patients with an IEM do not present with isolated dystonia, but have additional neurological and non-neurological symptoms. This combined or mixed presentation of dystonia and other symptoms may suggest an IEM as the underlying cause. Recognition of dystonia as a clinical feature of a given IEM is essential for diagnostic and targeted treatment strategies, because IEMs include a group of treatable disorders. In addition, symptomatic treatment of dystonia is important as movement disorders negatively impact on the quality of life and daily functioning in patients with an IEM [2].

This chapter on neurometabolic disorders as causes of dystonia in both children and adults starts with a description of the concept of dystonia in general, including phenomenology and classification. Next, a general diagnostic approach including alternative (non-metabolic) causes in patients presenting with dystonia is presented. Finally, the groups of IEMs associated with dystonia are discussed, including clinical clues, diagnostic tests, and treatment options.

Dystonia

Definition, Pathophysiology, and Prevalence

Dystonia is defined as a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions in one or more body parts causing abnormal, often repetitive, movements, abnormal posturing, or both. These movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and it is associated with an overflow of muscle activation [3]. Dystonia is a clinical diagnosis that can be caused by a wide range of genetic and acquired etiologies. The exact pathophysiology of dystonia is unknown. The basal ganglia are known to play an important role, as lesions within these nuclei may lead to dystonia. Recent imaging and neurobiological studies indicate a network disorder with involvement of the basal ganglia, thalamocortical connections, and the cerebellum. Dysfunction in any part of this network can give rise to dystonia [4].

Although the exact prevalence of dystonia is not known, it appears to be the most frequently diagnosed hyperkinetic movement disorder after tics and tremor. A meta-analysis of isolated forms of dystonia showed a prevalence of 16.4 in 100,000 [5]. This does not, however, include generalized and mixed forms of dystonia and probably it is an underestimate of the true prevalence. Among the extrapyramidal movement disorders associated with IEMs, dystonia is thought to be among the most prevalent [6].

Classification and Diagnosis

The heterogeneous nature of dystonic syndromes has led to the development of a classification system. In this system, dystonia is classified according to two axes: clinical manifestation and etiology (Table 8.1) [3].

Axis I, the clinical manifestation of dystonia, is based on five clinical characteristics: age at onset (from neonatal to late adulthood), body distribution (focal, segmental, multifocal, hemidystonia, or generalized), temporal pattern (diurnal variability, progression over time), coexistence of other movement

Table 8.1 Dystonia classification proposed by Albanese et al. [3]

Axis I. Clinical characteristics of dystonia	Axis II. Etiology
Age at onset • Infancy (birth to 2 years) • Childhood (3–12 years) • Adolescence (13–20 years) • Early adulthood (21–40 years) • Late adulthood (>40 years)	**Nervous system pathology** • Evidence of degeneration • Evidence of structural (often static) lesions • No evidence of degeneration or structural lesion
Body distribution • Focal • Segmental • Multifocal • Generalized (with or without leg involvement) • Hemidystonia	**Inherited or acquired** *Inherited*: • Autosomal-dominant • Autosomal recessive • X-linked recessive • Mitochondrial *Acquired*: • Perinatal brain injury • Infection • Drug • Toxic • Vascular • Neoplastic • Brain injury • Psychogenic *Idiopathic*: • Sporadic • Familial
Temporal pattern *Disease course*: • Static • Progressive *Variability*: • Persistent • Action-specific • Diurnal • Paroxysmal	
Associated features *Isolated dystonia or combined with another movement disorder*: • Isolated dystonia • Combined dystonia	
Occurrence of other neurological or systemic manifestations	

disorders (isolated versus combined forms), and the presence of other neurological manifestations (e.g., spasticity or epilepsy). The classification of the clinical characteristics ultimately leads to the definition of a "dystonia syndrome." This approach has been further developed by Fung and colleagues, who provided a list of 27 dystonic syndromes with potential etiologies to guide diagnostic testing [7].

Axis II of the dystonia classification focuses on etiology, as there are many possible acquired and genetic (including neurometabolic) causes. In addition to acquired and genetic causes, a third group consists of idiopathic forms. Young-onset dystonia is more likely to have an identifiable (acquired or genetic) cause, while many adult-onset focal dystonias are idiopathic.

Clinical Diagnostic Approach Toward a Patient with Dystonia

The recognition of dystonia and subsequent classification of the dystonic syndrome according to other neurological and non-neurological symptoms can be challenging, but it is essential to identify a diagnosis. A systematic stepwise diagnostic approach is helpful in a patient presenting with dystonia (Figure 8.1) (adjusted from van Egmond et al. [8]). The basis of this approach is that after ruling out the acquired forms of dystonia, the diagnostic yield for treatable neurometabolic causes is higher. Following prioritization of treatable causes, a genetic screening of all known inherited forms of dystonia is pursued. This again

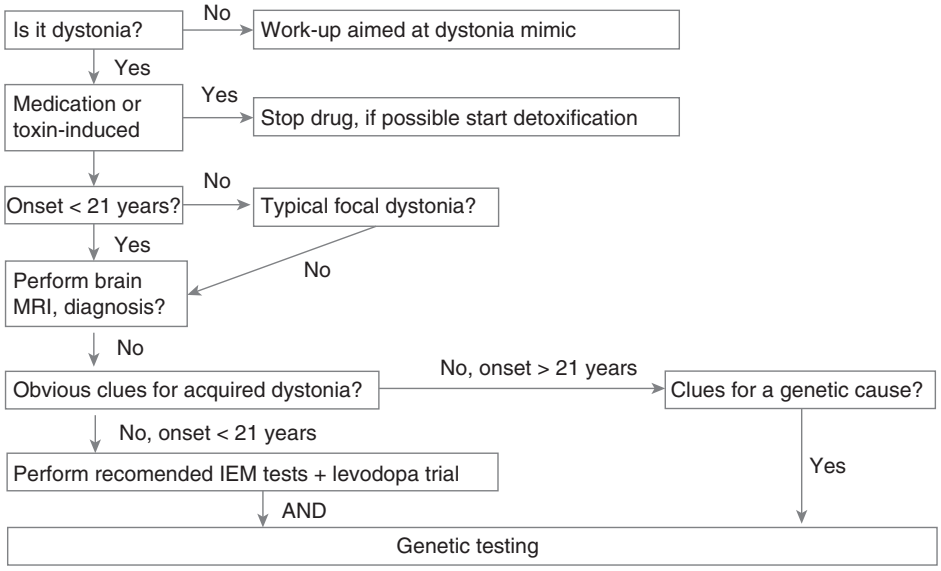

Figure 8.1 Diagnostic approach to dystonia with unknown cause.

includes many IEM presenting with dystonia. Each step of this approach will be discussed.

Is It Dystonia?

The first essential question in the diagnostic process is whether the observed symptoms are either dystonia or "dystonia mimics." For example, congenital muscular torticollis and Sandifer syndrome are conditions that may mimic dystonia in young children, whereas scoliosis or trochlear nerve palsy are known causes of pseudo-dystonia in both children and adults. Further, immaturity of the central nervous system can lead to "physiological" movement disorders, which are difficult to distinguish from "true" involuntary movements in young children [9].

Could the Dystonia Be Medication-Induced or Caused by Toxic Agents?

There are several drugs (dopamine-receptor blockers or stimulants, tricyclic antidepressants, antihistamines, serotonin reuptake inhibitors, cholinergic agonists, antiseizure drugs, antimalarial drugs, calcium channel blockers, disulfiram, lithium, and cocaine) and toxins (carbon monoxide, cyanide, manganese, methanol, and organophosphates) associated with the onset of dystonia. These agents should be ruled out before continuing the diagnostic process [8].

Childhood-Onset or Adult-Onset?

There is a clear relationship between the age at onset of dystonia and the clinical course and possible etiologies of the syndrome [3]. Therefore, the diagnostic approach depends on the age of onset. Patients with an onset before 21 years of age follow the diagnostic algorithm outlined in Figure 8.1. In patients with a typical focal dystonia manifesting above 21 years (usually above 40 years of age), additional investigations can be minimized, as these forms are mostly idiopathic, limiting the added value of further diagnostic investigations. These isolated focal dystonias include blepharospasm, oromandibular dystonia, Meige syndrome, cervical dystonia, task-specific dystonia, and isolated spasmodic dysphonia.

Neuroimaging

After ruling out a medication or toxin-induced dystonia, neuroimaging is the next step. Brain MRI should always be obtained in young-onset dystonia. For adult-onset focal dystonia, an MRI is only indicated in patients with additional "red flags." These red flags are an acute onset or progressive course of symptoms, hemidystonia, and atypical distributions (in one limb without task-specificity, generalized or isolated trunk dystonia). Basal ganglia abnormalities may be seen on brain MRI in neurometabolic disorders, such as Wilson disease, pyruvate dehydrogenase (PDH) deficiency, co-enzyme Q10 deficiency, cerebral folate

deficiency, thiamine transporter deficiency (biotin–thiamine-responsive basal ganglia disease), organic acidurias, and forms of neurodegeneration with brain iron accumulation (NBIA; i.e. the "eye of the tiger" sign due to pantothenate kinase-associated neurodegeneration [PKAN]) [6]. This can help with distinguishing the type of IEM before additional targeted biochemical or genetic testing.

Obvious Clues for Acquired Dystonia?

Acquired forms of dystonia mainly involve dystonia due to structural brain lesions, cerebral palsy, or autoimmune-associated dystonia. In children, cerebral palsy is the most frequent cause of dystonia, defined as a group of permanent disorders causing impairment of movement and posture, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain [10]. An abnormal birth or perinatal history is a positive clue for the diagnosis of cerebral palsy and brain MRI may reveal structural lesions [11]. Important clues for an autoimmune-associated dystonia are an acute or rapidly progressive course, unilateral symptoms (hemidystonia), and dystonia accompanied by psychiatric symptoms, seizures, or signs of a meningoencephalitis. In case the brain MRI does not show any structural lesions, additional investigations such as autoantibodies in the serum and cerebral spinal fluid (CSF) are recommended [8].

Clinical Clues That Might Suggest an IEM

In IEMs, dystonia is often part of a more complex, mixed movement disorder phenotype. Dystonia can present together with parkinsonism, ataxia, myoclonus, tremor, and, less common, chorea. Further, the dystonic symptoms are predominantly embedded in a complex clinical picture with other neurological and non-neurological symptoms, such as eye movement abnormalities, neuropathy, muscle weakness, dementia, psychiatric problems, organomegaly, ophthalmological or skin abnormalities, and deafness [12].

Dystonia as the presenting symptom of IEMs typically involves a generalized form of dystonia, with an early and acute or subacute onset and a progressive course. Other clues include diurnal variation, in which symptoms worsen toward the end of the day or with fasting [1].

Although the presence of these clues may lead in the right direction, the varieties of clinical presentations in IEM patients, and the importance of not missing a treatable condition, imply that all children presenting with dystonia of a non-acquired cause should undergo additional investigations to look for an IEM. Important IEMs for which the targeted treatment options exist include dopamine-responsive dystonia (DRD), the organic acidurias, glucose transporter type 1 (GLUT1) deficiency syndrome, and lysosomal storage disorders [13]. In these patients, early treatment may lead to stabilization or reduction of existing symptoms.

Because of the clinical complexity of dystonia in IEMs, often embedded in several other neurological and non-neurological symptoms, a multidisciplinary approach can have added value in the process of classification [14]. Neurometabolic disorders with dystonia are naturally at the interface of different specialists, including movement disorder experts, (pediatric) neurologists, metabolic specialists, and clinical geneticists.

Biochemical Investigations and a Levodopa Trial

Although the availability, turn-around time, and costs of next-generation sequencing (NGS) are improving, traditional biochemical tests in plasma, urine, and CSF often remain the fastest manner to obtain a diagnosis. Performing these tests is of critical value in treatable IEM, as a faster diagnosis means an earlier start of targeted treatment. It is therefore recommended to conduct the biochemical tests and NGS in parallel. An overview of the recommended biochemical tests can be found in Table 8.2 (adapted from van Egmond et al. [8]).

In addition to biochemical tests, a diagnostic trial of levodopa in all childhood-onset dystonia patients is important to reveal DRD. Recently, this diagnostic step was questioned based on the relatively low prevalence of DRD and in light of rapidly achievable results of NGS [15]. It is also important to realize that levodopa can also reduce dystonic symptoms in non-classic DRD dystonia (i.e. aromatic L-amino acid decarboxylase deficiency or GLUT1 deficiency) [15]. The recommended starting dose is 1 mg/kg per day with a gradual increase until the complete benefit or dose-limiting effects occur [16].

In adults, IEMs are relatively rare causes of dystonia and the usually slowly progressive course gives the clinician the possibility to wait for genetic test results and limits the advantages of biochemical tests.

Table 8.2 Treatable IEMs that present with dystonia: biochemical testing and treatment

Disorder	Biochemical test	Treatment
Glutaric aciduria type 1 (GA-1)	Organic acids (U), acylcarnitines (P/U)	Lysine restriction, carnitine supplementation, emergency treatment during intercurrent illness
Propionic aciduria (PA)	Organic acids (U), acylcarnitines (P), lactate, ammonia, blood gas (P)	Dietary protein restriction, carnitine supplementation Emergency treatment during intercurrent illness
Methylmalonic aciduria (MMA; mutase-deficient type)	Organic acids (U), acylcarnitines (P), methylmalonic acid (P), lactate, ammonia, blood gas (P)	Dietary protein restriction, carnitine supplementation Emergency treatment during intercurrent illness
Cobalamin deficiencies	Organic acids (U), homocysteine (P)	Hydroxy-/methyl- or cyanocobalamin, in some cases protein restriction, in some cases betaine
Homocystinuria	Homocysteine (P)	Methionine restriction, betaine in some cases Pyridoxine
Ornithine transcarbamylase (OTC)-deficiency	Amino acids (P), orotic acid (U)	Protein-restricted diet with arginine supplementation, sodium benzoate, citrulline
Maple syrup urine disease	Organic acids (U), amino acids (P)	Leucine-restricted diet, in some patients thiamine supplementation
AGAT deficiency	Creatine, creatinine, guanidinoacetate, (P/U)	Creatine
GAMT deficiency	Creatine, creatinine, guanidinoacetate, (P/U)	Creatine, ornithine, dietary arginine restriction
Tyrosine hydroxylase deficiency	HVA, 5-HIAA (CSF) Pterins (CSFU)	Levodopa/carbidopa
GTP cyclohydrolase 1 (GTPCH1) deficiency	HVA, 5-HIAA (CSF) Pterins (CSFU)	Levodopa/carbidopa (dominant form) Levodopa/carbidopa 5-hydroxytryptophan tetrahydrobiopterin (recessive form)
Dihydropteridine dehydrogenase (DHPR) deficiency	HVA, 5-HIAA (CSF Pterins (CSFU) Amino acids/phenylalanine (P)	Levodopa/carbidopa, 5-hydroxytryptophan, tetrahydrobiopterin, folinic acid, phenylalanine restricted diet
6-Pyruvoyltetrahydrobiopterin synthase (PTPS) deficiency	HVA, 5-HIAA (CSF) Pterins (CSF/U Amino acids/phenylalanine (P)	Levodopa/carbidopa, 5-hydroxytryptophan, tetrahydrobiopterin
Aromatic L-amino acid decarboxylase (AADC) deficiency	HVA, 5-HIAA (CSF Vanillactic acid (U)	Levodopa/dopamine agonists, pyridoxine, MAO inhibitors
Sepiapterin reductase deficiency	Sepiapterin (CSF)	Levodopa/carbidopa, 5-hydroxytryptophan
Glucose transporter type 1 (GLUT1) deficiency	Glucose (CSF)	Ketogenic diet
Cerebral folate deficiency	5-methyltetrahydrofolate (CSF)	Folinic acid
Biotinidase deficiency	Biotinidase activity (P)	Biotin
Biotin–thiamine-responsive basal ganglia disease (thiamine transporter deficiency)	Organic acids (U) Lactate (P)	Biotin and thiamine
Dystonia with brain manganese accumulation	Manganese (P)	Intravenous disodium calcium, ethylenediaminetetraacetic acid (EDTA)
Wilson disease	Copper, ceruloplasmin (P/U)	D-penicillamine/trientine, zinc, sodium dimercaptopropanesulfonate (DMPS)
Pyruvate dehydrogenase complex deficiency	Pyruvate, lactate (P/CSF)	Thiamine, ketogenic diet, dichloroacetate, triheptanoin
Ataxia with vitamin E deficiency	Vitamin E (alpha-tocopherol) (P)	Vitamin E (alpha-tocopherol)

Table 8.2 (cont.)

Disorder	Biochemical test	Treatment
Abetalipoproteinemia (Bassen–Kornzweig syndrome)	Cholesterol, low-/very low-density lipoproteins (P)	Vitamin E, fat reduced diet
Cerebrotendinous xanthomatosis	Cholestanol (P)	Chenodeoxycholic acid
Lesch–Nyhan disease	Uric acid (P/U)	Allopurinol
Molybdenum cofactor (sulfite oxidase) deficiency	Sulfite, hypoxanthine, xanthine (U), S-sulfocysteine (P/U), uric acid, amino acids (P)	Cyclic pyranopterin monophosphate for type A molybdenum cofactor deficiency
Niemann–Pick disease type C	Oxysterols, chitotriosidase (P)	Miglustat
Coenzyme Q10 deficiency	Coenzyme Q10 in muscle	Coenzyme Q10
Classic galactosemia	Galactitol (U) Erythrocyte galactose-1-phosphate, galactose (P)	Lactose restricted diet

Abbreviations: CSF (cerebrospinal fluid); 5-HIAA, 5-hyroxyindolacetic acid; HVA, homovanillic acid; P (plasma); U (urine).

Next-Generation Sequencing

The rapid developments in NGS now enable us to screen for a large number of genes at once, instead of sequencing genes individually. Currently used techniques include sequencing of the whole genome (whole-genome sequencing, WGS), the coding regions (or exomes) of each gene (whole-exome sequencing, WES), or sequencing of a panel of genes currently known to be associated with dystonia (multi-gene panel). A list of dystonia-associated genes is provided by van Egmond et al. [8].

After eliminating an acquired etiology, NGS is recommended in childhood-onset dystonia patients. In adult-onset dystonia, clues that might suggest a genetic cause are onset before the age of 40 years, a positive family history, a combined (not isolated) dystonia, and the presence of other neurological abnormalities. The application of NGS in movement disorders leads to a higher percentage of genetically defined dystonias [14]. A widespread use of NGS in patients with movement disorders is very likely to lead to more frequently detected and a broader phenotype of IEMs [17].

To obtain the highest possible yield of NGS techniques, close cooperation between clinical geneticists and the treating neurologist or metabolic specialist is essential. Results need to be carefully interpreted in order to decide whether a mutation is pathogenic or an incidental and unrelated finding [18]. In addition, some disorders might be missed with NGS, especially trinucleotide repeat disorders, but also deletions in genes are not always detected. In addition to routine NGS diagnostics for dystonia, mitochondrial DNA (mtDNA) can be tested as there are mitochondrial disorders with mutations in the mtDNA known to be associated with dystonia (i.e. mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes [MELAS] syndrome).

Neurometabolic Disorders with Dystonia

Distinctive features of the most notable groups of neurometabolic disorders that can present with dystonia are described. Table 8.2 summarizes the treatable IEMs presenting with dystonia, with an overview of the corresponding biochemical tests and disease-specific treatments.

Neurotransmitter Disorders

In neurotransmitter disorders, movement disorders are directly related to the biochemical defect. Biochemical tests to identify neurotransmitter disorders include dopaminergic, serotonergic, and tetrahydrobiopterin markers in CSF [19]. DRD is a well-known neurotransmitter disorder presenting with dystonia as the main symptom. Autosomal-dominant GTP cyclohydrolase 1 (GTPCH1) deficiency (or Segawa disease) is the most prevalent form. In classic DRD, dystonia arises from a dopaminergic deficit and a good response to levodopa-substitution therapy is one of the hallmarks. The dystonia has an early onset, usually starts in one limb and gradually spreads over the body. There is diurnal fluctuation and symptoms tend to worsen over the day and are associated with fatigue. Besides dystonia,

parkinsonian features are part of the clinical picture, particularly as adult-onset manifestations. Symptom severity is highly variable [20].

The rare recessive forms of DRD, sepiapterin reductase deficiency and tyrosine hydroxylase deficiency, usually have a more complex and severe phenotype with onset in infancy or early childhood. Besides the dystonic–hypokinetic picture, these patients also have an encephalopathic presentation and oculogyric crises. Other monoamine neurotransmitter disorders such as 6-pyruvoyltetrahydrobiopterin synthase (PTPS) deficiency, dihydropteridine dehydrogenase (DHPR) deficiency, and aromatic L-amino acid decarboxylase (AADC) deficiency can also cause dystonia and parkinsonism, frequently with a more complex phenotype and less obvious response to treatment with levodopa [19].

Metal Storage Disorders

The basal ganglia appear particularly vulnerable to the accumulation of different metal metabolites. The abnormal storage of copper in Wilson disease, iron accumulation in neurodegeneration with brain iron accumulation (NBIA), and manganese accumulation caused by *SLC30A10* mutations (dystonia with brain manganese accumulation), all present with dystonia. An early diagnosis of Wilson disease and dystonia with brain manganese accumulation is of particular importance because symptoms can be prevented by timely treatment. Neurological symptoms usually occur in Wilson disease in the second decade. Beside the presence of dystonia, Wilson disease and dystonia with brain manganese accumulation are known for involvement of the liver (elevated serum transaminases) and the Kayser–Fleischer corneal ring. The biochemical abnormalities are a low serum copper and ceruloplasmin for Wilson disease and hypermanganesemia in plasma for dystonia with brain manganese accumulation [21, 22].

PKAN, caused by mutations in the *PANK2* gene, is the most prevalent form of NBIA associated with dystonia. The disorder is characterized by generalized dystonia, often starting in childhood with dystonic gait abnormalities and prominent dystonia in the oromandibular region. Accumulation of iron in the globus pallidus results in a typical MRI pattern known as the "eye of the tiger" sign (pallidal hypointensity with central hyperintensity on T2 images). In addition to PKAN, other NBIA disorders such as *PLA2G6*-associated neurodegeneration can also present with dystonia [23].

Intoxication-Like IEMs

Several intoxication-like IEMs can give rise to dystonia, mostly caused by encephalopathic crises following intercurrent illnesses. Acute metabolic decompensation leads to basal ganglia lesions that are evident on brain MRI. The most frequent condition in this group is glutaric aciduria type 1 (GA-1). If untreated, the majority of patients suffer from an encephalopathic crisis before the age of three. This is often the first presentation of the disorder and can give rise to a severe generalized and disabling dystonia, which is irreversible. Fortunately, the occurrence of these acute crises can be largely prevented by timely treatment with a protein-restricted diet, medication, and vitamins, with a special emergency regime during periods of illness or fasting [24]. Besides the acute encephalopathic crises that lead to dystonia, a more gradual and later onset of dystonia is also possible, even in adulthood. Other organic acidurias that are well known to be associated with dystonia include propionic aciduria (PA) and methylmalonic aciduria (MMA). As with GA-1, dystonia is often the result of a metabolic crisis with an encephalopathic syndrome. However, while in GA-1 dystonia is the main presenting symptom, PA and MMA are characterized by other systemic features such as renal failure, cardiomyopathy, and pancreatitis [25].

Other intoxication-like IEMs or disorders of amino acid metabolism such as isovaleric acidemia, maple syrup urine disease, homocystinuria, and Hartnup disease can be associated with dystonia [13].

Lysosomal Storage Disorders

One of the best-known lysosomal storage disorders presenting with movement disorders is Niemann–Pick disease type C (NPC). NPC can lead to a spectrum of movement disorders, but a combination of cerebellar ataxia and dystonia of mainly the upper limbs and face is often described, as well as myoclonus [26]. One of the most distinct features is the frequently present vertical supranuclear gaze palsy. In addition, progressive cognitive decline and acute psychosis in adolescents and young adults is a well-known presentation [27]. In addition to NPC, GM1 type 3 gangliosidosis or fucosidosis can present with dystonia [28, 29]. Classically, lysosomal storage disorders are associated with coarse facial features and visceral organ involvement, but it is important to realize that in adults these signs can be subtle or absent.

Mitochondrial Disorders

Mitochondrial disorders form a clinically heterogeneous group as a result of disturbed cellular energy metabolism. Because the basal ganglia have a relatively high energy demand, it is not surprising that many mitochondrial disorders can lead to dystonia. Dystonia is common in children with a mitochondrial disorder with a reported prevalence up to 92% [30]. In adults, a combination of parkinsonism and dystonia is often seen. A classic mitochondrial disorder is Leigh syndrome, or subacute necrotizing encephalomyelopathy. During an intercurrent illness, encephalopathic decompensation leads to highly elevated levels of lactic acid and basal ganglia or brainstem lesions visible on brain MRI. Clinically, there is a broad range of neurological symptoms, including developmental delay, intellectual disability, and several movement disorders including dystonia. Systemic manifestations comprise cardiomyopathy, renal dysfunction, and liver involvement. The onset of symptoms is usually within the first year of life, but adult-onset cases have been described [31].

Importantly, in rare cases, Leigh syndrome is caused by a treatable defect in the cerebral thiamine transporter gene (*SLC19A3*). Clinically, this disorder presents in childhood with a Leigh-like syndrome consisting of acute encephalopathy, dystonia, and seizures. Brain MRI shows lesions in the cerebral cortex, basal ganglia, thalami, brainstem, and cerebellum. Timely treatment with thiamine and biotin has a positive effect [32]. Therefore, a therapeutic trial with thiamine and biotin can be considered in patients with clinical and radiological signs of Leigh syndrome, while awaiting further diagnostic tests.

Another mitochondrial disorder associated with dystonia is caused by mutations in the mitochondrial DNA polymerase gamma gene (*POLG*). The phenotype is heterogeneous, with dystonia being present in approximately a third of patients. There is also a high prevalence of other movement disorders such as ataxia, chorea, and myoclonus. Other characteristic signs are external ophthalmoplegia, areflexia, and loss of vibration sense [33].

Pyruvate dehydrogenase complex deficiency presents in infancy with paroxysmal dystonia, neuropathic (or sensory) ataxia, and epilepsy. It is an important diagnosis to consider as a ketogenic diet can substantially improve the paroxysmal dystonia and seizures [34].

Further, a clinical clue that should lead to the suspicion of a mitochondrial disorder is the combination of dystonia and deafness. Deafness–dystonia syndromes are for example MEGDEL syndrome (*SERAC1* mutations) and Mohr–Tranebjaerg syndrome (*TIMM8A* mutations) [13].

GLUT1 Deficiency

Deficiency of GLUT1 (encoded by the *SLC2A1* gene) is known for paroxysmal dystonia starting in adolescence, which is triggered by exercise or fasting. The more severe classic presentation includes developmental encephalopathy in infancy with intellectual disability, seizures, and movement disorder including ataxia, chorea, and myoclonus. However, in recent years, milder and varying presentations have been described, also with later onset of symptoms of not only paroxysmal, but sustained and generalized dystonia. The ketogenic diet is the mainstay of treatment and can result in strong improvement of symptoms [35].

Other Disorders

Examples of other treatable disorders related to energy metabolism are the creatine biosynthesis disorders L-arginine:glycine amidinotransferase (AGAT) and guanidinoacetate N-methyltransferase (GAMT) deficiency. These disorders are clinically characterized by intellectual disability, speech delay, and epilepsy, but dystonia can also occur. GAMT deficiency tends to lead to a more severe phenotype. Biochemically, the disorders are characterized by changes in guanidinoacetate concentration. Treatment with creatine, ornithine, and arginine supplementation can significantly improve clinical symptoms, including dystonia [36].

Cerebrotendinous xanthomatosis is caused by a deficiency of a mitochondrial enzyme in cholesterol metabolism leading to accumulation of cholestenol, affecting mainly the central nervous system, eyes, tendons, and blood vessels. Systemic features include xanthomas near large tendons as well as early-onset cataracts. Neurological features consist mainly of spasticity, ataxia, neuropathy, and seizures. Some cases have been reported to present with dystonia, manifesting as a rare form of myoclonus-dystonia. The disorder is responsive to chenodeoxycholic acid [37].

Movement disorders may be an important part of the phenotype in galactosemia. Dystonia, together with tremor, was found to be present in a large proportion of adult patients [38].

Table 8.3 Symptomatic treatment options in dystonia

Type of dystonia	Pharmacological options	Surgical interventions
Focal (blepharospasm)	Botulinum toxin injections Benzodiazepines	DBS
Focal (oromandibular)	Botulinum toxin injections Trihexyphenidyl	DBS
Focal (cervical)	Botulinum toxin injections Trihexyphenidyl Benzodiazepine Baclofen	DBS
Segmental and generalized	Levodopa/carbidopa Trihexyphenidyl Baclofen (oral or intrathecal) Benzodiazepines Gabapentin Clonidine	DBS
Paroxysmal kinesigenic dyskinesia (i.e. dystonia)	Carbamazepine	

DBS, deep brain stimulation.

Non-Motor Features and Quality of Life

In almost all genetically defined primary dystonias a broad range of non-motor symptoms is reported. The so-called non-motor symptoms do not only consist of psychiatric symptoms but also involve sleep, cognition, pain, and sensory problems [39]. It is very likely that dystonia occurring in the context of an IEM is associated with significant non-motor symptoms. In DRD, for example, many patients suffer from psychiatric and behavioral problems [40]. Compared to primary dystonias, patients with a neurometabolic cause of their dystonia often have a more compromised or even encephalopathic central nervous system. The mixed neurological phenotype of movement disorders, psychiatric, behavioral, and cognitive problems understandably has a strong impact on quality of life and daily functioning [2].

Treatment of Neurometabolic Dystonia

Dystonia, as well as other movement disorders in IEMs, can greatly impact the perceived quality of life in patients and their caregivers [2]. It is therefore important to try and minimize symptoms as much as possible. Treatment options can be roughly divided into disease-specific therapies in treatable IEMs and symptomatic treatments for dystonia in other IEMs. The focus is on dystonic symptoms, but as mentioned before, dystonia in an IEM is frequently only one of many symptoms present. Attention to other symptoms, including both motor and non-motor features, is of utmost importance to define goals of care and to optimize the quality of life.

Disease-Specific Treatment

An early recognition of treatable IEMs leads to timely treatment that may stabilize, improve, or even prevent the onset of symptoms. An overview of these targeted treatments can be found in Table 8.3. When dystonia is already present, the disease-specific treatment may be combined with symptomatic therapies to minimize the burden.

Symptomatic Treatment

Symptomatic treatment of dystonia in IEMs is similar to management in other forms of dystonia. There are three main categories: pharmacological treatment, botulinum toxin injections, and surgical treatment options. The choice between these options depends on the localization and extent of the dystonic symptoms. For instance, a focal problem may respond better to local botulinum toxin injections, whereas pharmacological or surgical options are preferable in generalized forms of dystonia. Despite the many options, scientific evidence for any intervention remains limited and most experience is based on

case reports or case series, none of them specifically focusing on IEMs [16].

Pharmacological Treatment

A frequently used oral medication in generalized dystonia is the anticholinergic drug **trihexyphenidyl**, which is the only drug supported by a randomized clinical trial showing effectiveness in segmental and generalized forms of dystonia in young patients [41]. Relatively high doses are tolerated in children, starting typically with 1–2 mg/day followed by progressive increased dosages (2mg/week) up to a usual maximum of 50mg/day [16]. Important side effects are dry mouth, urinary retention, and cognitive impairment. **Levodopa** might also be effective in non-DRD dystonias. Muscle relaxants, such as **baclofen**, may be of added value when dystonia coincides with spasticity. The tolerated dose is often limited by side effects such as sedation and weakness, in which cases continuous intrathecal administration by a pump may be considered. Possible serious side effects include respiratory depression and drooling. Benzodiazepines, predominantly **clonazepam**, may be used to terminate painful prolonged periods of dystonia or help with sleep, and may be of added value in combined spastic–dystonic patients [41]. **Gabapentin** and **clonidine** have been shown to significantly improve dystonia severity and improve quality of life in children with secondary dystonia including IEMs [42, 43]. For paroxysmal kinesigenic dyskinesia, as seen in GLUT1 deficiency syndrome, **carbamazepine** or oxcarbazepine in low doses may be effective [44]. Paroxysmal exercise-induced dyskinesia secondary to GLUT1 deficiency may respond to the ketogenic diet or modified Atkins diet. A full overview of the doses of the aforementioned options can be found in the review by Koy et al. [16].

In many cases, however, benefit is often limited and side effects frequently overshadow the positive effects. An extra concern in IEM patients is that a significant percentage of the patients is not able to communicate and therefore cannot express their experienced efficacy as well as side effects. In addition, frequently mentioned side effects such as urinary retention or constipation are already more prevalent in IEM patients, and clinicians and caregivers should therefore be mindful of these and other potential adverse effects.

Botulinum Toxin Injections

For focal forms of dystonia, botulinum toxin injections are the treatment of choice. Although focal dystonia is mainly present in adults, children with generalized dystonia also benefit when there is a local target [16, 45]. For instance, a painful hand dystonia or cervical dystonia can be targeted. Prevention of contractures and permanent deformities is another goal of treatment with botulinum toxin injections. The advantage of these injections is the reduced risk of side effects compared to systemic agents.

Surgical Treatment

For patients with severe and medically refractory dystonia, deep brain stimulation (DBS) can be an effective treatment. This therapy uses a small device similar to a pacemaker, called a neuro-stimulator, to send electrical pulses to discrete regions of the brain. In dystonia, the main target is the internal global pallidus nucleus. Strong (level B) evidence supports the use of DBS for inherited or idiopathic, isolated dystonia (both childhood- and adult-onset) with a mean improvement of dystonia severity of 40–60%. Unfortunately, a lesser benefit is generally seen in dystonia secondary to structural or neurodegenerative causes of brain dysfunction, including IEMs [46]. The reports in IEMs largely comprise case reports, NBIA being most frequently described with both positive and negative results [47]. In addition, there are a few case reports in Lesch–Nyhan disease, GM1 type 3 gangliosidosis, GA-1, homocystinuria, and MMA, again showing variable results [13]. There is an increased awareness that measuring the effectiveness of DBS, and other treatment options, by motor symptom reduction might not adequately reflect the true experienced effect [48]. Pain relief or improved sleep patterns as a result of DBS may be of great impact to the quality of life in severely impaired patients. The application of DBS in neurometabolic disorders should be evaluated on a case-by-case basis. Expectations should be discussed and careful counseling of the patient and/or caregivers should be provided.

Status Dystonicus

An important presentation of dystonia that should be recognized and treated as soon as possible is status dystonicus, or dystonic storm, recently defined as "a movement disorder emergency characterized by severe episodes of generalized or focal dystonia with or without other hyperkinetic movements that have necessitated urgent hospital admission because of the direct life-threatening complications of these movements, regardless of the patient's neurological condition at baseline" [49]. In this emergency situation, a severe worsening of dystonia leads to discomfort interfering

with sleep, and may lead to potentially lethal metabolic disarrangements including hyperthermia, rhabdomyolysis, and multi-organ failure when untreated [50]. It is important to realize that in approximately 67% of the status dystonicus, a trigger can be identified (e.g. infection, medication changes). The current management standard of status dystonicus is by the ABCD-approach: address precipitants, begin supportive care, calibrate sedation, and dystonia-specific medications. A constructive overview of the management is nicely summarized by Lumsden et al. [50].

Conclusions

Dystonia is an important symptom occurring in a broad range of metabolic disorders. Correct phenotyping of the motor symptoms remains crucial and it is the first step in diagnosing an underlying condition. Neurometabolic causes for dystonia include a group of treatable disorders, which should be prioritized during the diagnostic process. With new options for the treatment and prevention of acute and life-threatening symptoms in many IEMs, patients are surviving longer, and a focus is shifting toward the management of long-term complications and neurological sequelae. Here we foresee an important role for metabolic specialists that treat adults with IEMs. Awareness for the occurrence of dystonia and other movement disorders in neurometabolic diseases is of further importance since these symptoms can have a substantial impact on the quality of life and daily activities of patients, especially in conjunction with the associated non-motor features. Understandably, IEMs are often multi-organ disorders and there are many symptoms that deserve attention. However, accumulating evidence indicates that dystonia and other movement disorders should be included in the long-term management of patients with IEMs. The quality of life of patients can potentially be improved if clinicians are conscious about the presence of dystonia, since several therapeutic options are available.

Key Points and Clinical Pearls

- Dystonia is one of the most prevalent movement disorders in inborn errors of metabolism (IEMs).
- A complex clinical picture comprising multiple neurological and non-neurological features may point toward the diagnosis of an IEM.
- Recognition of dystonia is of importance for diagnostic and therapeutic management.
- Early identification and treatment of a number of treatable IEMs can improve or even prevent dystonia, which is why treatable IEMs should be prioritized in the diagnostic process.
- Dystonia and associated non-motor symptoms are important factors that can impact on the quality of life in patients with IEMs.

Directions for Future Research

- Targeted disease-specific treatments are a future direction.
- Dystonia, among other movement disorders, deserves more attention in IEM research as its prevalence and impact might be greater than anticipated.
- A shift of focus from acute treatment to long-term management will be necessary as many patients with IEMs survive into adulthood making chronic problems a treatment priority.

References

1. Garcia-Cazorla A, Wolf NI, Serrano M, et al. Inborn errors of metabolism and motor disturbances in children. J Inherit Metab Dis. 2009;**32**(5):618–29.
2. Eggink H, Kuiper A, Peall KJ, et al. Rare inborn errors of metabolism with movement disorders: A case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet J Rare Dis. 2014;**9**:177.
3. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: A consensus update. Mov Disord. 2013;**28**(7):863–73.
4. Lehericy S, Tijssen MA, Vidailhet M, Kaji R, Meunier S. The anatomical basis of dystonia: Current view using neuroimaging. Mov Disord. 2013;**28**(7):944–57.
5. Steeves TD, Day L, Dykeman J, Jette N, Pringsheim T. The prevalence of primary dystonia: A systematic review and meta-analysis. Mov Disord. 2012;**27**(14):1789–96.
6. Gouider-Khouja N, Kraoua I, Benrhouma H, Fraj N, Rouissi A. Movement disorders in neuro-metabolic diseases. Eur J Paediatr Neurol. 2010;**14**(4):304–7.
7. Fung VS, Jinnah HA, Bhatia K, Vidailhet M. Assessment of patients with isolated or combined dystonia: An

update on dystonia syndromes. Mov Disord. 2013;**28**(7):889–98.

8. van Egmond ME, Kuiper A, Eggink H, et al. Dystonia in children and adolescents: A systematic review and a new diagnostic algorithm. J Neurol Neurosurg Psychiatry. 2015;**86**(7):774–81.
9. Kuiper MJ, Brandsma R, Vrijenhoek L, et al. Physiological movement disorder-like features during typical motor development. Eur J Paediatr Neurol. 2018;**22**(4):595–601.
10. Rosenbaum P, Paneth N, Leviton A, et al. A report: The definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;**109**:8–14.
11. Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: The European Cerebral Palsy Study. JAMA. 2006;**296**(13):1602–8.
12. Schneider SA, Bhatia KP. Secondary dystonia: Clinical clues and syndromic associations. Eur J Neurol. 2010;**17** Suppl 1:52–7.
13. Kuiper A, Eggink H, Tijssen MA, de Koning TJ. Neurometabolic disorders are treatable causes of dystonia. Rev Neurol (Paris). 2016;**172**(8–9):455–64.
14. van Egmond ME, Eggink H, Kuiper A, et al. Crossing barriers: A multidisciplinary approach to children and adults with young-onset movement disorders. J Clin Mov Disord. 2018;**5**:3.
15. Maas R, Wassenberg T, Lin JP, van de Warrenburg BPC, Willemsen M. L-dopa in dystonia: A modern perspective. Neurology. 2017;**88**(19):1865–71.
16. Koy A, Lin JP, Sanger TD, et al. Advances in management of movement disorders in children. Lancet Neurol. 2016;**15**(7):719–35.
17. van Egmond ME, Lugtenberg CHA, Brouwer OF, et al. A post hoc study on gene panel analysis for the diagnosis of dystonia. Mov Disord. 2017;**32**(4):569–75.
18. Hennekam RC, Biesecker LG. Next-generation sequencing demands next-generation phenotyping. Hum Mutat. 2012;**33**(5):884–6.
19. Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders: Clinical advances and future perspectives. Nat Rev Neurol. 2015;**11**(10):567–84.
20. Lee WW, Jeon BS. Clinical spectrum of dopa-responsive dystonia and related disorders. Curr Neurol Neurosci Rep. 2014;**14**(7):461.
21. Taly AB, Meenakshi-Sundaram S, Sinha S, Swamy HS, Arunodaya GR. Wilson disease: Description of 282 patients evaluated over 3 decades. Medicine (Baltimore). 2007;**86**(2):112–21.
22. Stamelou M, Tuschl K, Chong WK, et al. Dystonia with brain manganese accumulation resulting from *SLC30A10* mutations: A new treatable disorder. Mov Disord. 2012;**27**(10):1317–22.
23. Schneider SA, Bhatia KP. Rare causes of dystonia parkinsonism. Curr Neurol Neurosci Rep. 2010;**10**(6):431–9.
24. Viau K, Ernst SL, Vanzo RJ, et al. Glutaric acidemia type 1: Outcomes before and after expanded newborn screening. Mol Genet Metab. 2012;**106**(4):430–8.
25. Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: Long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. J Inherit Metab Dis. 2006;**29**(2–3):383–9.
26. Koens LH, Kuiper A, Coenen MA, et al. Ataxia, dystonia and myoclonus in adult patients with Niemann–Pick type C. Orphanet J Rare Dis. 2016;**11**:121.
27. Patterson MC, Hendriksz CJ, Walterfang M, et al. Recommendations for the diagnosis and management of Niemann–Pick disease type C: An update. Mol Genet Metab. 2012;**106**(3):330–44.
28. Roze E, Paschke E, Lopez N, et al. Dystonia and parkinsonism in GM1 type 3 gangliosidosis. Mov Disord. 2005;**20**(10):1366–9.
29. Gautschi M, Merlini L, Calza AM, et al. Late diagnosis of fucosidosis in a child with progressive fixed dystonia, bilateral pallidal lesions and red spots on the skin. Eur J Paediatr Neurol. 2014;**18**(4):516–9.
30. Martikainen MH, Ng YS, Gorman GS, et al. Clinical, genetic, and radiological features of extrapyramidal movement disorders in mitochondrial disease. JAMA Neurol. 2016;**73**(6):668–74.
31. Rahman S, Thorburn D. Nuclear gene-encoded Leigh syndrome overview. GeneReviews®. 2015; Oct 1.
32. Ortigoza-Escobar JD, Molero-Luis M, Arias A, et al. Free-thiamine is a potential biomarker of thiamine transporter-2 deficiency: A treatable cause of Leigh syndrome. Brain. 2016;**139**(Pt 1):31–8.
33. Synofzik M, Srulijes K, Godau J, Berg D, Schols L. Characterizing POLG ataxia: Clinics, electrophysiology and imaging. Cerebellum. 2012;**11**(4):1002–11.
34. Barnerias C, Saudubray JM, Touati G, et al. Pyruvate dehydrogenase complex deficiency: Four neurological phenotypes with differing pathogenesis. Dev Med Child Neurol. 2010;**52**(2):e1–9.
35. Pearson TS, Akman C, Hinton VJ, Engelstad K, De Vivo DC. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep. 2013;**13**(4):342.
36. van de Kamp JM, Mancini GM, Salomons GS. X-linked creatine transporter deficiency: Clinical aspects and

pathophysiology. J Inherit Metab Dis. 2014;**37**(5):715–33.

37. Lagarde J, Roze E, Apartis E, Pothalil D, Sedel F, Couvert P, et al. Myoclonus and dystonia in cerebrotendinous xanthomatosis. Mov Disord. 2012;**27**(14):1805–10.
38. Rubio-Agusti I, Carecchio M, Bhatia KP, et al. Movement disorders in adult patients with classical galactosemia. Mov Disord. 2013;**28**(6):804–10.
39. Peall KJ, Kuiper A, de Koning TJ, Tijssen MA. Non-motor symptoms in genetically defined dystonia: Homogenous groups require systematic assessment. Parkinsonism Relat Disord. 2015;**21**(9):1031–40.
40. Timmers ER, Kuiper A, Smit M, et al. Non-motor symptoms and quality of life in dopa-responsive dystonia patients. Parkinsonism Relat Disord. 2017;**45**:57–62.
41. Balash Y, Giladi N. Efficacy of pharmacological treatment of dystonia: Evidence-based review including meta-analysis of the effect of botulinum toxin and other cure options. Eur J Neurol. 2004;**11**(6):361–70.
42. Liow NY, Gimeno H, Lumsden DE, et al. Gabapentin can significantly improve dystonia severity and quality of life in children. Eur J Paediatr Neurol. 2016;**20**(1):100–7.
43. Sayer C, Lumsden DE, Kaminska M, Lin JP. Clonidine use in the outpatient management of severe secondary dystonia. Eur J Paediatr Neurol. 2017;**21**(4):621–6.
44. Mink JW. Treatment of paroxysmal dyskinesias in children. Curr Treat Options Neurol. 2015;**17**(6):350.
45. Jankovic J. Medical treatment of dystonia. Mov Disord. 2013;**28**(7):1001–12.
46. Jinnah HA, Alterman R, Klein C, et al. Deep brain stimulation for dystonia: A novel perspective on the value of genetic testing. J Neural Transm (Vienna). 2017;**124**(4):417–30.
47. Ge M, Zhang K, Ma Y, et al. Bilateral subthalamic nucleus stimulation in the treatment of neurodegeneration with brain iron accumulation type 1. Stereotact Funct Neurosurg. 2011;**89**(3):162–6.
48. Lumsden DE, Gimeno H, Tustin K, Kaminska M, Lin JP. Interventional studies in childhood dystonia do not address the concerns of children and their carers. Eur J Paediatr Neurol. 2015;**19**(3):327–36.
49. Lumsden DE, Allen NM. Rethinking status dystonicus: A welcome start to a challenging problem. Mov Disord. 2018;**33**(2):344.
50. Lumsden DE, King MD, Allen NM. Status dystonicus in childhood. Curr Opin Pediatr. 2017;**29**(6):674–82.

Chapter 9

A Phenomenology-Based Approach to Inborn Errors of Metabolism with Parkinsonism

Claudio Melo de Gusmao and Laura Silveira-Moriyama

Introduction

Definitions and Historical Considerations

Parkinsonism is a syndrome diagnosed by the presence of cardinal motor features, generally defined as bradykinesia in combination with rigidity, resting tremor, flexed (stooped) posture, and freezing and/or impaired postural reflexes [1, 2]. Bradykinesia, the hallmark feature, is determined by the presence of the "sequence effect" (also known as fatiguing or decrement): repetition leads to progressive decrease in speed and/or amplitude of movements [3]. Hypokinesia describes a small amplitude of movements (with or without fatigue) and akinesia literally means "lack of movement." Hypokinesia is sometimes equated to parkinsonism (as in "infantile hypokinetic–rigid syndrome"), but technically is not the same phenomenon. Akinesia has been used interchangeably with bradykinesia to describe severe manifestations (as in "akinetic mutism") or to indicate parkinsonism without tremor (as in "akinetic–rigid syndrome").

The first description of the parkinsonian syndrome is attributed to James Parkinson and dates to the nineteenth century. Parkinson disease is still the most common cause of parkinsonism worldwide, but not all patients with parkinsonism actually have Parkinson disease, particularly those of younger age. Therefore, Parkinson disease is not synonymous with parkinsonism: the former designates a specific neurodegenerative disease, whereas the latter describes a clinical syndrome that has many different potential etiologies.

With recognition that etiologies may vary, some authors have attempted to clinically divide patients according to age of onset and response to levodopa. When levodopa-responsive parkinsonism occurs between the ages of 21 and 40 years, it has been labeled "young-onset Parkinson disease" (YOPD). This subset of patients generally resembles typical Parkinson disease, but there are notable clinical differences [4, 5]. If parkinsonism is apparent before the age of 21 years it is conventionally defined as juvenile parkinsonism, regardless of its responsiveness to levodopa. In this group of patients, clinical features are even more variable. For example, dystonia is frequently present and resting tremor is less common [6].

Many disorders classified into the category of YOPD (and some cases of juvenile parkinsonism) are caused by monogenic forms of classic Parkinson disease. Although not typically considered a classic inborn error of metabolism (IEM), the distinction has grown blurrier with a more inclusive definition of an IEM as any genetic disorder that primarily or secondarily impairs a metabolic pathway. For example, *LRRK2* mutations (accounting for up to a third of cases of Parkinson disease in selected populations) can cause changes in protein and membrane trafficking, leading to synaptic dysfunction and accumulation of alpha-synuclein (the neuropathological hallmark of "idiopathic" Parkinson disease) [7]. The clinical syndrome may be nearly indistinguishable from Parkinson disease, similar to mutations in *SNCA* and probably *TMEM230* [8, 9]. Overall, there is a convergence of pathobiological mechanisms for various monogenic forms of Parkinson disease, which often include primary or secondary disruptions to synaptic function (*SNCA*, *LRRK2*, *VPS35*, *DNAJC6*, *SYNJ1*) and mitochondrial function (*PARKIN*, *PINK1*, *DJ-1*, *FBX07*) leading to neuronal death [10]. Treatment for these monogenic forms usually follows clinical guidelines for idiopathic Parkinson disease. Response and tolerance to treatment may nevertheless vary with the mutation, and, when indicated, genetic testing may be of use for diagnosis, prognosis, and counseling.

Parkinsonism in Infants and Children

Ascertainment of the core feature of parkinsonism (bradykinesia) implies determining progressive

decrement in speed and amplitude of movement with repeated tasks. Examination maneuvers to elicit this finding, such as repeated finger or foot taps, may be particularly challenging in children. Patients may be too young to adequately perform such movements, present with physiological motor impersistence, or have associated cognitive or motor disabilities that preclude a formal assessment. In addition (and in contrast to adults), resting tremor is uncommon in children with parkinsonism [11].

Given these challenges, some authors have used the term "hypokinetic/akinetic–rigid" syndrome as synonymous to parkinsonism in pediatric patients. The reader should be cautious though: there are other causes for slowness or paucity of movements that are not parkinsonian, such as pyramidal weakness, cognitive slowing, dystonic slowness, stiffness syndromes, hypothyroidism, apraxia, and so forth. Parkinsonism in the context of IEMs often arises embedded precisely within this broad, complex neurological phenotype that can include one or more of these features. This superposition of different motor phenomenology may affect speed and fluidity of movement, and it can be difficult to parse out the main driver of motor impairment.

In this chapter, we try to focus on the disorders that either (a) have parkinsonism as the core, or a principal, motor feature, or (b) are complex phenotypes in which recognition of parkinsonism serves as a diagnostic red flag.

Epidemiology of Pediatric Parkinsonism

In the United States, the incidence of parkinsonism in patients 0–29 years old is estimated at 0.8 in 100,000 per year, rising to 3 in those aged 30–49 years [12]. The incidence of young-onset parkinsonism may differ geographically, and appears to be especially high in Japan where it may account for up to 10% of all parkinsonian cases. A prospective study suggested that parkinsonism represents approximately 2% of all patients seen in a tertiary pediatric movement disorder center [13]. The most common causes for acute and subacute parkinsonism are drug-induced, infectious, and immune-mediated disorders, although some monogenic disorders can present in such a fashion (e.g. *ATP1A3* mutations) [11, 14].

Unfortunately, epidemiological data regarding the prevalence and incidence of IEMs in patients presenting with parkinsonism have not been studied in a systematic fashion. Nevertheless, clinicians should consider an IEM in any patient with unexplained, insidiously progressive, and chronic juvenile parkinsonism. The main categories classically associated with this phenotype are neurotransmitter disorders, metal storage diseases, lysosomal storage disorders, and disorders of energy metabolism. Several other IEMs can cause juvenile parkinsonism, albeit more rarely (Box 9.1) [11, 15].

Groups of Disorders Associated with Parkinsonism

Neurotransmitter Disorders

Neurotransmitter disorders are a group of neurogenetic conditions that cause aberrant metabolism and/or transport of the biogenic amines (dopamine, norepinephrine, epinephrine, serotonin, and histamine), glycine, vitamin B6, gamma-aminobutyric acid (GABA), and glutamic acid [16]. For the purposes of this chapter, we will focus on disorders affecting the biochemical pathways leading to dopamine and serotonin synthesis (Figure 9.1). In these cases, parkinsonism may be an important and/or core clinical feature. We will not discuss disorders in which neurotransmitter deficits lead to different phenotypes or diseases in which neurotransmitter levels are altered as a secondary phenomenon (e.g. structural lesions, Rett syndrome, Aicardi–Goutières syndrome, etc.). For a more comprehensive discussion of the subject, the reader is directed to excellent published reviews [16–18].

Monoamine neurotransmitter disorders often present with motor disability. Almost invariably, patients will have dystonia. Axial hypotonia and parkinsonism often coexist. Clinical features are age-dependent, and include delayed motor milestones, gait disturbances, recognizable dystonic patterned movements (e.g. oculogyric crises, opisthotonus, limb dystonia), dyskinesia, and tremor. Diurnal variation may be a clue; in several disorders, symptoms are worse in the evening and improve after sleep. Other symptoms include seizures, headaches, autonomic manifestations (sweating, temperature dysregulation, ptosis, hypersalivation, nasal congestion), sleep disturbances, and neuropsychiatric features (anxiety, obsessive–compulsive symptoms, autism spectrum) [16, 17].

Diagnostic Approach to Neurotransmitter Disorders

Since many monoamine neurotransmitter disorders may present in similar fashion (often with normal imaging), it is useful to consider them as a group

Box 9.1 Main IEMs associated with parkinsonism

Neurotransmitter defects

Autosomal-dominant GTPCH1 deficiency (Segawa disease)

Autosomal-recessive GTPCH1 deficiency

6-Pyruvoyltetrahydropterin synthase (PTPS) deficiency

Sepiapterin reductase (SPR) deficiency

Dihydropterine reductase (DHPR) deficiency

Tyrosine hydroxylase (TH) deficiency

Aromatic L-amino acid decarboxylase (AADC) deficiency

Brain dopamine–serotonin transporter deficiency (*SLC18A2*)

Pyruvate carboxylase deficiency (*SLC6A3*)

Mitochondrial disorders and energy metabolism

Leber hereditary optic neuropathy plus

Pyruvate decarboxyalase deficiency

Respiratory chain deficiencies

POLG mutations

TWINKLE mutations

Pyruvate dehydrogenase deficiency

Phosphoglycerate kinase 1 deficiency

Glucose transporter type 1 deficiency

Metal storage disorders

Wilson disease

Pantothenate kinase-associated neurodegeneration (PKAN)

Phospholipase A2 group VI (*PLA2G6*)-associated neurodegeneration (PLAN)

Mitochondrial membrane protein-associated neurodegeneration (MPAN)

Beta-propeller protein-associated neurodegeneration (BPAN)

Kufor–Rakeb syndrome

Neuroferritinopathy

Manganese deposition disorders (*SLC39A14* and *SLC30A10*)

Lysosomal disorders

Neuronal ceroid lipofuscinoses

GM1 gangliosidosis

GM2 gangliosidosis

Niemann–Pick disease type C (NPC)

Box 9.1 (cont.)

Gaucher disease

Chédiak–Higashi syndrome

Mucolipidosis type III alpha/beta

Vitamin-responsive disorders

Biotin–thiamine-responsive basal ganglia disease

Molybdenum cofactor deficiency

Lipid storage diseases

Cerebrotendinous xanthomatosis

Organic acidurias and aminoacidopathies

Glutaric aciduria type 1 (GA-1)

Homocystinuria

Primary familial brain calcification (PFBC) syndromes

PFBC associated with *SLC20A2, PDGFRB, PDGFB, XPR1*

and interpret diagnostic findings in the context of the specific clinical features. Historically, some of these disorders in which there was detectable hyperphenylalaninemia were grouped under the header of "atypical phenylketonuria" to reflect the combination of elevated phenylalanine, a complex neurological phenotype, and the lack of improvement with a restricted diet. The availability of cerebrospinal fluid (CSF) neurotransmitter and pterin levels greatly aided the specification of these disorders, as many carry a specific CSF profile. Unfortunately, CSF neurotransmitter testing is not widely available and requires specialized processing for accurate interpretation. Subsequently, several genes have been identified in association with these diseases, and currently many patients are diagnosed by virtue of clinical presentation, response to levodopa, CSF analysis. and/or gene panels (Table 9.1).

Blood tests that may assist the clinician include phenylalanine (PA) and prolactin levels. In some diseases (e.g. due to *GCH1* or *SPR* mutations), the baseline PA level may be normal but an oral loading test will demonstrate an abnormally high PA:tyrosine ratio, indicating subclinical deficits in PA hydroxylation in the liver. This test may be useful when lumbar puncture and CSF analysis are not available, but false positives and false negatives have been reported [19]. Urine testing includes measurement of pterins and neurotransmitter metabolites. This may be particularly useful in aromatic L-amino acid decarboxylase (AADC) deficiency (increased 3-OMD and VLA with decreased VMA) and brain dopamine–serotonin transporter

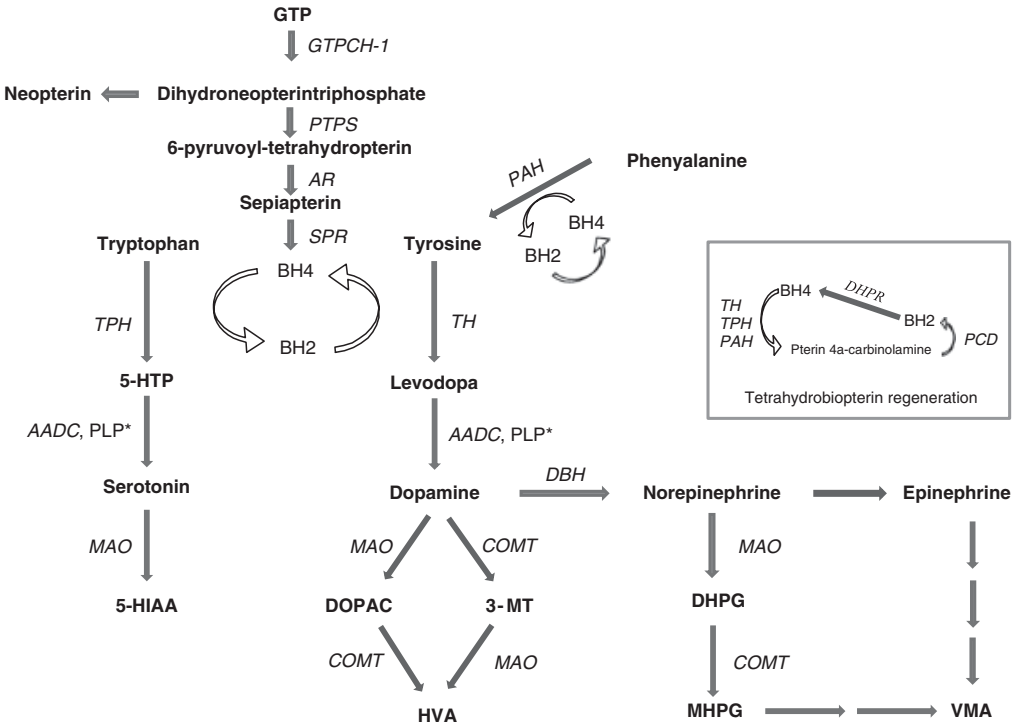

Figure 9.1 Monoamine synthetic pathway. Abbreviations that are not defined elsewhere: AR, aldose reductase; DBH, dopamine beta-hydroxylase; DOPAC, dihydroxyphenylacetic acid, 3-MT, 3-methoxytyramine; PAH, phenylalanine hydroxylase; PCD, pterin-4a-carbinolamine dehydratase; PLP, pyridoxal-5-phosphate; VMA,vanillylmandelic acid.

deficiency (elevations of urinary 5-HIAA and HVA with decreased neopterin and dopamine). CSF neurotransmitter analysis probably provides the most information, but unfortunately this may not be available in several parts of the world. Gene testing and/or functional assays (e.g. fibroblast enzyme assays) can help confirm the suspected diagnoses [20, 21].

Autosomal-Dominant GTP Cyclohydrolase 1 Deficiency (Segawa Disease)

Segawa disease, also known as DYT5a, is the prototype of dopa-responsive dystonia. The disorder results from mutations in the *GCH1* gene, responsible for the enzyme GTPCH1. The enzyme is involved in the first step in the synthesis of tetrahydrobiopterin (BH4), an important cofactor in the dopamine and serotonin synthetic pathway (Figure 9.1). The classic presentation occurs in childhood (mean age 6 years), starting with foot dystonia that is usually much worse at the end of the day. The disorder affects females more than males with a 2.5:1 ratio. Symptoms gradually progress to other limbs in the ensuing years, and diurnal fluctuation becomes less obvious. Postural tremor may appear in the second decade. Adolescents and older patients may present with upper-extremity tremor, parkinsonism, and rigidity. There is wide phenotypic variation, and other features have been described, such as paroxysmal dystonia. Untreated patients have been misdiagnosed with cerebral palsy or hereditary spastic paraplegia [17, 22].

The diagnosis of Segawa disease relies on a levodopa trial, biochemical tests, and genetic confirmation. A levodopa trial shows marked and sustained improvement, leading some authors to suggest that every child with unexplained dystonia merits a levodopa challenge. Plasma PA levels are normal, but a PA oral loading test may be abnormal. Serum prolactin may be elevated. CSF neurotransmitters may reveal low levels of HVA, 5-HIAA, BH4, and neopterin, although HVA and 5-HIAA may be only slightly reduced or normal. Several mutations in *GCH1* have been described; sequence analysis detects about 60% of patients. A portion of the remaining individuals with functional evidence of GTPCH1 deficiency may have deletions or duplications (potentially identified through multiplex-ligation-dependent

Table 9.1 Diagnostic investigations in select neurotransmitter gene disorders (adapted from [17])[a]

	AD *GCH1*	AR *GCH1*	PTPS	SPR	DHPR	TH	AADC	SLC18A2	SLC6A3
CSF									
HVA	↓↔	↓	↓	↓	↓	↓	↓	↔	↑
5-HIAA	↓↔	↓	↓	↓	↓	↔	↓	↔	↔
HVA:5-HIAA						↓			↑
BH2				↑	↑				
BH4	↓↔	↓	↓	↓↔	↓↔				
Neopterin	↓↔	↓	↑	↔	↔				
Sepiapterin				↑					
5-MTHF					↓		↓↔		
MHPG						↓	↓		
3-OMD							↑		
5-HTP							↑		
Blood									
PA		↑	↑		↑				
PA loading test[b]	**abnl**			**abnl**					
Prolactin	↑↔	↑↔	↑↔	↑↔	↑↔	↑↔	↑↔	↑↔	↑↔
Urine									
Biopterin		↓	↑						
Neopterin	↓	↓	↓						
5-HIAA								↑	
HVA								↑	
3-OMD							↑		
VLA							↑		
Clinical response									
Levodopa	+	+ / –	+/–	+/–		+/–	**May worsen**	**May worsen**	

[a] Abbreviations: AD, autosomal-dominant; AR, autosomal-recessive; BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; 5-HIAA, 5-hyroxyindolacetic acid; 5-HTP, 5-hydroxytryptophan; HVA, homovanillic acid; MHPG, methoxylhydroxyphenylglycol; 5-MTHF, 5-methyltetrahydrofolate; 3-OMD, 3-orthomethyldopa; PA, phenylalanine; VLA, vanillyllactic acid. ↑, increased; ↓, decreased; ↔, normal; abnl, abnormal; + indicates good treatment response; +/– indicates variable treatment response. [b] PA loading test: PA:tyrosine ratio measured in blood at 1, 2, 4, and 6 hours after oral loading with 100 mg/kg of PA. Grey boxes indicate uninformative results. Clinical response here defined as a diagnostic test, if other tests unavailable.

probe amplification or chromosomal microarray); others may harbor mutations in non-coding regions or in yet-unidentified regulatory genes [17].

Treatment with levodopa leads to a striking response with sustained benefits. Patients with Segawa disease may demonstrate peak-dose dyskinesias (especially when the dose is being uptitrated, but later as well). Nevertheless, they do not develop motor fluctuations or wearing off, and dyskinesias improve with reduction in levodopa dosage [17].

Autosomal-Recessive GTP Cyclohydrolase 1 Deficiency

Autosomal-recessive GTPCH1 deficiency may exist in a continuum, with phenotypic differences between homozygotes and compound heterozygotes [23]. Homozygous mutations more frequently lead to severe symptoms, including developmental delay, hypotonia, autonomic dysfunction, seizures, and a wide variety of movement disorders including dystonia and parkinsonism. Hyperphenylalaninemia can be detected on newborn screening [17]. Patients with compound heterozygous variants in *GCH1* may present with a phenotype labeled, "dystonia with motor delay," without overt hyperphenylalaninemia [23]. Nevertheless, this phenotype is not exclusive and has also been reported in the context of homozygous mutations [24]. Some patients present with hypotonia, dystonia, and parkinsonism with onset in the first year of life (Video 9.1). CSF neurotransmitter metabolites are usually reduced (HVA, 5-HIAA, BH4, neopterin); serum prolactin may be elevated and urine pterins are reduced. Treatment should include levodopa, 5-HTP, and BH4 replacement [17].

6-Pyruvoyltetrahydropterin Synthase Deficiency

6-Pyruvoyltetrahydropterin synthase (PTPS) deficiency is caused by mutations in the *PTS* gene and appears to be most frequent in Asian populations. Clinical features may include neonatal onset with intrauterine growth restriction, microcephaly, hypokinetic–rigid syndrome, and developmental delay. Dystonia, chorea, and oculogyric crises may be present, as well as seizures. Hyperphenyalaninemia is usually detected through newborn screening. CSF levels of HVA, 5-HIAA, and BH4 are low, but neopterin can be elevated. Urine shows elevated total biopterin with decreased neopterin. Patients are treated with a similar regimen as autosomal-recessive GTPCH1 deficiency, but may require slightly higher doses; occasionally dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors are necessary to avoid on–off phenomena [17].

Sepiapterin Reductase Deficiency

Sepiapterin reductase (SPR) deficiency is inherited in an autosomal-recessive manner, caused by mutations in the *SPR* gene, coding for the enzyme responsible for the final steps in BH4 synthesis. Symptoms are similar to other disorders with catecholamine and serotonin deficiency. In the largest series to date, limb dystonia, weakness, and oculogyric crises with diurnal fluctuation occurred in > 65% of patients. One or more parkinsonian features (tremor, bradykinesia, masked facies, and rigidity) were noted in 45–65% of patients [25]. Head and limb resting tremor (sometimes inhibited by touch or spontaneous movement) was reported. Diurnal fluctuation may be absent and some patients have been misdiagnosed with cerebral palsy. Other features, such as seizures, sleep disturbances, and cognitive disability, may be present [17, 25].

Plasma PA and urine pterins are normal, but the oral PA loading test is usually abnormal. CSF levels of HVA and 5-HIAA are low, with elevations in total biopterin, BH2, and sepiapterin levels. Treatment with levodopa often leads to improvement, but patients may be sensitive to early dyskinesias. Starting with a low dose, followed by slow titration, is advised. Adding 5-HTP may lead to additional benefits in motor and sleep symptoms beyond that achieved with levodopa. Additional carbidopa may be necessary to minimize 5-HTP related gastrointestinal distress [17, 25].

Dihydropteridine Reductase Deficiency

The dihydropteridine reductase (DHPR) enzyme is involved in BH4 regeneration as well as maintenance of cerebral folate. The disease is best detected on newborn screening, showing hyperphenylalaninemia. Newborns may be initially asymptomatic but, untreated, the disease may lead to developmental delay, bulbar dysfunction, axial hypotonia with limb dystonia, tremor, choreoathetosis, and seizures. Microcephaly, cerebral atrophy, and intracranial calcifications may be present [26]. Parkinsonism has been described in patients with longstanding disease [27]. CSF has low levels of HVA, 5-HIAA, and 5-MTHF, and high levels of BH2 and high or normal levels of biopterin. Treatment involves levodopa, 5-HTP, and folinic acid; occasionally a PA-restricted diet is required [17, 26].

Tyrosine Hydroxylase Deficiency (also known as DYT5b or DYT-TH)

Tyrosine hydroxylase (TH) is the rate-limiting enzyme in dopamine synthesis. Autosomal-recessive mutations in the *TH* gene can lead to two clinical phenotypes, although overlap exists: type A (69% of patients) have a dystonic and/or hypokinetic–rigid syndrome, also called "infantile parkinsonism," with onset in the first years of life [28]. Type B patients (31%) have early onset (0–3months) of a complex encephalopathy, including severe parkinsonism, autonomic dysfunction, oculogyric crises, and seizures [17, 28, 29].

In type A TH deficiency, the age at onset ranges from 2 months to 5 years. Symptoms may start in one limb and generalize. In the early phases of the disease, the severity of dystonia may fluctuate, either diurnally (worse in the afternoon) or in apparent episodic fashion within days. This latter aspect may mimic paroxysmal dystonia. Tremor, chorea, oculogyric crises, and autonomic and behavioral symptoms are either mild or absent. In some patients, parkinsonism may dominate the picture early with the later development of dystonia. Treatment with levodopa leads to improvement, some patients attaining the ability to walk and show normal cognitive skills [28].

Type B disease is often accompanied by perinatal complications (fetal distress, asphyxia), initially leading to a suspicion for epileptic encephalopathies or mitochondrial disease. There is usually marked hypokinesia and bradykinesia, hypotonia mixed with superimposed limb dystonia, or spells of generalized dystonia. The episodic worsening can have autonomic dysfunction with diaphoresis, drooling, and fever of unknown origin. EEG may indicate seizures, but not all clinical spells are epileptic. Movements are jerky, sometimes with tremors or myoclonus. Bilateral ptosis and oculogyric crises are seen. Treatment with levodopa is less consistently effective, and may take weeks to be noticeable. Patients with type B can be extremely sensitive to levodopa, developing dyskinesias at very low doses. Despite improvement in motor symptoms and development, many patients with type B TH deficiency are left with intellectual disability [28].

CSF testing demonstrates low HVA and normal levels of 5-HIAA (HVA:5-HIAA ratio < 1). Given the sensitivity that patients with TH may have to dyskinesias, some authors recommend starting levodopa at low doses (0.5–1 mg/kg per day, divided over four to six doses per day), increased gradually by 0.1–0.5 mg/kg per day every month. Dyskinesias may respond to lowering the levodopa dosage (sometimes with adjunct treatment using MAO-B inhibitors or anticholinergics) or using amantadine [28, 30].

Aromatic L-Aminoacid Decarboxylase Deficiency

This autosomal-recessive condition is caused by mutations in the *DDC* gene, which encodes for the AADC enzyme: the final step in dopamine and serotonin synthesis. AADC deficiency leads to a severe disease with combined deficiency of these neurotransmitters. In most patients, symptoms are evident before 18 months of life, with hypotonia (95%) and oculogyric crises (86%). Developmental delay with cognitive disability is common. Autonomic dysfunction is seen with several features (ptosis, diaphoresis, temperature dysregulation, nasal congestion, fasting hypoglycemia, and impaired stress response). The movement disorder phenotype is complex, and can be seen in about 50% of patients. This includes hypokinesia (32%), dystonia (53%), athetosis (27%), and chorea (22%) [17, 21].

Neuroimaging can be abnormal, with global atrophy, hypomyelination, a thin corpus callosum, or nonspecific white matter abnormalities. EEG may be slow or with polyspike activity. CSF testing demonstrates low levels of HVA, 5-HIAA, and MHPG. There is elevation of 5-HTP and 3-OMD. Urine levels of catecholamine metabolites can be helpful in AADC deficiency, with elevations of 3-OMD and VLA [17, 21].

Treatment of AADC deficiency involves using dopamine agonists and MAO-B inhibitors with supplementation of pyridoxine (or PLP) and folinic acid. Usually the two latter agents are started first, as pyridoxine (after conversion to PLP) can boost residual AADC activity and folinic acid prevents cerebral folate deficiency. Dopamine agonists such as bromocriptine, pramipexole, and ropinirole are beneficial; rotigotine may have an advantage given its wide D1–D5 receptor activity and additional serotoninergic and noradrenergic effects [17]. Levodopa is not first-line therapy, and if used the commercially available forms with decarboxylase inhibitors should be avoided.

Preliminary, open-label phase 1/2 data have shown promising results for gene therapy for AADC deficiency. The human *AADC* gene was injected in the bilateral putamina through stereotactic surgery using an adeno-associated virus (AAV) vector [31]. Further research is underway (ClinicalTrials.gov NCT02852213).

Brain Dopamine–Serotonin Vesicular Transport Disease (*SLC18A2*)

Mutations in the *SLC18A2* gene, encoding for the vesicular transport protein VMAT2, causes this autosomal-recessive transportopathy with deficiencies in dopamine, norepinephrine, and serotonin. This rare disorder has been described in two different kindreds only. The VMAT2 protein facilitates neurotransmitter loading into synaptic vesicles. Clinical features included an early-onset disorder with axial hypotonia, superimposed limb dystonia, developmental delay, and oculogyric crises. As with other neurotransmitter disorders, autonomic dysfunction and sleep disturbances are observed. Parkinsonism, manifested by hypomimia, hypokinesia, and shuffling gait were observed in adolescent patients. Neuroimaging and CSF analysis are nondiagnostic, but a specific pattern on urine testing was seen with high levels of HVA and 5-HIAA and low dopamine and epinephrine. Treatment with levodopa may lead to clinical worsening, but dopamine agonists caused motor improvement [20, 32].

Dopamine Transporter Deficiency Syndrome (*SLC6A3*)

This autosomal-recessive condition is caused by mutations in the *SLC6A3* gene encoding for a dopamine transporter. This protein is located at the presynaptic membrane and is responsible for the uptake of dopamine from the synaptic cleft. Typical cases present in the first year of life with developmental delay, axial hypotonia, and hyperkinetic movements (dystonia and dyskinesias), occasionally misdiagnosed as dyskinetic cerebral palsy. With time, hypomimia, rigidity, and bradykinesia may ensue. Atypical cases with presentation in the second decade of life with tremor, focal dystonia, and bradykinesia have been described. Oculogyric crises and ocular flutter are seen. CSF analysis demonstrates an elevation in the dopamine metabolite HVA, with associated elevation in the HVA:5-HIAA ratio. Neuroimaging is structurally normal, but functional imaging with ^{123}I (DaTscan ©) demonstrates a loss of dopamine transporter activity in the basal ganglia. Levodopa and dopamine agonists may provide modest benefit.

Metal Storage Disorders

Copper

Wilson disease is an autosomal-recessive disorder in the *ATP7B* gene leading to copper overload in several tissues. The disease has protean manifestations, including hepatic, neurologic, and psychiatric symptoms. In general, children are more likely to have disease-onset with liver failure (age ranging from 9 years to 13 years); teenagers and young adults can present with psychiatric and neurological symptoms (age ranging from 15 years to 21 years) [33]. Systemic features may range from asymptomatic elevation in liver function or visceromegaly to hemolytic anemia, frank liver failure, and cirrhosis. The most common neurological symptoms include dysarthria, gait abnormalities, tremor, dystonia, and parkinsonism [34, 35]. Practically every movement disorder has been described in Wilson disease (e.g., chorea, ataxia, myoclonus), as well as atypical features such as seizures, pyramidal signs, neuropathy, autonomic dysfunction, and others. Neurological features are so broad that authors have tried to classify patients by predominant phenotype; one such division separates into four groups: dystonia, tremor, rigidity–tremor, or rigidity [34]. The distinction is challenging since frequently there will be mixed symptoms. Psychiatric symptoms are equally diverse and often precede neurological manifestations [35].

Parkinsonism may occur in 30–66% of patients with Wilson disease. When present, it is more often in association with other neurological features – uncommonly, it may be an isolated, presenting manifestation. Patients present with rigidity, bradykinesia with micrographia, hypomimia, and postural instability. Resting tremor can occur, but is uncommon. Treatment with levodopa is usually ineffective or leads to a modest improvement [34, 35].

A characteristic neurological feature of Wilson disease is an exaggerated, unnatural smile caused by dystonic retraction of the upper lip and orofacial musculature, termed "risus sardonicus." The vast majority of patients with neurological manifestations (100% in some series) will have copper deposition in Descemet's membrane of the cornea, leading to a brownish discoloration at the limbus, termed a Kayser–Fleischer ring [34, 35]. Clinicians should suspect Wilson disease in any patient with an unexplained movement disorder and/or liver disease, especially if some of these characteristic features are present.

Important tests in Wilson disease (besides liver function and tests for hemolytic anemia) include serum ceruloplasmin and 24-hour urine copper excretion. Slit-lamp examination is necessary to evaluate for Kayser–Fleischer rings. Molecular testing can

be helpful. If suspicion is high, a liver biopsy can demonstrate hepatic copper deposition. MRI is often abnormal in patients with neurological symptoms and demonstrates T2 hyperintense signals in the basal ganglia, thalamus, midbrain, and pons. The disorder is treatable with chelating agents to prevent copper overload.

Iron

Iron accumulation in the brain occurs in a group of disorders named neurodegeneration with brain iron accumulation (NBIA) disorders. This group encompasses several diseases with the shared feature of high levels of iron in the basal ganglia. There is some variation in the clinical presentation and etiology, but presumably similar pathophysiology based on degenerative changes in the substantia nigra and globus pallidus [36]. The diagnosis is most commonly considered when signal changes are found in iron-sensitive sequences in MRI (susceptibility-weighted imaging [SWI], T2* and R2* mapping) in a patient with a movement disorder, or when a pathogenic mutation is found in one of genes associated with NBIA disorders. The current classification system organizes disorders by their genetic basis, recognizing allelic heterogeneity within each disease. The most common NBIA disorder is pantothenate kinase-associated neurodegeneration (PKAN; associated with mutations in the *PANK2* gene). Together with PKAN, three other genes (*PLA2G6, C19orf12, WDR45*) comprise 85% of all NBIA disorders [36].

Pantothenate-Kinase Associated Neurodegeneration

PKAN accounts for half of cases of NBIA disorders. Due to population allele frequency, the prevalence in certain geographic areas (e.g. Dominican Republic) may be higher. The disorder spans a continuum of phenotypical presentations: on one end, patients present with developmental delay and focal limb dystonia in the first decade (mean age 3 years). Dystonia frequently involves the lower extremities, leading to falls and gait changes. Dystonia tends to generalize with time and there may be superimposed spasticity. Pigmentary retinopathy and acanthocytes on a peripheral blood smear can be detected in some patients. On the other end of the spectrum (so-called atypical cases), there is a later age of onset, with parkinsonism, neuropsychiatric symptoms, and dystonia. Patients with onset in the second decade of life often have mixed dystonia and parkinsonism, and are more likely to have parkinsonism dominating the motor phenotype [36]. MRI reveals a pathognomonic signature on T2-weighted sequences consisting of central hyperintensity of the globus pallidus with a halo of hypointense signal ("eye of the tiger" sign; Figure 9.2).

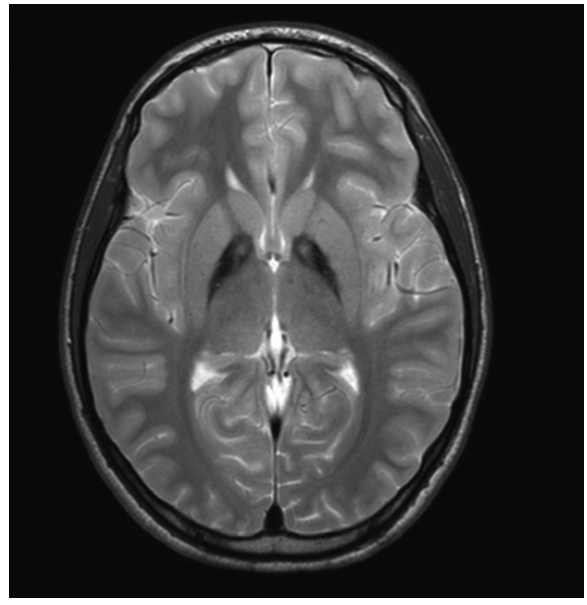

Figure 9.2 MRI of a patient with PKAN. Axial T2-weighted imaging of the globus pallidus demonstrating a central pallidal hyperintense signal surrounded by hypointense signal ("eye of the tiger").

Phospholipase-Associated Neurodegeneration

Phospholipase A2 Group VI (*PLA2G6*)-associated neurodegeneration (PLAN) is caused by mutations in the *PLA2G6* gene. A phenotypic spectrum with three distinct groups according to the age of onset is present: infantile-onset, childhood-onset, and adult-onset variants. Regardless of the phenotype, one key feature is that brain iron accumulation may not be visible early in the course. Other suggestive imaging features include cerebellar or optic-nerve atrophy and sometimes generalized brain atrophy. Parkinsonism is most common in the adult form, then also referred to as *PLA2G6*-associated dystonia–parkinsonism. These patients often have a history of mild cognitive disability and develop dystonia and parkinsonism in adolescence or early adulthood [36]. As previously mentioned, iron accumulation may not be immediately visible but cerebellar atrophy may be a clue. Eventually, dedicated MRI sequences may identify iron deposition in the substantia nigra and globus pallidus. The infantile-onset form, also known as infantile neuroaxonal dystrophy, manifests with developmental regression and hypotonia progressing

to spastic tetraplegia. Seizures are common and visual impairment may occur due to involvement of the optic nerves. The childhood-onset form has a less specific presentation, with neuropsychiatric features (e.g. autism) and different motor symptoms (ataxia, dystonia, spasticity).

Mitochondrial Membrane Protein-Associated Neurodegeneration

Mitochondrial membrane protein-associated neurodegeneration (MPAN) is associated with autosomal-recessive mutations in the *C19orf12* gene. In a case series, the disease had a mean age of onset of 11 years (range 4–30 years) [37]. Common presenting symptoms included gait changes, followed by weakness and pyramidal features. Nearly all patients have cognitive decline and neuropsychiatric symptoms. Spasticity and/or limb dystonia appear to be common motor features; parkinsonism can be seen especially in later-onset patients. Other symptoms include visual impairment associated with optic atrophy, dysphagia, dysarthria, and bowel/bladder incontinence. Imaging shows hypointensity in the globus pallidus and substantia nigra; occasionally, a T2-hyperintense linear streak separating the globus pallidus internus and externus is visible (medial medullary lamina) [36, 37].

Beta-Propeller Protein-Associated Neurodegeneration

Beta-propeller protein-associated neurodegeneration (BPAN) is the only NBIA disorder with an X-linked dominant pattern of inheritance and is associated with mutations in the *WDR45* gene. Patients may have a history of developmental delay with limited expressive language capacity and midline hand stereotypies, similar to Rett syndrome. Other features include seizures, spasticity, and disordered sleep. Over the years (most commonly adolescence or adulthood) patients develop parkinsonism or dystonia. Levodopa may provide benefit, but its use is limited by dyskinesias. Imaging can be normal in the early phases of disease, but over time characteristic changes develop. These include hyperintensity on T1 sequences forming a "halo" in the substantia nigra and cerebral peduncle, as well as T2 hypointensity in the substantia nigra and globus pallidus [36, 38].

Other

Other NBIA disorders that have been associated with parkinsonism include Kufor–Rakeb syndrome (further commented on within this chapter, also considered part of the neuronal ceroid lipofuscinoses) and coenzyme A synthase protein-associated neurodegeneration (CoPAN). These disorders may have superimposed dystonia, spasticity, and cognitive impairment. CoPAN may have obsessive–compulsive features and peripheral neuropathy. Additional NBIA disorders include fatty acid-2 hydroxylase-associated neurodegeneration (FAHN), aceruloplasminemia, and neuroferritinopathy. The movement phenotype and associated features in these subtypes have been characterized in a recent review, but parkinsonism does not seem to be a major component [36].

In addition to the NBIA disorders, hereditary hemochromatosis (HH) is another iron storage condition in which parkinsonism has been reported. Typically in HH, iron deposition occurs in the liver, heart, pancreas, and pituitary. Typical symptoms include liver failure, endocrinopathy, cardiac conduction disturbance, and impotence. Rarely, symptoms resembling idiopathic Parkinson may arise in patients with an established diagnosis of HH, possibly secondary to iron deposition in the basal ganglia. Other neurological complications of HH include cognitive decline, gait difficulties, and cerebellar ataxia [39, 40]. It is likely that other diseases, from genetic and non-genetic etiologies, will be discovered to account for the portion of patients with iron accumulation in which no causative mutation is identified to date [36].

Manganese

Manganese deposition in the basal ganglia leads to toxicity with a progressive dystonia–parkinsonism syndrome. Manganese accumulation occurs from acquired causes or as a result of genetic mutations in *SLC30A10* and *SLC39A14*, coding for transporters involved in manganese homeostasis. Acquired causes include toxic exposure (contaminated water, drug use, miners, welders, and others), iatrogenic complication (total parental nutrition), or in the context of liver disease (acquired hepatocerebral degeneration) [41].

In patients with biallellic mutations in *SLC39A14*, manganese accumulation occurs predominantly in the brain. Symptoms are primarily neurological, with onset in infancy of developmental delay, progressive dystonia, and bulbar dysfunction. Generalized dystonia–parkinsonism ensues while cognitive function may be preserved [42]. Some patients were reported with acute presentation of generalized dystonia after a mild intercurrent infection [41].

Patients with bi-allelic mutations in *SLC30A10* have manganese accumulation in the brain and other tissues, leading to dystonia–parkinsonism with hepatic cirrhosis and polycythemia. Affected

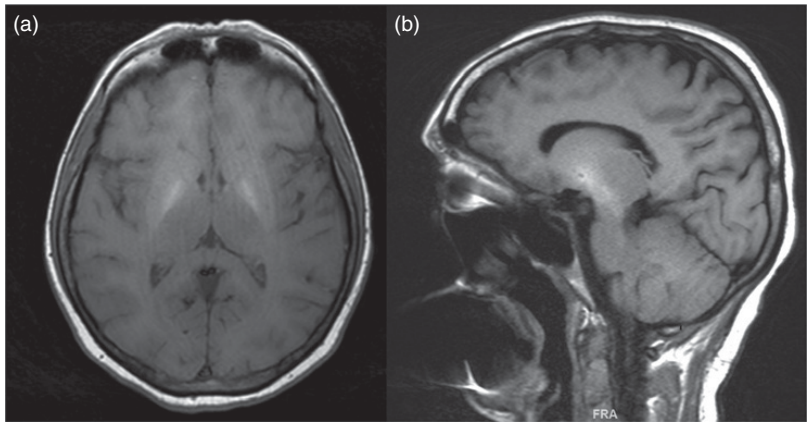

Figure 9.3 MRI of a patient with bi-allelic mutation in *SLC30A10* leading to syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia. (a) Axial T1 imaging demonstrating signal hyperintensity in the bilateral globus pallidus. (b) Sagittal T1-weighted imaging demonstrating signal hyperintensity extending to the midbrain/substantia nigra

individuals present in the first or second decade with gait disturbance and limb dystonia, sometimes accompanied by dysarthria and parkinsonian features such as bradykinesia and tremor. Developmental milestones are usually intact and intellect appears normal. Systemic features include elevated liver enzymes, hyperbilirubinemia, polycythemia with low iron stores, and high erythropoietin levels [43] (Video 9.2).

In both *SLC39A14* and *SLC30A10*-related disorders, blood manganese levels are increased and MRI demonstrates T1 hyperintense signals in the basal ganglia and pituitary gland (Figure 9.3). Hyperintense T1 signals may also be seen in the white matter (*SLC39A14*) or thalamus, brainstem, and cerebellum (*SLC30A10*). Additional features may include cerebral or cerebellar atrophy. Treatment is available with chelation agents.

Lysosomal Storage Disorders

Lysosomal storage disorders encompass more than 60 different diseases, with a variety of neurological manifestations. In a review series, the most common lysosomal storage disorderassociated with any movement disorder was Niemann–Pick type C (NPC), followed by different types of neuronal ceroid lipofuscinoses and mucopolyssacharidoses [44]. Parkinsonism is uncommon, but has been described in association with several types of lysosomal storage disorders.

Before discussing individual diseases, a few words are necessary to put the complex relationship between lysosomal function and parkinsonism into context. There is accumulating evidence demonstrating a close relationship between lysosomal function and parkinsonism. First, classic autosomal-recessive lysosomal storage disorders can have parkinsonism as a manifestation, as will be described here. In addition, dysfunction in the autophagy–lysosomal pathway has been demonstrated to promote an accumulation of alpha-synuclein, a major contributor to Parkinson disease, in experimental studies [45, 46]. Furthermore, genes associated with monogenic forms of Parkinson disease are involved in vesicular trafficking and degradation of proteins and organelles by the autophagy–lysosome pathway, including *SNCA, LRRK2*, *VPS35*, *DNAJC6* and *SYNJ1* [10]. *ATP1A3*, encoding for a lysosomal ATPase, causes a form of rapid-onset parkinsonism, with a complex constellation of symptoms. The gene *WDR45*, an essential component of the autophagy pathway, causes parkinsonism in the context of BPAN, a brain iron accumulation disorder discussed earlier in this chapter. Last but not least, heterozygous mutations in the *GBA* gene have been increasingly recognized as a risk factor for development of Parkinson disease. When present in the homozygous or compound heterozygous state, mutations in the *GBA* gene lead to Gaucher disease, the most common inherited lysosomal disorder. Parkinson disease has been described in patients with Gaucher disease, albeit infrequently and in the context of other typical symptoms of the disease [47].

Niemann–Pick Disease Type C

NPC is an autosomal-recessive neurodegenerative disorder caused by mutations in the *NPC1* or *NPC2*

genes, leading to an accumulation of glycosphingolipids in the brain, liver, and other tissues [48]. The core neurological manifestations include movement disorders (e.g. ataxia, dystonia), dysarthria, dysphagia, seizures, neuropsychiatric changes, and supranuclear gaze palsy. Systemic symptoms include cholestasis and hepatosplenomegaly. Parkinsonism has been described in heterozygous carriers of mutations in *NPC1*, or in patients with NPC in the context of other prevailing neurological symptoms, such as dysarthria, dysphagia, or ataxia [49]. NPC may present as an early-onset atypical parkinsonian syndrome reminiscent of progressive supranuclear palsy, with vertical supranuclear oculomotor palsy, cognitive decline, and levodopa unresponsiveness [48].

Neuronal Ceroid Lipofuscinoses

This group of diseases shares the feature of intracellular accumulation of autofluorescent lipopigment. Clinically, the neuronal ceroid lipofuscinoses present with visual deterioration, intellectual and motor disability, and seizures. Mutations in 13 different genes have been identified causing diseases with differing phenotypes and varied ages of onset [50, 51]. Of these, two are of interest in relationship to parkinsonism: ceroid lipofuscinosis type 3 (CLN3), also known as Batten disease, has a disease onset between 4 years and 7 years, with rapidly progressive vision loss. This is followed by cognitive decline and myoclonic seizures. Neuropsychiatric changes and parkinsonism appear in the second decade [50, 52]. Mutations in *ATP13A2*, associated with Kufor–Rakeb syndrome, present with bradykinesia, rigidity, spasticity, supranuclear gaze palsy, and dementia. Disease onset usually occurs in the second decade. Suggestive features include face and finger mini-myoclonus and evidence of metal deposition in T2*/SWI sequences, leading some authors to categorize Kufor–Rakeb syndrome within the spectrum of the NBIA disorders [53].

GM1 Gangliosidoses

GM1 gangliosidosis represents a phenotypic spectrum of diseases caused by autosomal-recessive mutations in the beta-galactosidase gene, *GLB1*. Besides GM1 gangliosidosis, mutations in this gene can cause a phenotypically distinct disorder, mucopolyssacharidosis type IVB (also known as Morquio B disease). GM1 gangliosidosis is divided into three different forms: infantile (type 1, most frequent), late-infantile and juvenile (type 2), and type 3, with onset in the second or third decade. The forms are ranked in descending forms of severity. Patients with type 3 usually survive into adulthood and have selective GM1 ganglioside accumulation in the striatum, leading to occasional T2 hyperintensity visible on MRI. The onset of symptoms often occurs before the age of 20 years with generalized dystonia, prominent dysarthria, and gait disturbance. Dystonia dominates the picture, but superimposed parkinsonism has been described, with variable levels of pyramidal signs, cognitive impairment, skeletal dysplasia, short stature, and scoliosis. Mild cardiac valve disorders have been described [54].

GM2 Gangliosidoses

GM2 gangliosidoses are a group of diseases characterized by the accumulation of ganglioside GM2 and related glycolipids in the lysosomes. The hydrolysis of GM2 depends on the enzyme beta-hexosaminidase and the substrate-specific cofactor GM2 activator. Beta-hexosaminidase exists in two isoforms according to their subunits: Hex A (αβ), Hex B (ββ). Of these, only Hex A can act on the ganglioside GM2/GM2 activator complex. There are three genes involved in this process: *HEXA* (involved in the synthesis of the alpha subunit of hexosaminidase), *HEXB* (involved in the synthesis of the beta subunit of hexosaminidase), and *GM2A* (involved in the synthesis of the GM2 activator). Hex A deficiency causes Tay–Sachs disease, Hex B causes Sandhoff disease, and *GM2A* mutations lead to GM2 activator deficiency. Despite wide phenotypic differences (e.g. visceral involvement in Sandhoff disease), all three diseases are characterized pathologically by swollen neurons with storage material in their lysosomes [55]. The predominant neurological manifestations of GM2 gangliosidoses relate to cerebellar, pyramidal, and autonomic system dysfunction, often with cognitive changes [56]. Nevertheless, parkinsonism has been described in association with Hex A deficiency, in the context of other symptoms typical of the disease [44, 56] (Video 9.3).

Other Lysosomal Storage Diseases

Juvenile parkinonism has also been described in the adult form of Chédiak–Higashi syndrome, a rare lysosomal trafficking disorder leading to recurrent bacterial infections, partial albinism, and several hematological abnormalities. Symptoms may be levodopa-responsive [57] (Figure 9.4). Mucopolysacharidosis type III alpha/beta (also known as pseudo-Hurler pseudodystrophy), a disorder characterized by dysostosis multiplex and cardiorespiratory complications, has been reported in association with juvenile parkinsonism [58].

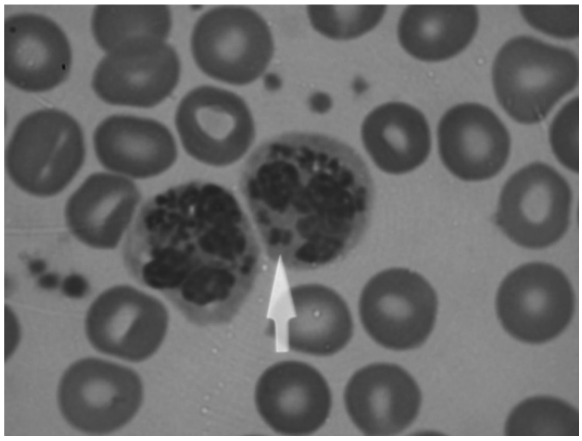

Figure 9.4 Chédiak–Higashi syndrome: classic giant azurophilic granules seen in peripheral blood smear (arrow). These accumulations can be seen in neutrophils, eosinophils, and other granulocytes.

Mitochondrial Disease and Disorders of Energy Metabolism

The relationship between mitochondrial dysfunction and parkinsonism is multifaceted. Mitochondrial diseases, arising from mutations in mitochondrial or nuclear DNA genes, may cause parkinsonism in the context of multisystem disease or as a dominant clinical feature, mimicking idiopathic Parkinson disease. Furthermore, a subset of patients with idiopathic Parkinson disease has evidence of subclinical mitochondrial dysfunction, even in the absence of an identifiable nuclear or mitochondrial DNA mutation. Finally, some of the inherited parkinsonian syndromes have in vitro evidence of impaired mitochondrial function (*PINK1*, *Parkin*, *DJ1*, *FBXO7*) [59].

When parkinsonism arises in the context of mitochondrial disorders, the additional neurological manifestations may include associated movement disorders (e.g. ataxia, dystonia, myoclonus) and myopathy, stroke-like episodes, lactic acidosis, epilepsy, and ophthalmoplegia. Multi-organ involvement may be seen. Generally speaking, dystonia is the most common movement disorder in pediatric patients whereas parkinsonism tends to be most common in adults [60]. Clinical syndromes due to mitochondrial DNA (mtDNA) mutations in which parkinsonism has been described to be responsive to levodopa include myoclonic epilepsy associated with ragged red fibers (MERRF), mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, Leber hereditary optic neuropathy, and Leigh syndrome [59, 61]. In patients with mitochondrial disease in which parkinsonism was the dominant or presenting feature, notable clinical features besides parkinsonism include a positive family history, dystonia, lactic acidosis, evidence of myopathy, oculomotor dysfunction, or ataxia [59].

Parkinsonism due to mtDNA mutations include mutations in several genes, including *tRNA(Lys)*, *tRNA(Gln)*, *ND1*, *ND2*, *ND3*, *ND4*, *ND6*, *MTCYB* as well as multiple mtDNA deletion syndromes. Mutations in nuclear DNA genes associated with parkinsonism include *POLG1*, *TWNK (C10orf2)*, *SDHA*, *RRM2B*, *OPA1* [59–61]. The most prevalent appears to be *POLG1*. It can mimic idiopathic Parkinson disease or potentially act as a risk factor for its development [60, 62]. Dysfunction in this protein may cause multiple mtDNA deletions in affected tissues, and when parkinsonism develops it may be levodopa-responsive. Some patients may have additional clinical features, such as progressive external ophthalmoplegia (mimicking progressive supranuclear palsy) and early menopause [61, 63].

Other defects in energy metabolism not directly related to the mitochondrial respiratory chain may cause parkinsonism as well. Defects in pyruvate carboxylase, an enzyme involved in gluconeogenesis and energy production, may cause a syndrome involving hypokinesia and tremors, in addition to hypotonia, nystagmus, seizures, liver failure, and lactic acidosis [64]. Phosphoglycerate kinase 1 deficiency (classically associated with recurrent hemolytic anemia, myopathy, seizures, and intellectual disability) has also been described in association with early-onset parkinsonism [65, 66]. Finally, mutations in *SLC2A1* (glucose transporter type 1 deficiency) can have a plethora of neurological manifestations, including paroxysmal spells with parkinsonian features [67].

Other Disorders

Vitamin-Responsive Disorders

Biotin–Thiamine Responsive Basal Ganglia Disease

This treatable IEM is associated with mutations in the *SLC19A3* gene, encoding a thiamine transporter. The disease seems to be most prevalent on the Arabian peninsula, but has been described in different ethnic groups [68]. Patients present in the first decade of life with episodes triggered by fever and intercurrent illnesses. The most common manifestations include subacute encephalopathy, dysphagia, ophthalmoplegia, and

generalized dystonia. If left untreated the disease may progress to coma or even death [68, 69]. Imaging has characteristic changes, sharing some features common to Wernicke encephalopathy such as involvement of the mediodorsal nucleus of the thalamus, periventricular regions of the third ventricle, central gray matter, and cerebellum. Early treatment with biotin and thiamine may completely reverse the course of disease, but delayed treatment can result in chronic dystonia or parkinsonism, epilepsy, and intellectual disability with gliosis of the striatum [68].

Molybdenum Cofactor Deficiency

Molybdenum cofactor is synthesized by a complex pathway that involves four genes (*MOCS1*, *MOCS2*, *MOCS3*, and *GPHN*). The disorder typically presents in infancy with intractable seizures and encephalopathy, but there have been case reports of dystonia or spastic quadriparesis mimicking cerebral palsy. Lens dislocation, low uric acid levels, and cerebral atrophy can be clues to the diagnosis [70]. In one case report, a patient presented with dystonia and rapidly progressive parkinsonism in the third decade of life, in the setting of basal ganglia signal hyperintensity and a previous history of lens dislocation [71].

Lipid Storage Diseases

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis is an autosomal-recessive disorder due to mutations in the *CYP27A1* gene. This gene codes for the enzyme sterol 27-hydroxylase, responsible for oxidizing cholesterol to 27-hydroxycholesterol in the bile acid synthetic pathway [72]. Deficiency of this enzyme leads to an accumulation of cholestanol. The earliest clinical manifestations may be chronic diarrhea and cataracts, followed by xanthomas in the second decade (most commonly in the Achilles tendon, but other sites have also been described) and several neuropsychiatric symptoms [73]. Motor manifestations typically include cerebellar ataxia and spasticity, most often in the third decade. When parkinsonism occurs, it tends to manifest in the third or fourth decade, along with pre-existing spasticity, ataxia, neuropsychiatric changes, or seizures. Imaging may demonstrate diffuse cerebral and cerebellar white matter lesions and some patients may show evidence of decreased presynaptic dopaminergic uptake [74]. Cerebrotendinous xanthomatosis can be treated with bile acid replacement and parkinsonism may respond to levodopa [72, 74].

Organic Acidurias and Aminoacidopathies

Glutaric Aciduria Type 1

Glutaric aciduria type 1 (GA-1) is an autosomal-recessive condition caused by mutations in the glutaryl-coenzyme A dehydrogenase (*GCDH)* gene. The enzyme is involved in the catabolic pathway of lysine, hydroxylysine, and tryptophan. Patients with GA-1 have a toxic accumulation of 3-hydroxyglutaric acid and glutaric acid. Typically, patients may present with macrocephaly or hypotonia that precedes acute metabolic crises manifesting with generalized dystonia and encephalopathy after some trigger (infection, vaccination, dehydration), usually before the age of 2 years. In the acute setting, imaging may demonstrate cytotoxic edema in the striatum, but over time there is basal ganglia atrophy with signal hyperintensity. Other characteristic findings on imaging include widened Sylvian fissures and mesencephalic cisterns, and hyperintense signals in other deep nuclei and white matter. After an acute metabolic crisis, patients are often left with generalized dystonia and axial hypotonia. A particular feature seems to be early orofacial involvement [75]. When patients develop parkinsonism, it occurs superimposed on generalized dystonia, most often in the context of several years of disease leading to fixed dystonia and a hypokinetic–rigid syndrome [75, 76].

Homocystinuria

This autosomal-recessive disorder is characterized by defects in the metabolism of sulfur-containing aminoacids, resulting in gradual accumulation of homocysteine, homocysteine disulphide, and methionine [77]. There is excessive excretion of homocysteine in the urine and elevated plasma homocysteine. The most common cause is deficiency of the cystathionine-beta-synthase enzyme. The typical features of this condition include intellectual disability, lens dislocation, atherosclerosis, skeletal abnormalities, and Marfanoid habitus. Rarely, patients with homocystinuria may develop dystonia or parkinsonism that is not secondary to thromboembolic strokes to the basal ganglia [77, 78]. In these cases, parkinsonism usually occurred in the context of other features more suggestive of the disease, such as intellectual disability, ocular disease, or a positive family history.

Primary Familial Brain Calcification Syndromes

Primary familial brain calcification (PFBC) denotes a group of disorders, usually with autosomal-

dominant inheritance, where there are calcium phosphate deposits in the microvasculature of the basal ganglia and other brain structures leading to motor, cognitive, and neuropsychiatric symptoms. There are four causative genes identified so far: *SLC20A2*, *PDGFRB*, *PDGFB*, and *XPR1* [79]. The first step to a diagnosis relies on excluding secondary causes of basal ganglia calcifications. Examples include infections, parathyroid hormonal disturbances, mitochondrial disease, congenital syndromes, and necrosis due to traumatic, toxic, inflammatory, or physical insults. Furthermore, physiological brain calcification may be observed in up to 20% of individuals [80]. The PFBC designation is preferred to the older term "Fahr's disease," a non-specific designation that has been used in the context of either primary or secondary calcifications leading to neurological symptoms.

Clinical symptoms often appear in the third or fourth decade (median 31 years) but onset across the life spectrum has been reported. Movement disorders and neuropsychiatric disturbances are the main manifestations. PFBC is thought to be 100% penetrant in regards to neuroradiological evidence of basal ganglia calcification (usually evident by the age of 50 years), but up to 40% of subjects may be clinically asymptomatic. Parkinsonism is the most frequent manifestation, mostly with an akinetic–rigid presentation. This may occur in combination with other movement disorders, such as ataxia, dystonia, or paroxysmal dyskinesia. Most common neuropsychiatric issues include cognitive impairment, depression, anxiety, and psychosis. Other neurological signs may include migraines, dysarthria/dysphagia, seizures, or urinary urge-incontinence [79, 81].

The diagnosis of PFBC may be suspected in patients with movement disorders (especially parkinsonism) associated with dementia, cerebellar symptoms, and evidence of basal ganglia calcification on imaging. CT has the highest sensitivity. Calcium deposits may be visualized in the basal ganglia, cerebellar dentate nucleus, or other areas such as the subcortical white matter and brainstem. MRI is less sensitive but may show iso- or hyperintense signals in T1 and hypointense signals on T2. The most commonly mutated gene is *SLC20A2* (17–55% of cases), followed by *PDGFB* (3.4–31% of cases) and *PDGFRB* (1.7–11% of cases). Genetic testing fails to identify a causative mutation in 46% of cases [79, 80, 82].

Final Considerations

It is challenging and potentially misleading to try and devise simplistic diagnostic strategies in the context of parkinsonism associated with IEMs. First, most cases of juvenile parkinsonism are not caused by IEMs, and a complete and careful drug history (both recreational and prescription drugs), a high index of suspicion for neuro-inflammation, and obtaining appropriate neuroimaging studies are paramount at initial evaluation. A case-by-case approach and the opinion of a specialist in movement disorders may be warranted. Brain imaging can be useful in developing a differential diagnosis. Structural MRI including sequences sensitive to iron accumulation are desirable (although brain calcifications may be better appreciated on CT imaging). CSF testing for pterins and neurotransmitters (when available) can be useful to diagnose neurotransmitter disorders that can be treated with precursors, inhibitors of neurotransmitter break-down, receptor agonists, and cofactors. Laboratory testing strategies should be prioritized for disorders that have specific treatment: chelation therapy for Wilson disease and manganese storage disorders; chenodeoxycholic acid and hydroxymethylglutaryl-coenzyme A (HMG–CoA) inhibitors for cerebrotendinous xanthomatosis; enzyme replacement for some lysosomal storage disorders; mitochondrial cocktails; vitamin replacement (biotin and thiamine deficiency, homocystinuria) and dietary interventions (glutaric aciduria, homocystinuria), among other strategies. Although gene panels for parkinsonism are available, the genes to be included vary between laboratories. An individualized approach is needed to assess whether metabolic testing, a gene panel, or exome sequencing is more likely to elucidate a rapid diagnosis. Ultimately, a diagnosis is desirable in all cases (even those without specific treatment), as it will provide information on natural history, enable enrolment in registries and clinical trials, and allows for genetic counseling.

In patients with parkinsonism as the predominant phenotype, it is reasonable to consider using levodopa or other antiparkinsonian medications. These patients may have a good likelihood of responding, especially if parkinsonism is isolated or associated with mild to moderate dystonia. Familiarity with prescribing levodopa is important, as side effects such as debilitating dyskinesias may be an early and unpleasant complication (especially in some neurotransmitter disorders). Small doses, sometimes even below 0.5 mg/kg per day, with slow and careful increases, might be a reasonable

strategy. This is in stark contrast to the higher starting doses typically used in classic Parkinson disease. Complex presentations that include parkinsonism may or may not respond to levodopa. It is reasonable to consider using anticholinergic agents in this context. Other pharmacological strategies used when treating parkinsonism, including dopamine agonists, COMT (catechol-O-methyltransferase) inhibitors, MAO-B inhibitors, and amantadine should be considered on a case-by-case basis, and expert consultation may be desirable.

Key Points and Clinical Pearls

- An underlying IEM should be considered in any child or young adult with unexplained, insidiously progressive, and chronic parkinsonism.
- Brain imaging can be useful in developing a differential diagnosis and should include sequences sensitive to iron accumulation.
- CSF testing for pterins and neurotransmitters (if available) can be useful to diagnose neurotransmitter disorders.
- Laboratory testing strategies should prioritize disorders that have a specific treatment.
- Metabolic testing, gene panels, or clinical exome sequencing should be considered as first line diagnostic tests depending on the clinical presentation and available resources.
- In patients with parkinsonism as the predominant phenotype, it is reasonable to consider a trial of levodopa or other antiparkinsonian medications.

Directions for Future Research

- Development of disease registries and detailed longitudinal studies of IEMs that present with parkinsonism.
- Development of evidence-based guidelines for the diagnostic work-up and treatment of primary neurotransmitter disorders.
- Development of a better understanding of the molecular mechanisms that lead to parkinsonism in a variety of different IEMs.
- Development of targeted therapies, including gene therapy, as well as novel approaches to the symptomatic treatment of parkinsonism.

References

1. Fahn S, Jankovic J, Hallett M. Principles and Practice of Movement Disorders, 2nd edn. Philadelphia, PA: Elsevier; 2011.
2. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;**30**(12):1591–601.
3. Kang SY, Wasaka T, Shamim EA, et al. Characteristics of the sequence effect in Parkinson's disease. Mov Disord. 2010;**25**(13):2148–55.
4. Golbe LI. Young-onset Parkinson's disease: A clinical review. Neurology. 1991;**41**(2(Pt 1)):168–73.
5. Quinn N, Critchley P, Marsden CD. Young onset Parkinson's disease. Mov Disord. 1987;**2**(2):73–91.
6. Paviour DC, Surtees RA, Lees AJ. Diagnostic considerations in juvenile parkinsonism. Mov Disord. 2004;**19**(2):123–35.
7. Correia Guedes L, Ferreira JJ, Rosa MM, et al. Worldwide frequency of G2019S *LRRK2* mutation in Parkinson's disease: A systematic review. Parkinsonism Relat Disord. 2010;**16**(4):237–42.
8. Schneider SA, Alcalay RN. Neuropathology of genetic synucleinopathies with parkinsonism: Review of the literature. Mov Disord. 2017;**32**(11):1504–23.
9. Mandemakers W, Quadri M, Stamelou M, Bonifati V. *TMEM230*: How does it fit in the etiology and pathogenesis of Parkinson's disease? Mov Disord. 2017;**32**(8):1159–62.
10. Kumaran R, Cookson MR. Pathways to Parkinsonism redux: Convergent pathobiological mechanisms in genetics of Parkinson's disease. Hum Mol Genet. 2015;**24**(R1):R32-44.
11. Garcia-Cazorla A, Duarte ST. Parkinsonism and inborn errors of metabolism. J Inherit Metab Dis. 2014;**37**(4):627–42.
12. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol. 2006;**5**(4):355–63.
13. Fernandez-Alvarez E. Frequency of movement disorders in children. Rev Neurol. 2001;**33**(3):228–9.
14. Fernandez-Alvarez E, Aicardi J. Movement Disorders in Children. London: Mac Keith Press; 2001.
15. Garcia-Cazorla A, Ortez C, Perez-Duenas B, et al. Hypokinetic–rigid syndrome in children and inborn

errors of metabolism. Eur J Paediatr Neurol. 2011;**15**(4):295–302.

16. Kurian MA, Gissen P, Smith M, Heales S, Jr., Clayton PT. The monoamine neurotransmitter disorders: An expanding range of neurological syndromes. Lancet Neurol. 2011;**10**(8):721–33.
17. Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders: Clinical advances and future perspectives. Nat Rev Neurol. 2015;**11**(10):567–84.
18. Rodan LH, Gibson KM, Pearl PL. Clinical use of CSF neurotransmitters. Pediatr Neurol. 2015;**53**(4):277–86.
19. Wijemanne S, Jankovic J. Dopa-responsive dystonia: Clinical and genetic heterogeneity. Nat Rev Neurol. 2015;**11**(7):414–24.
20. Rilstone JJ, Alkhater RA, Minassian BA. Brain dopamine–serotonin vesicular transport disease and its treatment. N Engl J Med. 2013;**368**(6):543–50.
21. Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology. 2010;**75**(1):64–71.
22. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol. 2003;**54** Suppl 6:S32-45.
23. Furukawa Y, Kish SJ, Bebin EM, et al. Dystonia with motor delay in compound heterozygotes for GTP-cyclohydrolase I gene mutations. Ann Neurol. 1998;**44**(1):10–6.
24. Opladen T, Hoffmann G, Horster F, et al. Clinical and biochemical characterization of patients with early infantile onset of autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia. Mov Disord. 2011;**26**(1):157–61.
25. Friedman J, Roze E, Abdenur JE, et al. Sepiapterin reductase deficiency: A treatable mimic of cerebral palsy. Ann Neurol. 2012;**71**(4):520–30.
26. Opladen T, Hoffmann GF, Blau N. An international survey of patients with tetrahydrobiopterin deficiencies presenting with hyperphenylalaninaemia. J Inherit Metab Dis. 2012;**35**(6):963–73.
27. Takahashi Y, Manabe Y, Nakano Y, et al. Parkinsonism in association with dihydropteridine reductase deficiency. Case Rep Neurol. 2017;**9**(1):17–21.
28. Willemsen MA, Verbeek MM, Kamsteeg EJ, et al. Tyrosine hydroxylase deficiency: A treatable disorder of brain catecholamine biosynthesis. Brain. 2010;**133**(Pt 6):1810–22.
29. Hoffmann GF, Assmann B, Brautigam C, et al. Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. Ann Neurol. 2003;**54** Suppl 6:S56-65.
30. Pons R, Syrengelas D, Youroukos S, et al. Levodopa-induced dyskinesias in tyrosine hydroxylase deficiency. Mov Disord. 2013;**28**(8):1058–63.
31. Chien YH, Lee NC, Tseng SH, et al. Efficacy and safety of *AAV2* gene therapy in children with aromatic L-amino acid decarboxylase deficiency: An open-label, phase 1/2 trial. Lancet Child Adolesc Health. 2017;**1**(4):265–73.
32. Jacobsen JC, Wilson C, Cunningham V, et al. Brain dopamine–serotonin vesicular transport disease presenting as a severe infantile hypotonic parkinsonian disorder. J Inherit Metab Dis. 2016;**39**(2):305–8.
33. Saito T. Presenting symptoms and natural history of Wilson disease. Eur J Pediatr. 1987;**146**(3):261–5.
34. Czlonkowska A, Litwin T, Chabik G. Wilson disease: Neurologic features. Handb Clin Neurol. 2017;**142**:101–19.
35. Machado A, Chien HF, Deguti MM, et al. Neurological manifestations in Wilson's disease: Report of 119 cases. Mov Disord. 2006;**21**(12):2192–6.
36. Hayflick SJ, Kurian MA, Hogarth P. Neurodegeneration with brain iron accumulation. Handb Clin Neurol. 2018;**147**:293–305.
37. Hogarth P, Gregory A, Kruer MC, et al. New NBIA subtype: Genetic, clinical, pathologic, and radiographic features of MPAN. Neurology. 2013;**80**(3):268–75.
38. Hayflick SJ, Kruer MC, Gregory A, et al. Beta-propeller protein-associated neurodegeneration: A new X-linked dominant disorder with brain iron accumulation. Brain. 2013;**136**(Pt 6):1708–17.
39. Costello DJ, Walsh SL, Harrington HJ, Walsh CH. Concurrent hereditary haemochromatosis and idiopathic Parkinson's disease: A case report series. J Neurol Neurosurg Psychiatry. 2004;**75**(4):631–3.
40. Sedel F, Saudubray JM, Roze E, Agid Y, Vidailhet M. Movement disorders and inborn errors of metabolism in adults: A diagnostic approach. J Inherit Metab Dis. 2008;**31**(3):308–18.
41. Marti-Sanchez L, Ortigoza-Escobar JD, Darling A, et al. Hypermanganesemia due to mutations in *SLC39A14*: Further insights into Mn deposition in the central nervous system. Orphanet J Rare Dis. 2018;**13**:28.
42. Tuschl K, Meyer E, Valdivia LE, et al. Mutations in *SLC39A14* disrupt manganese homeostasis and cause childhood-onset parkinsonism–dystonia. Nat Commun. 2016;**7**:11601.
43. Tuschl K, Clayton PT, Gospe SM, Jr., et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in *SLC30A10*, a manganese transporter in man. Am J Hum Genet. 2016;**99**(2):521.

44. Ebrahimi-Fakhari D, Hildebrandt C, Davis PE, et al. The spectrum of movement disorders in childhood-onset lysosomal storage diseases. Mov Disord Clin Pract. 2018;**5**(2):149–55.
45. Dehay B, Martinez-Vicente M, Caldwell GA, et al. Lysosomal impairment in Parkinson's disease. Mov Disord. 2013;**28**(6):725–32.
46. Liu JP, Tang Y, Zhou S, et al. Cholesterol involvement in the pathogenesis of neurodegenerative diseases. Mol Cell Neurosci. 2010;**43**(1):33–42.
47. Kraoua I, Stirnemann J, Ribeiro MJ, et al. Parkinsonism in Gaucher's disease type 1: Ten new cases and a review of the literature. Mov Disord. 2009;**24**(10):1524–30.
48. Hendriksz CJ, Anheim M, Bauer P, et al. The hidden Niemann–Pick type C patient: Clinical niches for a rare inherited metabolic disease. Curr Med Res Opin. 2017;**33**(5):877–90.
49. Coleman RJ, Robb SA, Lake BD, Brett EM, Harding AE. The diverse neurological features of Niemann–Pick disease type C: A report of two cases. Mov Disord. 1988;**3**(4):295–9.
50. Mole SE, Williams RE. Neuronal ceroid-lipofuscinoses. GeneReviews®. 2001;Oct 10 (updated Aug 1, 2013).
51. Bras J, Verloes A, Schneider SA, Mole SE, Guerreiro RJ. Mutation of the parkinsonism gene *ATP13A2* causes neuronal ceroid-lipofuscinosis. Hum Mol Genet. 2012;**21**(12):2646–50.
52. Mink JW, Augustine EF, Adams HR, Marshall FJ, Kwon JM. Classification and natural history of the neuronal ceroid lipofuscinoses. J Child Neurol. 2013;**28**(9):1101–5.
53. Behrens MI, Bruggemann N, Chana P, et al. Clinical spectrum of Kufor–Rakeb syndrome in the Chilean kindred with *ATP13A2* mutations. Mov Disord. 2010;**25**(12):1929–37.
54. Roze E, Paschke E, Lopez N, et al. Dystonia and parkinsonism in GM1 type 3 gangliosidosis. Mov Disord. 2005;**20**(10):1366–9.
55. Gravel RA, Kaback MM, Proia RL, et al. The GM2 gangliosidoses. In Beaudet AL, Vogelstein B, Kinzler KW, et al., editors. The Online Metabolic and Molecular Bases of Inherited Disease. New York, NY: McGraw-Hill; 2014. [Online, accessed Dec 1, 2019; doi:10.1036/ommbid.184.]
56. Inzelberg R, Korczyn AD. Parkinsonism in adult-onset GM2 gangliosidosis. Mov Disord. 1994;**9**(3):375–7.
57. Silveira-Moriyama L, Moriyama TS, Gabbi TV, Ranvaud R, Barbosa ER. Chédiak–Higashi syndrome with parkinsonism. Mov Disord. 2004;**19**(4):472–5.
58. Hara M, Inokuchi T, Taniwaki T, et al. An adult patient with mucolipidosis III alpha/beta presenting with parkinsonism. Brain Dev. 2013;**35**(5):462–5.
59. Finsterer J. Parkinson's syndrome and Parkinson's disease in mitochondrial disorders. Mov Disord. 2011;**26**(5):784–91.
60. Martikainen MH, Ng YS, Gorman GS, et al. Clinical, genetic, and radiological features of extrapyramidal movement disorders in mitochondrial disease. JAMA Neurol. 2016;**73**(6):668–74.
61. Ghaoui R, Sue CM. Movement disorders in mitochondrial disease. J Neurol. 2018;**265**(5):1230–40.
62. Luoma PT, Eerola J, Ahola S, et al. Mitochondrial DNA polymerase gamma variants in idiopathic sporadic Parkinson disease. Neurology. 2007;**69**(11):1152–9.
63. Luoma P, Melberg A, Rinne JO, et al. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: Clinical and molecular genetic study. Lancet. 2004;**364**(9437):875–82.
64. Garcia-Cazorla A, Rabier D, Touati G, et al. Pyruvate carboxylase deficiency: Metabolic characteristics and new neurological aspects. Ann Neurol. 2006;**59**(1):121–7.
65. Sakaue S, Kasai T, Mizuta I, et al. Early-onset parkinsonism in a pedigree with phosphoglycerate kinase deficiency and a heterozygous carrier: Do *PGK-1* mutations contribute to vulnerability to parkinsonism? NPJ Parkinsons Dis. 2017;**3**:13.
66. Sotiriou E, Greene P, Krishna S, Hirano M, DiMauro S. Myopathy and parkinsonism in phosphoglycerate kinase deficiency. Muscle Nerve. 2010;**41**(5):707–10.
67. Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in Glut-1 deficiency. Mov Disord. 2010;**25**(3):275–81.
68. Tabarki B, Al-Shafi S, Al-Shahwan S, et al. Biotin-responsive basal ganglia disease revisited: Clinical, radiologic, and genetic findings. Neurology. 2013;**80**(3):261–7.
69. Ozand PT, Gascon GG, Al Essa M, et al. Biotin-responsive basal ganglia disease: A novel entity. Brain. 1998;**121** (Pt 7):1267–79.
70. Kikuchi K, Hamano S, Mochizuki H, Ichida K, Ida H. Molybdenum cofactor deficiency mimics cerebral palsy: Differentiating factors for diagnosis. Pediatr Neurol. 2012;**47**(2):147–9.
71. Alkufri F, Harrower T, Rahman Y, et al. Molybdenum cofactor deficiency presenting with a parkinsonism–dystonia syndrome. Mov Disord. 2013;**28**(3):399–401.
72. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: A comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;**9**:179.

73. Federico A, Dotti MT, Gallus GN. Cerebrotendinous xanthomatosis. GeneReviews®. 2003; Jul 16 (updated Apr 14, 2016).
74. Su CS, Chang WN, Huang SH, et al. Cerebrotendinous xanthomatosis patients with and without parkinsonism: Clinical characteristics and neuroimaging findings. Mov Disord. 2010;**25**(4):452–8.
75. Gitiaux C, Roze E, Kinugawa K, et al. Spectrum of movement disorders associated with glutaric aciduria type 1: A study of 16 patients. Mov Disord. 2008;**23**(16):2392–7.
76. Gascon GG, Ozand PT, Brismar J. Movement disorders in childhood organic acidurias. Clinical, neuroimaging, and biochemical correlations. Brain Dev. 1994;**16** Suppl:94–103.
77. Sinclair AJ, Barling L, Nightingale S. Recurrent dystonia in homocystinuria: A metabolic pathogenesis. Mov Disord. 2006;**21**(10):1780–2.
78. Ekinci B, Apaydin H, Vural M, Ozekmekci S. Two siblings with homocystinuria presenting with dystonia and parkinsonism. Mov Disord. 2004;**19**(8):962–4.
79. Ramos EM, Carecchio M, Lemos R, et al. Primary brain calcification: An international study reporting novel variants and associated phenotypes. Eur J Hum Genet. 2018;**26**(10):1462–77.
80. Batla A, Tai XY, Schottlaender L, et al. Deconstructing Fahr's disease/syndrome of brain calcification in the era of new genes. Parkinsonism Relat Disord. 2017;**37**:1–10.
81. Manyam BV, Walters AS, Keller IA, Ghobrial M. Parkinsonism associated with autosomal dominant bilateral striopallidodentate calcinosis. Parkinsonism Relat Disord. 2001;**7**(4):289–95.
82. Ramos EM, Oliveira JR, Sobrido MJ, Coppola G. Primary familial brain calcification. GeneReviews®. 2004;Apr 18 (updated Aug 24, 2017).

Chapter

10

A Phenomenology-Based Approach to Inborn Errors of Metabolism with Spasticity

Laura Tochen and Toni S. Pearson

Introduction

Spasticity is a motor abnormality characterized by increased muscular tone. It results from a lesion of the corticospinal (or pyramidal) tract, which includes motor neurons in the cerebral cortex and their axonal white matter projections through the brain and spinal cord, to the point of synapse with lower motor neurons in the spinal cord. Patients with spasticity, or their caregivers, typically complain of stiffness, and the predominant associated examination findings are a velocity-dependent resistance to passive movement of an affected limb, hyperreflexia, and pathological reflexes such as a Babinski sign. Spasticity is typically accompanied by weakness and impaired motor control in affected muscle groups. Depending on the site of the lesion in the central nervous system, spasticity may be present in both legs (termed diparesis or paraparesis), all four limbs (quadriparesis or tetraparesis), or one side of the body (hemiparesis).

The upper motor neurons forming the corticospinal tracts have considerable energy and transport demands that may make them particularly vulnerable to metabolic disruption [1]. Spasticity is therefore a feature of many metabolic disorders that affect the nervous system. Usually, spasticity is one feature of a more complex syndrome that includes other neurological and systemic symptoms and signs. Importantly, a number of metabolic diseases that cause spasticity are treatable. This chapter provides an overview of the metabolic disorders in which spasticity is a prominent feature, including clinical and imaging characteristics that may help to narrow the differential diagnosis.

Clinical Evaluation

A small number of conditions may initially present with relatively isolated spastic paraparesis. These include arginase deficiency, dopa-responsive dystonia, X-linked adrenoleukodystrophy (X-ALD; adrenomyeloneuropathy subtype), homocysteine remethylation defects, and hyperammonemia–hyperornithinemia–homocitrullinemia (HHH) syndrome.

In contrast, many disorders associated with spasticity present with mixed symptoms, or with initial neurological symptoms other than spasticity. Seizures and intellectual disability are common, and therefore relatively non-specific, accompanying features. The presence of some neurological features, such as ataxia, involuntary movements, or peripheral neuropathy (Table 10.1) often help to narrow the differential diagnosis considerably. In addition, some disorders are associated with distinctive systemic features, such as skin rash (e.g. biotinidase deficiency, Sjögren–Larsson syndrome), or organomegaly (e.g. lysosomal storage disorders, peroxisome biogenesis disorders). Ophthalmological evaluation is also an important step, because a number of disorders are associated with eye findings, such as optic atrophy, retinopathy, or cataracts (Table 10.1).

Neuroimaging

Brain MRI is a first-line investigation that can provide helpful diagnostic clues. For patients with progressive spasticity, involvement of the pyramidal tract is likely, and a disease-specific pattern of involvement should be sought. MRI patterns that may be suggestive of a specific disorder can then guide the provider to targeted biochemical or genetic confirmatory testing (Table 10.2). White matter involvement that is parieto-occipital may be suggestive of X-ALD, while a more frontal pattern may be more suggestive of metachromatic leukodystrophy (MLD). T2 lesions of cerebellar and dentate nuclei may be a feature of Krabbe disease or cerebrotendinous xanthomatosis. Variable basal ganglia involvement may point to other lysosomal storage disorders, but basal ganglia involvement (or necrosis in severe cases) can also be found in mitochondrial disorders and organic acidurias (Table 10.2). Additional imaging techniques,

Table 10.1 Neurological and non-neurological findings associated with inborn errors of metabolism that cause spasticity

Clinical features	Conditions
Neurological features	
Episodic encephalopathy with vomiting	Homocysteine remethylation defects, arginase deficiency, HHH syndrome, MMA, PA
Seizures	Glycine encephalopathy, serine deficiency, molybdenum cofactor deficiency, asparagine synthetase deficiency, GLUT1 deficiency syndrome, cerebrotendinous xanthomatosis, biotinidase deficiency, cerebral folate deficiency, HHH syndrome, homocysteine remethylation defects, arginase deficiency, PKU, MLD, Krabbe disease (late feature), multiple sulfatase deficiency, GM1 gangliosidosis, GM2 gangliosidosis, fucosidosis, X-ALD, peroxisome biogenesis disorders, PDH deficiency, LBSL, LTBL, INAD
Ataxia	GLUT1 deficiency syndrome, cerebrotendinous xanthomatosis, cerebral folate deficiency, biotinidase deficiency, HHH syndrome, Homocysteine remethylation defects, Gaucher (type 3), GM2 gangliosidosis, peroxisome biogenesis disorders, PDH deficiency, LBSL, ARSAL, INAD, mitochondrial disorders
Dystonia and/or chorea	Dopa-responsive dystonia, GLUT1 deficiency syndrome, MMA, PA, maple syrup urine disease, Lesch–Nyhan disease, cerebral folate deficiency, cerebrotendinous xanthomatosis, biotinidase deficiency, vitamin E deficiency, Gaucher disease, GM2 gangliosidosis, LTBL, ARSAL, PKAN, INAD, mitochondrial disorders
Parkinsonism	Dopa-responsive dystonia, PKU (adult), PKAN
Mood/behavior disturbance	Serine deficiency, PKU, maple syrup urine disease, homocysteine methylation defects, Lesch-Nyhan disease, cerebral folate deficiency, cerebrotendinous xanthomatosis, X-ALD, MLD (adult-onset), GM2 gangliosidosis (adult-onset)
Peripheral neuropathy	Cerebrotendinous xanthomatosis, biotinidase deficiency, serine deficiency, homocysteine remethylation defects, Krabbe disease, MLD, multiple sulfatase deficiency, X-ALD, INAD, mitochondrial disorders, vitamin E deficiency
Non-neurological features	
Ocular signs	*Optic atrophy*: cerebral folate deficiency, homocysteine remethylation defects, MMA, PA, PKU, cerebral folate deficiency, biotinidase deficiency, Krabbe disease, INAD *Retinopathy*: homocysteine remethylation defects, MMA, PA, Sjögren–Larsson syndrome, vitamin E deficiency, PKAN *Cataracts*: cerebrotendinous xanthomatosis, serine deficiency
Cutaneous signs	Biotinidase deficiency (seborrheic dermatitis, alopecia), cerebrotendinous xanthomatosis (xanthomas), Sjögren -Larsson syndrome, multiple sulfatase deficiency, and Gaucher disease (ichthyosis), PKU (reduced skin/hair pigmentation)
Other systemic signs	*Organomegaly*: lysosomal storage disorders, peroxisome biogenesis disorders *Adrenal insufficiency*: X-ALD *Pancytopenia*: homocysteine remethylation defects, MMA, Gaucher disease, *Diarrhea*: cerebrotendinous xanthomatosis

Abbreviations: ARSAL, autosomal-recessive spastic ataxia with leukoencephalopathy; GLUT1, glucose transporter type 1; INAD. infantile neuroaxonal dystrophy; LBSL: leukoencephalopathy with brain and spinal cord involvement with lactate elevation; LTBL, leukoencephalopathy with thalamus and brainstem involvement and high lactate; MLD, metachromatic leukodystrophy; MMA, methylmalonic acidemia; PA, propionic acidemia; PDH, pyruvate dehydrogenase; PKAN, pantothenate kinase-associated neurodegeneration; PKU, phenylketonuria; X-ALD, X-linked adrenoleukodystrophy.

such as MRS can also be helpful tools. A lactate peak may be present on MRS in mitochondrial encephalopathies, and an elevated N-acetyl-aspartate (NAA) peak suggests a possible diagnosis of Canavan disease.

Treatable Disorders

A number of metabolic disorders that cause spasticity are treatable. It is important to consider screening for them early in the course of evaluation (Table 10.3), particularly if brain imaging is normal or shows mild, non-specific abnormalities.

Urea Cycle Defects

Arginase deficiency, also known as argininemia, is an autosomal-recessive urea cycle disorder caused by mutations in *ARG1*. Symptoms typically begin in late infancy, following a period of normal motor development in the first year, but the insidious onset and gradual progression of symptoms may lead to an initial misdiagnosis of spastic diplegic cerebral palsy. The progressive nature of both the spasticity and cognitive dysfunction eventually becomes evident if the disease is not diagnosed and treated early.

Table 10.2 Characteristic brain MRI findings in selected inborn errors of metabolism with spasticity

Disease	Characteristic brain MRI findings
Disorders with white matter involvement	
Krabbe disease	Periventricular white matter changes, deep gray or cerebellar/dentate changes, enhancement of cranial/spinal nerve roots
MLD	Frontal/periventricular white matter changes, tigroid appearance, sparing of U-fibers
Multiple sulfatase deficiency	Frontal/periventricular white matter changes, sparing of U-fibers, hydrocephalus
GM1 gangliosidosis	Progressive atrophy, hypomyelination, basal ganglia T2 hyperintensity
GM2 gangliosidosis	Hypomyelination, basal ganglia T2 hyperintensity
Fucosidosis	Hypomyelination, basal ganglia T2 hypointensity
X-ALD	Cerebral- posterior predominant with enhancement at leading edge of demyelination
Peroxisome biogenesis disorders	Gyral abnormalities (severe), parieto-occipital white matter changes
LBSL	White matter changes, spinal cord T2 hyperintensity, lactate peak on MRS
LTBL	White matter changes, thalamic and brainstem T2 hyperintensity, lactate peak
ARSAL	White matter changes, cerebellar atrophy
Canavan disease	T2 hyperintensity of white matter, NAA peak on MRS
Sjögren–Larsson syndrome	T2 hyperintensity of periventricular white matter (mild to severe)
Cerebrotendinous xanthomatosis	T2 hyperintensity in dentate nuclei and cerebral, cerebellar white matter
PKU	T2 hyperintensity in posterior more than anterior cerebral white matter
Disorders with deep gray matter involvement	
MMA, PA	"Metabolic stroke" of globus pallidus pars externa
PDH deficiency	Ventriculomegaly, basal ganglia/thalamus/brainstem lesions, callosal dysgenesis
Molybdenum cofactor deficiency	Cystic white matter lesions, corpus callosum dysgenesis, symmetrical pallidal lesions
Gaucher disease (type 2)	Initially normal, late thalamic/dentate T2 hyperintensity
PKAN	"Eye of the tiger"-pallidal T2 hyperintensity surrounded by T2 hypointensity
INAD	Cerebellar atrophy, abnormal splenium, pallidal T2 hypointensity

Note that several leukoencephalopathies (top of table) may also be associated with deep gray matter lesions: GM1 and GM2 gangliosidosis, fucosidosis, LTBL, cerebrotendinous xanthomatosis. Abbreviations as in Table 10.1

Table 10.3 Screening biochemical investigations for treatable disorders associated with spasticity

Test	Disease(s)
Ammonia (plasma)	Arginase deficiency, homocysteine remethylation defects, HHH syndrome
Amino acids (plasma, urine, CSF*)	Arginase deficiency, homocysteine remethylation defects, HHH syndrome, PKU, serine deficiency*
Total homocysteine and folate (blood)	Homocysteine remethylation defects
Biotinidase activity (plasma)	Biotinidase deficiency
Cholestanol (plasma)	Cerebrotendinous xanthomatosis
Vitamin E (plasma)	Vitamin E deficiency
Glucose (CSF, serum), lactate (CSF)	GLUT1 deficiency syndrome
Monoamine neurotransmitter metabolites (CSF)	Dopa-responsive dystonia
5-Methyltetrahydrofolate (CSF)	Cerebral folate deficiency

Common accompanying neurological features are intellectual disability and seizures. Some patients experience intermittent episodes of irritability, vomiting, and lethargy associated with hyperammonemia, but unlike other urea cycle defects, episodes of recurrent hyperammonemic encephalopathy may be absent in patients with arginase deficiency. The diagnosis is suggested by the detection of elevated plasma arginine. In many countries, this is performed as part of newborn screening. In an older child, it can be detected on plasma amino acid analysis. The diagnosis is now typically confirmed with molecular genetic

analysis for sequence or copy number variants in *ARG1*. Red blood cell arginase enzyme analysis is an alternative confirmatory test if results of molecular analysis are inconclusive.

HHH syndrome is a rare urea cycle disorder caused by mutations in the *SLC25A15* gene, which encodes for the mitochondrial ornithine carrier ORC1 [2]. In infancy and early childhood, the disorder tends to present acutely with encephalopathy and seizures, or with fulminant liver failure and coagulopathy, with or without overt hyperammonemia. Patients with later-onset disease may present more insidiously, with slowly progressive spasticity, intellectual disability, ataxia, and myoclonic seizures. Disease severity is quite variable, and does not correlate reliably with genotype, recorded ammonia levels, or age of onset. The long-term treatment consists of a low-protein diet supplemented with citrulline or arginine. In addition, some patients require sodium benzoate and/or sodium phenylbutyrate to maintain blood ammonia in a safe range.

Dopa-Responsive Dystonia

Dopa-responsive dystonia is a disorder of monoamine neurotransmitter synthesis, most commonly caused by deficiency of GTP cyclohydrolase type 1. The classic presentation is of childhood-onset progressive limb dystonia with diurnal variation. The finding of hyperreflexia is not uncommon, and this, in combination with dystonic leg posturing, may mimic spastic paraparesis. Worsening of symptoms in the afternoon and evening is an important diagnostic clue, if present. A trial of levodopa typically leads to a rapid and dramatic improvement in symptoms, and should be considered in any child who presents with lower limb spasticity or dystonia in the context of normal brain imaging.

GLUT1 Deficiency Syndrome

Spasticity is one of the core motor features in glucose transporter type 1 (GLUT1) deficiency syndrome, a disorder in which glucose transport across the blood–brain barrier is impaired due to a deficiency of GLUT1, usually resulting from a heterozygous loss-of-function mutation in *SLC2A1*. In the classic, infantile-onset form of the disorder, spasticity is typically accompanied by ataxia and dystonia, and patients have a spastic–ataxic gait pattern. The earliest symptoms in infants are usually either seizures, or characteristic episodes of repetitive, multidirectional shifts of gaze that manifest as eye–head movements. Ataxia often fluctuates, worsening in the context of exercise, illness or fasting. Some patients develop paroxysmal exercise-induced dyskinesia during childhood. Intellectual disability in this disorder ranges from mild to severe. Cerebrospinal fluid (CSF) analysis reveals low CSF glucose in the setting of a normal blood glucose concentration, and CSF lactate is low or low–normal. Treatment with the ketogenic diet leads to a dramatic improvement in the paroxysmal and fluctuating symptoms (including ataxia, seizures, and paroxysmal dyskinesia), and may improve the long-term developmental outcome.

Homocysteine Remethylation Defects

The homocysteine remethylation disorders are rare autosomal-recessive conditions that have the common feature of deficient activity of methionine synthase, the enzyme responsible for the remethylation of homocysteine to form methionine. This may result from an abnormality of methionine synthase itself, deficiency of the related enzyme (methionine synthase reductase) or cofactor (methylcobalamin), or insufficient supply of the substrate (methionine tetrahydrofolate, MTHF). As a result, there is accumulation of homocysteine, and in the case of some cobalamin transport defects, combined accumulation of homocysteine and methylmalonic acid [3]. The two most common remethylation disorders are MTHF reductase deficiency and cobalamin C deficiency. Remethylation defects usually present in early childhood with seizures, cognitive impairment, and acquired microcephaly. Gait abnormalities due to spasticity and peripheral neuropathy become increasingly evident with age [3]. Older patients may develop dementia and subacute combined degeneration of the spinal cord. Presentation with encephalopathy, accompanied by hypotonia and feeding difficulties, is typical in neonates and young infants, but acute encephalopathy may occur at any age. There is considerable clinical variability in presentation, but the combination of the central and peripheral nervous system and bone marrow involvement may alert the clinician to the diagnosis. The finding of elevated plasma total homocysteine on biochemical screening should be followed by analysis of plasma methionine, blood acylcarnitine profile, serum vitamin B12 and folate, and urinary (or plasma) methylmalonic acid prior to starting treatment. Treatment with betaine, in combination with parenteral hydroxycobalamin for the cobalamin-related disorders, improves outcome and prevents long-term neurological complications.

Biotinidase Deficiency

Biotinidase deficiency is a treatable autosomal-recessive disorder that classically presents in infancy with seizures, hypotonia, and developmental delay, usually accompanied by seborrheic skin rash and alopecia. If untreated, other neurological features develop in time, including ataxia, hearing loss, and vision loss [4]. Some children develop progressive spastic paraparesis associated with myelopathy [5]. Patients have also been reported who were asymptomatic in childhood and developed acute vision loss with optic neuropathy and progressive spastic paraparesis in adolescence [6]. Critically, biotin supplementation can reverse neurological deficits and prevents disease progression.

Cerebral Folate Deficiency

Cerebral folate deficiency is associated with low levels of 5-methyltetrahydrofolate in the CSF with normal plasma folate levels. The most common cause of cerebral folate deficiency is blocking autoantibodies to the folate receptor that inhibit methyltetrahydrofolate transport across the choroid plexus [7]. Bi-allelic mutations in *FOLR-1*, encoding the folate receptor, are comparatively rare. Symptom onset typically occurs at 4–6 months of age with hypotonia, irritability, developmental delay, and acquired microcephaly. A mixed motor syndrome, variably characterized by hypotonia, ataxia, spasticity, dystonia, and chorea, develops during childhood. Patients often have epilepsy and autistic behavioral features. If untreated, visual and hearing loss may develop. Treatment with folinic acid may result in significant clinical improvement.

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis is an autosomal-recessive lipid storage disease caused by mutations in the *CYP27A1* gene, which encodes sterol 27-hydroxylase, an enzyme involved in bile acid synthesis. The resulting bile acid deficiency leads to increased liver production of cholesterol metabolites, including cholestanol, and their accumulation in multiple body tissues. The disease typically presents during childhood with bilateral cataracts and intractable diarrhea, followed in adolescence or early adulthood by the development of characteristic Achilles tendon xanthomas. Progressive neurological symptoms typically become evident in early adulthood, with ataxia, spasticity, and cognitive decline. Seizures, psychiatric symptoms, and peripheral neuropathy are less common disease features [8, 9]. A rare spinal form of the disease is characterized by slowly progressive myelopathy with pyramidal-tract and dorsal-column signs [10]. Treatment with chenodeoxycholic acid normalizes bile acid synthesis and plasma and CSF cholestenol concentration, and can prevent progression of the neurological manifestations.

Phenylketonuria (PKU)

PKU is an autosomal-recessive disorder caused by deficiency of phenylalanine hydroxylase, leading to hyperphenylalaninemia. Patients are now typically diagnosed by newborn screening. The early-onset classic form is characterized by intellectual disability, behavior problems, microcephaly, and seizures. The goal of treatment is to normalize blood concentrations of phenylalanine which is achieved with dietary restriction of phenylalanine, together with sapropterin (tetrahydrobiopterin) cofactor supplementation in patients who are responsive. Treatment effectively prevents the development of spastic quadriparesis and intellectual disability, associated with signs of progressive white matter disease on MRI, which would develop during the natural course of the untreated disease. Development of spastic quadriparesis upon cessation of a phenylalanine-restricted diet in young adulthood, and subsequent improvement with reintroduction of dietary therapy, has been reported [11].

Molybdenum Cofactor Deficiency

Molybdenum cofactor deficiency is a rare autosomal-recessive disorder that classically presents with neonatal onset of intractable seizures and feeding difficulties, followed by progressive microcephaly, intellectual disability, and spastic quadriparesis. Patients also have dysmorphic facial features, and may develop lens subluxation during childhood. The disease is caused by mutations in either *MOCS1*, *MOCS2*, or *GPHN*. Once the disease is suspected based on clinical and biochemical features, molecular analysis should be performed to identify the subtype: in patients with type A (*MOCS1*, approximately two-thirds of cases) early treatment with cyclic pyranopterin monophosphate dramatically improves the neurological outcome [12].

Disorders Associated with Leukoencephalopathy

Lysosomal Storage Disorders

Krabbe disease, or globoid cell leukodystrophy, inherited in an autosomal-recessive manner, is due to mutations in the *GALC* gene and is associated with very low enzymatic activity of galactocerebrosidase. The majority of patients have infantile-onset symptoms. Typically, after a brief period of normal development, infants develop inconsolable irritability, limb hypertonia, and truncal hypotonia [13]. Symptoms are progressive, with poor feeding, blindness, seizures, and loss of milestones, ultimately leading to death within the first 2 years [14]. MRI shows periventricular T2 hyperintensity and dentate/deep cerebellar T2 hyperintensity, although the dentate/cerebellar findings may not be present in later-onset cases [15]. A demyelinating peripheral neuropathy on nerve conduction studies is also characteristic [16], with diminished or absent reflexes on examination. Early stem-cell transplantation has been shown to provide improved function, but still with variable motor and cognitive involvement, and some patients continue to have moderate to severe spasticity [17].

Metachromatic leukodystrophy (**MLD**), or arylsulfatase A deficiency, is caused by mutations in the *ARSA* gene and leads to accumulation of sulfatides in the nervous system causing damage to the myelin sheath. MLD is commonly divided into three categories based on age of presentation: late-infantile MLD presents at 30 months or younger, juvenile MLD presents between 30 months and 16 years, and adult MLD presents after age 16 years. Earlier presentation usually portends a more rapid neurological decline. Late-infantile MLD patients often present with motor decline, spasticity, and seizures, while later-onset MLD (juvenile and adult) presents with both motor and cognitive decline, such as worsening school performance or psychosis in adults [18]. Demyelinating neuropathy is a common feature in all subtypes of MLD, with notable multifocal slowing of nerve conduction velocities [19]. MRI changes start with frontal and periventricular white matter T2 hyperintensity, and progress to include subcortical white matter with a characteristic tigroid appearance (due to sparing of perivascular white matter) [20]. Systemic involvement may include gallbladder polyposis and increased risk of gallbladder carcinoma due to sulfatide accumulation [21]. Treatment with stem-cell transplantation in the presymptomatic or very early symptomatic stage of disease may halt disease progression [22].

In **multiple sulfatase deficiency**, caused by autosomal-recessive mutations in the *SUMF1* gene, there is faulty post-translational activation of all sulfatases and thus a clinical presentation that combines MLD with other sulfatase deficiencies including multiple mucopolysaccharidoses, X-linked ichthyosis, and chondrodysplasia punctata with coarse features, organomegaly, dermatological abnormalities, and dysostosis multiplex [23]. Neurologically, motor deterioration, peripheral neuropathy, and seizures may all be features; imaging may be similar to MLD but hydrocephalus is also a reported feature [23].

GM1 gangliosidosis, associated with mutations in the *GLB1* gene, results in the accumulation of GM1 ganglioside in tissues including the central nervous system. GM1 gangliosidosis has a range of phenotypic presentations from early infantile to adult onset. The infantile presentation (type 1) is the most severe, and is associated with motor delay, hypotonia that progresses to spasticity, and occasionally seizures. Accompanying systemic features include a retinal cherry red spot, skeletal dysplasia, hepatosplenomegaly, and cardiomyopathy [24]. Type 2 GM1 gangliosidosis, or the late-infantile/juvenile type, has a later age of onset and a slower progression; skeletal dysplasia may be present but juvenile onset disease is less likely to have organomegaly [24]. On MRI, hypomyelination with T2 hyperintensity of the basal ganglia can be found in infantile-onset GM1 but later-onset disease may have normal imaging [25]. Extrapyramidal symptoms such as dystonia and parkinsonism can be present in an adult onset form of the disease, but are not typically features of earlier onset GM1 [26]. In a very limited case series of patients with juvenile or adult-onset GM1, there was a slowing of progression or an improvement in some motor symptoms with substrate reduction therapy [27]

GM2 gangliosidosis refers to several different disorders that result in the abnormal accumulation of GM2 gangliosides: hexosaminidase A deficiency (Tay–Sachs), Sandhoff disease, or AB variant GM2 gangliosidosis. Phenotypically these disorders all appear relatively similarly, but can be distinguished biochemically; there is absent HEX A enzymatic activity but increased HEX B activity in individuals with Tay Sachs, absent HEX A and HEX B activity in Sandhoff

disease, and normal HEX A and HEX B activity in the AB variant, as this variant is due to an abnormality in the GM2 activator. Clinically, these may be indistinguishable. GM2 gangliosidosis is often divided into categories based on severity and age at presentation: infantile/acute, juvenile/subacute, and adult/chronic forms. Infantile acute-onset disease presents in infancy and is characterized by developmental regression, axial hypotonia with limb spasticity, seizures, and blindness with a characteristic cherry-red spot on the fovea that can be seen on funduscopic examination [28]. Hypomyelination with T2 hyperintensity of the basal ganglia on MRI is not distinguishable from findings on MRI for infantile GM1 gangliosidosis, as above [25]. Juvenile GM2 gangliosidosis often starts with gait and coordination disturbance but may then be followed by spasticity, seizures, and cognitive decline [29]. Adult-onset hexosaminidase deficiency presents with cognitive decline that can include psychiatric features or psychosis, a combination of spasticity and lower motor neuron features such as fasciculations that can resemble amyotrophic lateral sclerosis, ataxia, and dystonia/parkinsonism [30].

Fucosidosis is a storage disorder caused be deficiency of alpha-L-fucosidase. There is a clinical continuum of severity, but a more severe phenotype (type 1) that rapidly progresses to death within the first decade and milder phenotype (type 2) with a more prolonged survival have been described, although different types can coexist within the same family [31]. Patients present with neurological features including motor regression, spasticity, and seizures, and systemic features including coarse facial features, organomegaly, skin changes such as angiokeratoma corporis diffusum and telangiectasias, and dysostosis multiplex [31]. Brain MRI shows characteristic basal ganglia T2 hypointensity in addition to hypomyelination [25].

Peroxisomal Disorders

X-linked adrenoleukodystrophy (**X-ALD**) is a peroxisomal disorder that results in very long chain fatty acid (VLCFA) accumulation in tissues, most predominantly affecting the brain, adrenal cortex, and Leydig cells of the testes. Mutations in the *ABCD1* gene on the X chromosome underlie the faulty VLCFA transport into the peroxisome. There is a wide range of phenotypic variability, but most common phenotypes of X-ALD that present with spasticity include the childhood cerebral form, and adrenomyeloneuropathy (AMN) in older individuals. An Addison's disease-only phenotype without neurological involvement, and thus without spasticity, can also be present. Childhood cerebral X-ALD may start with behavioral changes and attention difficulties that progress to spasticity, quadriparesis, blindness, and further cognitive deterioration [32]. In most individuals with cerebral X-ALD, classic findings of parieto-occipital white matter changes are present, at times with contrast enhancement at the border of the white matter changes, although frontal white matter changes or other variants occur as well [33]. Early presymptomatic identification of cerebral imaging abnormalities is important as early intervention with hematopoetic stem-cell transplantation can prevent disease progression [34]. Approximately 40% of individuals will present with AMN in their 20s to 40s, with a progressive spastic paraparesis, bowel/bladder or sexual dysfunction, adrenal insufficiency, and neuropathy [32]. Women who are carriers of an *ABCD1* mutation may be asymptomatic early in life, but may develop a phenotype similar to AMN by middle age or later in adulthood with spasticity, neuropathy, and incontinence [35].

Disorders of peroxisome biogenesis were historically divided into Zellweger disease, neonatal adrenoleukodystrophy, and infantile Refsum disease, based on age of presentation and severity of symptoms, but these are now understood to be more of a continuum of disease that are collectively called peroxisome biogenesis disorders or Zellweger spectrum disorders (ZSDs). There are many different *PEX* genes that are essential for the formation and maintenance of function of peroxisomes that are associated with ZSDs; biochemical evidence of peroxisomal dysfunction will also exist in these disorders with abnormalities of VLCFA, phytanic acid, pipecolic acid, and bile acid intermediates. The most severe neonatal presentation of a ZSD consists of profound hypotonia with hepatic dysfunction and dysmorphic features; these individuals often do not survive infancy and may not progress to a spastic phenotype. However, milder forms of the disease may present with abnormalities of myelination and leukodystrophy resulting in spasticity; retinitis pigmentosa and sensorineural hearing loss may also be present [36]. Mutations in *PEX16*, while often associated with a severe phenotype, have also been described with onset of disease after 1–2 years of normal development that presents with spastic paraparesis progressing to spastic quadriparesis, neuropathy, ataxia, and MRI evidence of leukodystrophy [37].

Mitochondrial Disorders

Pyruvate dehydrogenase (**PDH**) complex deficiency can involve changes in any of a number of proteins or subunits within the PDH complex that is involved in aerobic respiration within the mitochondria, although they are all encoded by nuclear DNA. Lactic acidosis is associated with neurological abnormalities including hypotonia or spasticity, developmental delay, seizures, or ataxia [38]. Neuroimaging may show symmetrical basal ganglia changes consistent with Leigh syndrome, dysgenesis of the corpus callosum, or ventriculomegaly [38], while MRS often demonstrates an elevated lactate peak [39].

Transfer RNA Synthetase Disorders

Aminoacyl-tRNA-synthetases are the proteins that are responsible for linking the appropriate amino acid with transfer RNA (tRNA), which is crucial for protein synthesis. Interestingly, disorders of cytosolic aminoacyl tRNA synthetases result in a Charcot–Marie–Tooth phenotype, but disorders of mitochondrial aminoacyl tRNA synthetases have a more varied presentation where spasticity may likely be a feature [40]. Mutations in *DARS2*, or leukoencephalopathy with brain and spinal cord involvement with lactate elevation (LBSL), can present in childhood or adulthood with spasticity, impaired dorsal column function, and ataxia [41]. Corresponding white matter changes in both brain and spine on MRI with a lactate peak on MRS may provide clues to diagnosis. Mutations in *EARS2* lead to leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL), which presents with spasticity, dystonia, and seizures. White matter changes along with hyperintensity within the thalami and midbrain/brainstem are generally present [41]. Bi-allelic mutations in *MARS2* cause autosomal-recessive spastic ataxia with leukoencephalopathy (ARSAL) and has been described in a French Canadian cohort [42]. Here, leukodystrophy and cerebellar atrophy may be present on imaging [41].

Canavan Disease

Canavan disease results from a deficiency of aspartoacylase, an enzyme that cleaves NAA to aspartate and acetate. The build-up of NAA within the brain leads to spongy degeneration of the white matter. Symptoms may become apparent in infancy, with poor head control and motor delay, macrocephaly, and initial hypotonia that progresses to spasticity. Very elevated NAA excretion can be detected in the urine, and an elevated NAA peak on MRS along with diffuse white matter signal changes on conventional MRI is also diagnostic [43].

Other Selected Conditions

Disorders of Amino Acid Metabolism

Glycine encephalopathy, also called non-ketotic hyperglycinemia, is caused by deficient glycine cleavage system enzyme activity, leading to glycine accumulation in the brain and other body tissues. It is associated with bi-allelic mutations in *GLDC*, *AMT*, or *GCSH*. Spasticity develops in the first 6 months of life in nearly all patients with the severe neonatal form, and by the age of 2 years in attenuated neonatal and infantile forms of the disease [44]. Several patients with atypical late-onset forms of non-ketotic hyperglycinemia have been described who had progressive spastic paraparesis without seizures, variably associated with optic atrophy and spinocerebellar degeneration [45, 46] or imaging evidence of leukodystrophy [47]. The underlying genetic etiology in these cases is not known.

Serine deficiency may arise from a defect in any one of the three enzymes in the L-serine biosynthetic pathway. Clinical presentations range from a severe, lethal antenatal form (Neu–Laxova syndrome) to adult-onset progressive polyneuropathy. The severe infantile form is characterized by congenital microcephaly, early feeding difficulties and irritability, followed typically by the onset of seizures during the first months of life. Spasticity emerges towards the end of the first year, evolving into spastic quadriparesis during early childhood [48]. Brain MRI demonstrates hypomyelination and delayed myelination, with marked loss of white matter volume [49]. Juvenile-onset disease manifests with intellectual disability, seizures, and behavioral dysfunction with normal brain MRI; while the adult-onset form is characterized by progressive polyneuropathy and ataxia [48]. Treatment with L-serine supplementation leads to a marked improvement in seizures and irritability in patients with the severe infantile form, but the impact on long-term developmental outcome is unfortunately limited in patients who begin treatment after they have become symptomatic.

Asparagine synthetase deficiency is a recently described autosomal-recessive disorder, characterized clinically by congenital microcephaly, intractable early-onset epilepsy, spastic quadriparesis, and global developmental delay [50]. Brain MRI demonstrates cerebral atrophy, delayed myelination, and in many cases, a simplified gyral pattern. Plasma and CSF asparagine levels may be low, but have also been reported to be normal in affected patients [50, 51]. Diagnosis may therefore require detection of bi-allelic pathogenic variants in *ASNS*. No disease-modifying treatment has been described yet for this condition.

Organic Acidurias

Methylmalonic acidemia (**MMA**) and **propionic acidemia** (**PA**) are rare, autosomal-recessive disorders of propionate catabolism that classically present with neonatal encephalopathy associated with metabolic acidosis, hyperammonemia, and pancytopenia [52]. Infants who present after the newborn period typically do so with acute metabolic decompensation (anorexia, vomiting, lethargy) in the context of catabolic stress such as illness or fasting. Progressive spastic quadriparesis occurs as a chronic complication.

Gaucher Disease

Gaucher disease is an autosomal-recessive lysosomal storage disorder caused by mutations in the glucocerebrosidase (*GBA*) gene. Phenotypically, Gaucher disease is often divided into several different types. Type 1 Gaucher disease usually consists of visceral involvement and is considered "non-neuronopathic"; although several neurological features such as peripheral neuropathy and increased risk of parkinsonism have been associated with type 1 Gaucher disease, spasticity is not typically a feature of type I disease [53]. Type 2 Gaucher disease, or acute neuronopathic Gaucher disease, presents in infancy and is usually rapidly progressive with severe motor involvement and spasticity, resulting in death before the age of 3 years. Spasticity with neck flexion/opisthotonus and brainstem-related features predominate; additional brainstem symptoms include dysphagia, apnea, and heart-rate instability [54]. Systemic involvement includes hepatosplenomegaly and pancytopenia. A severe phenotype (perinatal-lethal) can present very early with non-immune hydrops, arthrogryposis, and ichthyosis, and may be considered a separate phenotype or could be on the continuum of severity with type 2 Gaucher disease [54]. Type 3 Gaucher disease is a subacute neuronopathic form in which visceral involvement is also present, but neurological features may be more mild and with a slower progression. Ataxia, oculomotor apraxia, supranuclear gaze palsy, and myoclonic seizures may also be present in addition to milder spasticity compared to type 2 Gaucher disease [55, 56]. Imaging is often normal early in the disease course, but may progress to generalized atrophy or thalamic T2 hyperintensity [57]. Enzyme-replacement therapy is available for Gaucher disease; it is helpful for reducing organomegaly and other visceral involvement, but it does not treat the neurological manifestations of type 2 Gaucher disease [58].

Neurodegeneration with Brain Iron Accumulation

Pantothenate kinase associated neurodegeneration (**PKAN**) is the prototypical neurodegeneration with brain iron accumulation (NBIA) disorder, resulting from bi-allelic mutations in the *PANK2* gene that encodes pantothenate kinase 2, part of the CoA biosynthesis pathway. PKAN typically presents with dystonia and spasticity; either feature may predominate. The classic MRI finding of the "eye of the tiger" with pallidal T2 hyperintensity surrounded by hypointensity is essentially diagnostic [59].

Mutations in *PLA2G6*, which encodes a phospholipase protein involved in phospholipid remodeling, can cause several phenotypes. The most severe is **infantile neuroaxonal dystrophy** (**INAD**) that presents in early childhood with hypotonia progressing to spastic quadriparesis, optic atrophy, and evidence of axonal sensorimotor neuropathy on nerve conduction studies. There is also a later presentation, atypical INAD, which lacks initial hypotonia but still has progressive spasticity. Cerebellar ataxia and extrapyramidal features may also be present. There is also an adult *PLA2G6*-related dystonia–parkinsonism. Cerebellar atrophy is typical on imaging, and iron deposition may be variable [60].

Sjögren–Larsson Syndrome

Classically associated with the clinical triad of spastic diplegia, intellectual disability, and congenital ichthyosis, Sjögren–Larsson syndrome is caused by deficiency of fatty aldehyde dehydrogenase caused by autosomal-recessive mutations in *ALDH3A2*. Ichthyosis is typically the earliest sign, and may be congenital. The skin rash is generalized, sparing the

central face, and develops a yellowish-brown hyperkeratotic appearance by late infancy. Patients also develop a characteristic macular dystrophy during infancy. Spasticity affects the legs more than the arms, and most patients also have pseudobulbar dysarthria [61]. Brain MRI demonstrates abnormal signals in the periventricular white matter that may range from mild to severe.

Conclusions

In summary, spasticity in inborn errors of metabolism is often one feature of a more complex syndrome that includes other neurological and systemic symptoms and signs. Importantly, a number of metabolic diseases that cause spasticity are treatable and should be prioritized in the diagnostic work-up. Knowledge of clinical and imaging characteristics can help narrow the differential diagnosis.

Key Points and Clinical Pearls

- Spasticity rarely occurs as an isolated finding in inborn errors of metabolism.
- Associated neurological and systemic features, as well as characteristic brain MRI findings, may provide valuable diagnostic clues
- Treatable metabolic disorders associated with spasticity should be diagnosed early. Therefore, in any patient with spasticity of unknown etiology, check plasma ammonia, amino acids, biotinidase activity, total homocysteine, folate, cholestanol, and vitamin E. Also consider CSF studies (monoamine neurotransmitter metabolites, glucose, lactate, and 5-methyltetrahydrofolate) and a trial of levodopa.

Directions for Future Research

- Improved natural history data for rare disorders
- Options for treatment development, including multicenter therapeutic trials

References

1. Sedel F, Fontaine B, Saudubray JM, Lyon-Caen O. Hereditary spastic paraparesis in adults associated with inborn errors of metabolism: A diagnostic approach. J Inherit Metab Dis. 2007;**30**(6):855–64.
2. Martinelli D, Diodato D, Ponzi E, et al. The hyperornithinemia–hyperammonemia–homocitrullinuria syndrome. Orphanet J Rare Dis. 2015;**10**:29.
3. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis. 2017;**40**(1):21–48.
4. Wolf B. The neurology of biotinidase deficiency. Mol Genet Metab. 2011;**104**(1–2):27–34.
5. Chedrawi AK, Ali A, Al Hassnan ZN, Faiyaz-Ul-Haque M, Wolf B. Profound biotinidase deficiency in a child with predominantly spinal cord disease. J Child Neurol. 2008;**23**(9):1043–8.
6. Ramaekers VT, Brab M, Rau G, Heimann G. Recovery from neurological deficits following biotin treatment in a biotinidase Km variant. Neuropediatrics. 1993;**24**(2):98–102.
7. Ramaekers V, Sequeira JM, Quadros EV. Clinical recognition and aspects of the cerebral folate deficiency syndromes. Clin Chem Lab Med. 2013;**51**(3):497–511.
8. Federico A, Dotti MT, Gallus GN. Cerebrotendinous xanthomatosis. GeneReviews®. 2003;Jul 16 (updated Apr 14, 2016).
9. Wong JC, Walsh K, Hayden D, Eichler FS. Natural history of neurological abnormalities in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2018;**41**(4):647–56.
10. Abe R, Sekijima Y, Kinoshita T, et al. Spinal form cerebrotendinous xanthomatosis patient with long spinal cord lesion. J Spinal Cord Med. 2016;**39**(6):726–9.
11. McCombe PA, McLaughlin DB, Chalk JB, et al. Spasticity and white matter abnormalities in adult phenylketonuria. J Neurol Neurosurg Psychiatry. 1992;**55**(5):359–61.
12. Atwal PS, Scaglia F. Molybdenum cofactor deficiency. Mol Genet Metab. 2016;**117**(1):1–4.
13. Duffner PK, Barczykowski A, Jalal K, et al. Early infantile Krabbe disease: Results of the World-Wide Krabbe Registry. Pediatr Neurol. 2011;**45**(3):141–8.
14. Duffner PK, Jalal K, Carter RL. The Hunter's Hope Krabbe family database. Pediatr Neurol. 2009;**40**(1):13–8.
15. Abdelhalim AN, Alberico RA, Barczykowski AL, Duffner PK. Patterns of magnetic resonance imaging abnormalities in symptomatic patients with Krabbe

disease correspond to phenotype. Pediatr Neurol. 2014;**50**(2):127–34.

16. Husain AM, Altuwaijri M, Aldosari M. Krabbe disease: Neurophysiologic studies and MRI correlations. Neurology. 2004;**63**(4):617–20.
17. Wright MD, Poe MD, DeRenzo A, Haldal S, Escolar ML. Developmental outcomes of cord blood transplantation for Krabbe disease: A 15-year study. Neurology. 2017;**89**(13):1365–72.
18. Mahmood A, Berry J, Wenger DA, Escolar M, Sobeih M, Raymond G, et al. Metachromatic leukodystrophy: A case of triplets with the late infantile variant and a systematic review of the literature. J Child Neurol. 2010;**25**(5):572–80.
19. Cameron CL, Kang PB, Burns TM, Darras BT, Jones HR, Jr. Multifocal slowing of nerve conduction in metachromatic leukodystrophy. Muscle Nerve. 2004;**29**(4):531–6.
20. Eichler F, Grodd W, Grant E, et al. Metachromatic leukodystrophy: A scoring system for brain MR imaging observations. AJNR Am J Neuroradiol. 2009;**30**(10):1893–7.
21. van Rappard DF, Bugiani M, Boelens JJ, et al. Gallbladder and the risk of polyps and carcinoma in metachromatic leukodystrophy. Neurology. 2016;**87**(1):103–11.
22. Groeschel S, Kuhl JS, Bley AE, et al. Long-term outcome of allogeneic hematopoietic stem cell transplantation in patients with juvenile metachromatic leukodystrophy compared with nontransplanted control patients. JAMA Neurol. 2016;**73**(9):1133–40.
23. Ahrens-Nicklas R, Schlotawa L, Ballabio A, et al. Complex care of individuals with multiple sulfatase deficiency: Clinical cases and consensus statement. Mol Genet Metab. 2018;**123**(3):337–46.
24. Brunetti-Pierri N, Scaglia F. GM1 gangliosidosis: Review of clinical, molecular, and therapeutic aspects. Mol Genet Metab. 2008;**94**(4):391–6.
25. Steenweg ME, Vanderver A, Blaser S, et al. Magnetic resonance imaging pattern recognition in hypomyelinating disorders. Brain. 2010;**133**(10):2971–82.
26. Roze E, Paschke E, Lopez N, et al. Dystonia and parkinsonism in GM1 type 3 gangliosidosis. Mov Disord. 2005;**20**(10):1366–9.
27. Deodato F, Procopio E, Rampazzo A, et al. The treatment of juvenile/adult GM1-gangliosidosis with miglustat may reverse disease progression. Metab Brain Dis. 2017;**32**(5):1529–36.
28. Smith NJ, Winstone AM, Stellitano L, Cox TM, Verity CM. GM2 gangliosidosis in a UK study of children with progressive neurodegeneration: 73 cases reviewed. Dev Med Child Neurol. 2012;**54**(2):176–82.
29. Maegawa GH, Stockley T, Tropak M, et al. The natural history of juvenile or subacute GM2 gangliosidosis: 21 new cases and literature review of 134 previously reported. Pediatrics. 2006;**118**(5):e1550-62.
30. Frey LC, Ringel SP, Filley CM. The natural history of cognitive dysfunction in late-onset GM2 gangliosidosis. Arch Neurol. 2005;**62**(6):989–94.
31. Willems PJ, Gatti R, Darby JK, et al. Fucosidosis revisited: A review of 77 patients. Am J Med Genet. 1991;**38**(1):111–31.
32. Moser HW, Raymond GV, Dubey P. Adrenoleukodystrophy: New approaches to a neurodegenerative disease. JAMA. 2005;**294**(24):3131–4.
33. Loes DJ, Fatemi A, Melhem ER, et al. Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. Neurology. 2003;**61**(3):369–74.
34. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: A comparison study. Lancet Neurol. 2007;**6**(8):687–92.
35. Engelen M, Barbier M, Dijkstra IM, et al. X-linked adrenoleukodystrophy in women: A cross-sectional cohort study. Brain. 2014;**137**(Pt 3):693–706.
36. Steinberg SJ, Dodt G, Raymond GV, et al. Peroxisome biogenesis disorders. Biochim Biophys Acta. 2006;**1763**(12):1733–48.
37. Ebberink MS, Csanyi B, Chong WK, et al. Identification of an unusual variant peroxisome biogenesis disorder caused by mutations in the *PEX16* gene. J Med Genet. 2010;**47**(9):608–15.
38. Patel KP, O'Brien TW, Subramony SH, Shuster J, Stacpoole PW. The spectrum of pyruvate dehydrogenase complex deficiency: Clinical, biochemical and genetic features in 371 patients. Mol Genet Metab. 2012;**106**(3):385–94.
39. Cross JH, Connelly A, Gadian DG, et al. Clinical diversity of pyruvate dehydrogenase deficiency. Pediatr Neurol. 1994;**10**(4):276–83.
40. Boczonadi V, Jennings MJ, Horvath R. The role of tRNA synthetases in neurological and neuromuscular disorders. FEBS Lett. 2018;**592**(5):703–17.
41. Diodato D, Ghezzi D, Tiranti V. The mitochondrial aminoacyl tRNA synthetases: Genes and syndromes. Int J Cell Biol. 2014;**2014**:787956.
42. Bayat V, Thiffault I, Jaiswal M, et al. Mutations in the mitochondrial methionyl-tRNA synthetase cause a neurodegenerative phenotype in flies and a recessive ataxia (ARSAL) in humans. PLoS Biol. 2012;**10**(3):e1001288.

43. Matalon RM, Michals-Matalon K. Spongy degeneration of the brain, Canavan disease: Biochemical and molecular findings. Front Biosci. 2000;**5**:D307-11.
44. Hennermann JB, Berger JM, Grieben U, Scharer G, Van Hove JL. Prediction of long-term outcome in glycine encephalopathy: A clinical survey. J Inherit Metab Dis. 2012;**35**(2):253–61.
45. Steiman GS, Yudkoff M, Berman PH, Blazer-Yost B, Segal S. Late-onset nonketotic hyperglycinemia and spinocerebellar degeneration. J Pediatr. 1979;**94** (6):907–11.
46. Bank WJ, Morrow G, 3rd. A familial spinal cord disorder with hyperglycinemia. Arch Neurol. 1972;**27** (2):136–44.
47. Chiong MA, Procopis P, Carpenter K, Wilcken B. Late-onset nonketotic hyperglycinemia with leukodystrophy and an unusual clinical course. Pediatr Neurol. 2007;**37**(4):283–6.
48. van der Crabben SN, Verhoeven-Duif NM, Brilstra EH, et al. An update on serine deficiency disorders. J Inherit Metab Dis. 2013;**36**(4):613–9.
49. de Koning TJ, Jaeken J, Pineda M, et al. Hypomyelination and reversible white matter attenuation in 3-phosphoglycerate dehydrogenase deficiency. Neuropediatrics. 2000;**31**(6):287–92.
50. Ruzzo EK, Capo-Chichi JM, Ben-Zeev B, et al. Deficiency of asparagine synthetase causes congenital microcephaly and a progressive form of encephalopathy. Neuron. 2013;**80**(2):429–41.
51. Alfadhel M, Alrifai MT, Trujillano D, et al. Asparagine synthetase deficiency: New inborn errors of metabolism. JIMD Rep. 2015;**22**:11–6.
52. Fraser JL, Venditti CP. Methylmalonic and propionic acidemias: Clinical management update. Curr Opin Pediatr. 2016;**28**(6):682–93.
53. Cherin P, Rose C, de Roux-Serratrice C, et al. The neurological manifestations of Gaucher disease type 1: The French Observatoire on Gaucher disease (FROG). J Inherit Metab Dis. 2010;**33** (4):331–8.
54. Mignot C, Doummar D, Maire I, De Villemeur TB, French Type 2 Gaucher Disease Study Group. Type 2 Gaucher disease: 15 new cases and review of the literature. Brain Dev. 2006;**28** (1):39–48.
55. Roshan Lal T, Sidransky E. The spectrum of neurological manifestations associated with Gaucher disease. Diseases. 2017;**5**(1).
56. Nagappa M, Bindu PS, Taly AB, Sinha S. Oculomotor apraxia in Gaucher disease. Pediatr Neurol. 2015;**52** (4):468–9.
57. Perucca G, Soares BP, Stagliano S, et al. Thalamic and dentate nucleus abnormalities in the brain of children with Gaucher disease. Neuroradiology. 2018;**60** (12):1353–6.
58. Weiss K, Gonzalez A, Lopez G, et al. The clinical management of type 2 Gaucher disease. Mol Genet Metab. 2015;**114**(2):110–22.
59. Hogarth P, Kurian MA, Gregory A, et al. Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). Mol Genet Metab. 2017;**120**(3):278–87.
60. Illingworth MA, Meyer E, Chong WK, et al. *PLA2G6*-associated neurodegeneration (PLAN): Further expansion of the clinical, radiological and mutation spectrum associated with infantile and atypical childhood-onset disease. Mol Genet Metab. 2014;**112** (2):183–9.
61. Fuijkschot J, Theelen T, Seyger MM, van der Graaf M, de Groot IJ, Wevers RA, et al. Sjögren–Larsson syndrome in clinical practice. J Inherit Metab Dis. 2012;**35**(6):955–62.

Chapter 11

A Phenomenology-Based Approach to Inborn Errors of Metabolism with Myoclonus

Lisette H. Koens, Rodi Zutt, Tom J. de Koning, and Marina A. J. Tijssen

Introduction: Definition and Prevalence of Myoclonus

Myoclonus is a hyperkinetic movement disorder defined as a sudden, brief, involuntary jerk of a muscle or a muscle group. Myoclonus can be caused by muscle contraction (positive myoclonus) or by loss of muscle tone (negative myoclonus). The prevalence of myoclonus is largely unknown. Symptoms are not always severe enough to attract medical attention and signs of myoclonus can be hard to recognize. One study showed a prevalence of myoclonus of 8.6 cases in 100,000, with symptomatic myoclonus being the most common cause (72%) [1]. Even less is known about the prevalence of myoclonus in patients with an inborn error of metabolism (IEM). A prospective study of 170 patients with a confirmed or highly suspected IEM detected a movement disorder in 29% of the patients. In 28% of these patients, the movement disorder was classified as myoclonus [2]. This, however, is likely an underestimation as other symptoms can mask myoclonus and combinations of movement disorders are common in IEMs.

Classification of Myoclonus

Myoclonus can be classified based on its anatomical origin: cortical, subcortical, spinal, and peripheral myoclonus (Table 11.1). For further details about the anatomical classification, see step 2 of the algorithm presented in Fig. 11.1 [3]. A second classification is based on clinical phenotype. This describes myoclonus in relation to its distribution (focal, segmental, generalized), and in relation to activity (rest, action, or task-specific). Positive and negative myoclonus can be distinguished as well [4]. Cortical myoclonus, the most common form of myoclonus in metabolic disorders, is often multifocal, affecting the distal body parts and the mouth. It is frequently stimulus-sensitive. In particular, fingers and toes are sensitive to tactile stimuli, which can induce a series of myoclonus. Unexpected visual, verbal, or auditory stimuli can provoke myoclonus as well. The third classification is based on etiology, and divides myoclonus into four subgroups: physiological, essential, epileptic, and symptomatic (secondary) myoclonus.

Table 11.1 Classification of myoclonus (adapted from Zutt et al. [3])

Subtype of myoclonus	Clinical characteristics
Cortical	(Multi) focal or generalized Affects face, distal limbs Spontaneous, action induced or stimulus-sensitive Negative myoclonus
Subcortical	
• Brainstem myoclonus	Generalized or synchronous Axial Affects proximal limbs Spontaneous or stimulus-sensitive
• Myoclonus-dystonia	(Multi)focal Axial Affects proximal limbs Spontaneous or action-induced
Spinal	
• Segmental myoclonus	Focal or segmental Spontaneous (sometimes action-induced)
• Propriospinal myoclonus	Fixed pattern Affects axial muscles Spontaneous or stimulus-sensitive
Peripheral	Focal Affects distal limbs in case of polyminimyoclonus Spontaneous or action induced Often accompanied by weakness/ atrophy

Physiological myoclonus can be found in otherwise healthy people. Examples of physiological myoclonus include hiccups, which are myoclonus of the diaphragm, and sleep jerks. Essential myoclonus can be idiopathic or sporadic, but is usually hereditary. Many of the patients that were previously diagnosed as

having essential myoclonus are now considered to have myoclonus-dystonia. In epileptic myoclonus, epileptic syndromes are associated with myoclonus. The combination of myoclonus and epilepsy is frequent in IEMs. The most common form is the non-metabolic juvenile myoclonus epilepsy, characterized by primary generalized epilepsy and myoclonus, occurring particularly in the morning. The progressive myoclonus epilepsies (PMEs) are characterized by prominent myoclonus, epilepsy, and progressive cognitive decline. PMEs are often fatal neurodegenerative diseases in children and young adults. The largest group of PMEs includes the group of neuronal ceroid lipofuscinoses (NCLs) [5]. With PMEs occurring in all NCL subtypes, it is important to discriminate PMEs from progressive myoclonus ataxia (PMA), in which cognitive decline and seizures are usually not prominent. PMA is characterized by progressive ataxia and myoclonus, without prominent cognitive decline, and with or without epilepsy. PMA is also frequently caused by metabolic disorders, in particular by mitochondrial disorders such as myoclonic epilepsy associated with ragged red fibers (MERRF) [6]. The last largest group is symptomatic myoclonus, and comprises many different causes. Here myoclonus is secondary to a defined neurological or medical disorder including acquired and genetic disorders. For an overview of the etiological classification of myoclonus, we refer to a review by Caviness [7].

Clinical Diagnostic Approach towards a Patient with Myoclonus Focusing on IEMs

Figure 11.1 shows a seven-step algorithm for myoclonus based on the algorithm of Zutt et al. [3], focusing on diagnosing an underlying IEM as the cause of myoclonus.

Step 1: Is It Myoclonus?

Myoclonus must be distinguished from other movement disorders, including dystonic jerks, tics, tremor, chorea, or functional movement disorders. A few principles can help to distinguish between the different types of jerky movement disorders. First, the speed of the movement is important. Movements in myoclonus are fast, whereas the movements in dystonia and chorea are usually relatively slower. Furthermore, rhythmicity may help to differentiate between tremor and myoclonus. Tics may be suppressed for a while, whereas this is not possible with myoclonus. Functional jerks are inconsistent, reduced with distraction, and may be influenced by entrainment. Finally, it is important to define whether the abnormal movements occur at rest, during action, or during both. Ataxia is per definition only present during action, while myoclonus can get worse during action, but may also be present during posture and

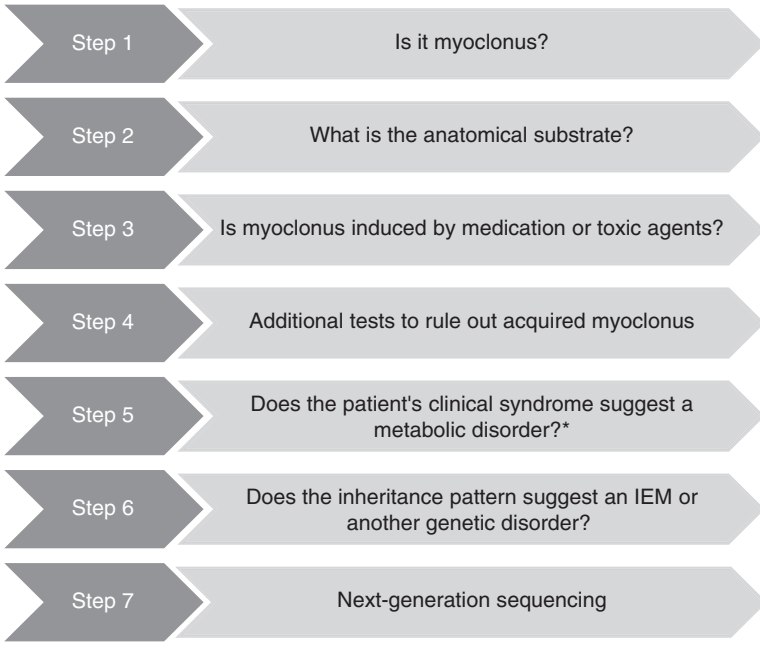

Figure 11.1 Approach to myoclonus in inborn errors of metabolism (adapted from Zutt et al. [3]). *If there is a high suspicion of a specific metabolic disorder, target additional investigations and/or genetic analysis.

rest. In practice, myoclonus is frequently misclassified as ataxia in IEMs [8]. In metabolic disorders in particular, the differentiation between myoclonus and other movement disorders can be difficult because multiple movement disorders can be present in one patient, and myoclonus can be subtle. Clinical classification can be difficult, and in these cases electrophysiological testing can help to define the anatomical subtype of myoclonus. The basic electrophysiological test is polymyography (multiple electromyography [EMG] channels) to detect myoclonus (both positive and negative myoclonus), and to register both the burst duration and the recruitment of muscles.

Step 2: What is the Anatomical Substrate?

Anatomical classification of the myoclonus subtype is important to diagnose the underlying cause of myoclonus and to guide tailored treatment. Although myoclonus is a complication of many IEMs, in only a few reports the myoclonus is actually described in the context of the anatomical classification. However, the clinical presentation of distal and action-induced myoclonus, often in combination with epilepsy, strongly points towards a cortical origin of the myoclonus in most patients. Cortical myoclonus is caused by abnormal firing of the sensorimotor cortex, leading to short-lasting, often multifocal myoclonus affecting the face, hands, and feet. Involvement of a network of the fronto-temporal cortex, hippocampus, thalamus, and cerebellum has been suggested based on neuropathological studies. Myoclonus can be both positive and negative. It can be evoked by voluntary movements or unexpected stimuli. Next to myoclonus originating from the cortex, myoclonus can have an origin between the cortex and spinal cord. Important areas include the basal ganglia and brainstem. This subtype is classified as subcortical (sometimes also called non-cortical) myoclonus. An important example of subcortical myoclonus is myoclonus-dystonia, which is characterized by multifocal myoclonus combined with dystonia predominantly affecting the upper limbs and neck. In about 50% of the patients, myoclonus-dystonia is due to a mutation in the *SGCE* gene, encoding epsilon-sarcoglycan [9]. The myoclonus-dystonia phenotype is infrequently caused by an IEM. Brainstem myoclonus is characterized by a generalized, predominantly axial, and often stimulus-sensitive myoclonus. The main example is the genetically determined hyperekplexia [10]. Spinal myoclonus is generated in the spinal cord. It can be divided into segmental myoclonus and propriospinal myoclonus. Segmental myoclonus is very rare and is usually based on a lesion in the spinal cord. Propiospinal myoclonus is characterized by a fixed pattern of muscle activation in the trunk and abdominal muscles. Although propiospinal myoclonus can have an organic substrate, it is often thought to be a functional movement disorder. Finally, myoclonus can have a peripheral origin, and is caused by damage of the peripheral nerve system. Clinically, this results in polyminimyoclonus.

EEG–EMG polygraphy can not only be used to determine whether jerks are myoclonus or not, but can also be used to define the anatomical substrate of the myoclonus. Burst duration in cortical myoclonus, but also in peripheral myoclonus, is shorter than 100 ms, whereas it is larger than 100 ms in the other subtypes of myoclonus. Other electrophysiological characteristics of cortical myoclonus include positive back-averaging, positive coherence, giant somatosensory evoked potentials, and a C-reflex.

Step 3: Is Myoclonus Induced by Medication or Toxic Agents?

Before considering a metabolic disorder as the cause of myoclonus, other causes of myoclonus must be excluded. The most common cause of myoclonus is medication-induced myoclonus. This is often related to the start of a new treatment, although patients who develop myoclonus after chronic use of a drug have been described. To complicate matters further, drugs that may cause myoclonus include many antiseizure drugs and serotonin reuptake inhibitors. After withdrawal of the drug, myoclonus usually disappears. For a complete overview of drugs and toxic agents see the review of Zutt et al. [3].

Step 4: Additional Tests to Rule Out Acquired Myoclonus

Routine Laboratory Tests

Electrolyte imbalance is also a common cause of myoclonus. General blood tests can be easily performed to exclude homeostatic or electrolyte imbalance, organ failure, or infection as a cause of myoclonus. Immune-mediated disorders (autoimmune or paraneoplastic encephalitis) and rare infectious disorders (e.g. Whipple's disease) should also be excluded in the appropriate clinical context.

Brain MRI

MRI can be helpful to differentiate between the different causes of myoclonus. It can reveal acquired causes of myoclonus, for example post-hypoxic lesions, demyelination, tumors, or abnormalities due to different types of encephalitis. In the diagnosis of metabolic disorders, MRI can be supportive. Recommended protocols involve T1- and T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI) to detect iron accumulation, and administration of gadolinium contrast [3].

Step 5: Does the Patient's Clinical Syndrome Suggest a Metabolic Disorder?

Once acquired myoclonus is determined unlikely, a genetic cause must be considered. Some combinations of clinical features point towards a metabolic disorder in patients with myoclonus. In particular, the combination of myoclonus with other movement disorders, other neurological features, or systemic symptoms may point to an underlying metabolic disorder. If a treatable metabolic disorder is suspected, metabolic testing can be performed before or in parallel with genetic testing in order to reduce diagnostic delay.

Step 6: Does the Inheritance Patterns Suggest an IEM or Another Genetic Disorder?

Many IEMs, including those that cause myoclonus, are autosomal-recessive disorders, so a positive family history, i.e. with multiple affected family members or reported consanguinity, are important clues. However, a few autosomal-dominant metabolic disorders can cause myoclonus as well, including several forms of NCL (Kufs disease), and glucose transporter type 1 (GLUT1) deficiency syndrome. If there is a strong suspicion of a specific IEM, it is sometimes possible to do a specific biochemical test. Metabolic testing can be performed in parallel with genetic testing, or can be performed afterwards, in order to confirm the metabolic disorder found with genetic testing.

Step 7: Next-Generation Sequencing

If there is no strong suspicion of a specific IEM, testing multiple genes at the same time is not only faster but also cost-effective [11, 12]. The costs of sequencing three individual genes are comparable to the costs of whole-exome sequencing (WES). However, there are a few pitfalls. First, large structural rearrangements can be missed due to technical reasons. Second, mitochondrial DNA (mtDNA) is not tested in these gene panels, and analysis of mtDNA should be requested separately. Third, it is sometimes difficult to interpret a variant, in particular because little information is available about clinical phenotypes of some late-onset IEMs, which may be different from the early-onset classic presentations. It is especially difficult to interpret heterozygous mutations that can cause classic IEMs in adults due to dominant negative effects of the mutations [13]. In this case, results of genetic testing need to be confirmed by a biochemical test.

Metabolic Myoclonus

Many metabolic disorders can give rise to myoclonus. The majority of these will have an onset in childhood, although over the last decades adolescent- and adult-onset forms are increasingly described. Table 11.2 presents an overview of metabolic disorders in which myoclonus has been reported, summarizing genetic and neurological features. Major groups of IEMs are discussed below.

Multiple movement disorders can be seen in one patient with a metabolic disorder; the combination of myoclonus with ataxia or dystonia is especially frequent.

Other Neurological Features

Epilepsy

In 40% of the patients with a metabolic disorder, epilepsy is part of the phenotype [14]. Epilepsy can be part of PMEs, and may be found in many lysosomal storage disorders, such as the NCLs, Gaucher disease types 2 and 3, Tay–Sachs disease, and sialidosis type 1, but is also frequent in mitochondrial disorders, for example in MERRF [15, 16]. Furthermore, epilepsy in metabolic disorders can be part of the spectrum of early myoclonic encephalopathy (EME). This presents during infancy with focal seizures and prominent myoclonus [17]. Given the fact that IEMs frequently result in encephalopathy, a considerable number of IEMs have been found to present with EME.

Eye Movement Disorders

It is important to realize that eye movement disorders are common in metabolic disorders, although they are frequently overlooked. For example, a vertical

Table 11.2 Overview of IEMs associated with myoclonus

Metabolic disorder	Gene	Inheritance	Onset	OMIM number	Other neurological symptoms
Lysosomal storage disorders					
Ceroid lipofuscinosis type 1 (CLN1)	*PPT1*	AR	Infantile	600722	Progressive loss of motor milestones Dementia Seizures Psychiatric manifestations
Ceroid lipofuscinosis type 2 (CLN2)	*TPP1*	AR	Late-infantile	607998	Seizures Intellectual deterioration Ataxia Spasticity Vision loss
Ceroid lipofuscinosis type 3 (CLN3; Batten disease; Spielmeyer–Vogt–Sjogren–Batten disease)	*CLN3*	AR	Juvenile	607042	Dementia Seizures Behavioral disorders
Ceroid lipofuscinosis type 4 (CLN4; Parry type)	*DNAJC5*	AD	Adulthood	611203	Seizures Dementia Ataxia Parkinsonism Behavioral changes Depression Hallucinations
Ceroid lipofuscinosis type 5 (CLN5)	*CLN5*	AR	Childhood–adolescence, one family with adult-onset	608102	Hypotonia Seizures Progressive dementia
Ceroid lipofuscinosis type 7 (CLN7)	*MFSD8*	AR	Childhood	611124	Progressive loss of vision Delayed psychomotor development Seizures Sleep disorders
Ceroid lipofuscinosis type 8 (CLN8)	*CLN8*	AR	Childhood	607837	Epilepsy Myoclonus Ataxia Progressive visual loss Dementia
Galactosialidosis	*CTSA*	AR	Infantile–adulthood	613111	Dementia Seizures
Gaucher disease (mainly type 3)	*GBA*	AR	Childhood–juvenile	606463	Supranuclear gaze palsy (horizontal) Cognitive impairment Seizures Ataxia
Atypical Gaucher disease due to saposin C deficiency	*PSAP*	AR	Childhood	176801	Seizures Progressive horizontal ophthalmoplegia Ataxia Pyramidal signs
Kufs disease type A	*CLN6*	AR/AD	Childhood–adolescence (11–50 years)	606725	Ataxia Dementia Seizures
Niemann–Pick disease type C (NPC)	*NPC1*	AR	Childhood–adulthood	607623	Ataxia Dystonia Cognitive decline Supranuclear gaze palsy (vertical) Psychiatric symptoms Gelastic cataplexy

Table 11.2 (cont.)

Metabolic disorder	Gene	Inheritance	Onset	OMIM number	Other neurological symptoms
Niemann-Pick disease, type C2	*NPC2*	AR	Childhood–adulthood	601015	Developmental delay Dystonia Ataxia Psychiatric symptoms Gelastic cataplexy Supranuclear gaze palsy (vertical)
Sandhoff disease	*HEXB*	AR	Childhood	606873	Psychomotor retardation Seizures Ataxia
Sialidosis types 1 and 2	*NEU1*	AR	Childhood–adulthood	608272	Seizures (tonic clonic) Ataxia Intellectual deficiency
Tay–Sachs disease	*HEXA*	AR	Childhood	606869	Developmental delay or regression Seizures
Disorders of lipid metabolism					
Cerebrotendinous xanthomatosis	*CYP27A1*	AR	Childhood–adulthood	606530	Ataxia Intellectual deficiency Psychiatric manifestations Spasticity
Disorders of amino acid and other organic acid metabolism					
Glycine encephalopathy	*AMT*	AR	Neonatal, milder form in childhood	238310	Seizures Hypotonia Lethargy Intellectual deficiency Hyperactivity, impulsivity, and aggressiveness
Glycine encephalopathy	*GCSH*	AR	Neonatal, milder form in childhood	238330	Seizures Hypotonia Lethargy Intellectual deficiency Hyperactivity, impulsivity and aggressiveness
Non-ketotic hyperglycinemia, neonatal glycine encephalopathy	*GLDC*	AR	Neonatal, milder form in adulthood	238300	Seizures Hypotonia Lethargy Intellectual deficiency Hyperactivity, impulsivity and aggressiveness
Disorders of carbohydrate metabolism					
GLUT1 deficiency syndrome	*SLC2A1*	AD	Early infancy–childhood	138140	Paroxysmal exercise-induced dyskinesia Paroxysmal abnormal eye movements Ataxia Seizures Developmental delay Spasticity
Disorders of mineral, metal, or vitamin metabolism					
Adult-onset dystonia–parkinsonism (PLAN, PLA2G6-associated neurodegeneration)	*PLA2G6*	AR	Adulthood	603604	Parkinsonism Dystonia Spasticity Frontotemporal dementia Supranuclear gaze palsy

Table 11.2 (cont.)

Metabolic disorder	Gene	Inheritance	Onset	OMIM number	Other neurological symptoms
Biotinidase deficiency	*BTD*	AR	Early childhood, sometimes late-onset	609019	Seizures Hypotonia Ataxia Developmental delay
Hereditary hemochromatosis	*HFE*	AR	Childhood – adulthood	613609	Cognitive decline Ataxia Dystonia Parkinsonism
Menkes disease	*ATP7A*	X-linked recessive	Early infancy	300011	Intellectual deficiency Seizures Hypertonia
Neurodegeneration due to cerebral folate transport deficiency	*FOLR1*	AR	Early childhood	136430	Developmental regression Seizures Motor dysfunction
Pantothenate kinase-associated neurodegeneration (PKAN)	*PANK2*	AR	Childhood–adolescence	606157	Dystonia Pyramidal syndrome Cognitive decline Psychiatric symptoms
Wilson's disease	*ATP7B*	AR	Early childhood – adulthood	606882	Tremor Dystonia Parkinsonism Psychiatric symptoms
Neurotransmitter disorders					
Aromatic L-amino acid decarboxylase deficiency	*DDC*	AR	Usually infantile, sometimes late-onset	107930	Dystonia Psychomotor retardation Spasticity Autonomic dysfunction
P5P-dependent epilepsy	*PNPO*	AR	Neonatal	610090	Seizures Hypotonia Erratic eye movements
Pyridoxine-dependent epilepsy	*ALDH7A1*	AR	Neonatal	107323	Seizures Hypotonia Delayed psychomotor development
Tyrosine hydroxylase deficiency	*TH*	AR	Infantile, sometimes late-onset	191290	Dystonia Psychomotor retardation Spasticity Autonomic dysfunction
Energy metabolism disorders					
Coenzyme Q10 deficiency	*ADCK3* *ANO10* *COQ2* *PDSS2* *COQ4* *PDSS1* *COQ6* *COQ7* *COQ9*	AR	Childhood–adulthood	606980 613726 609825 610564 612898 607429 614647 601683 612837	Encephalopathy Seizures Intellectual deficiency Ataxia
Combined oxidative phosphorylation defect type 27	*CARS2*	AR	Childhood	612800	Intellectual deficiency Epilepsy Progressive tetraparesis Chorea Dystonia
Combined oxidative phosphorylation defect type 14	*FARS2*	AR	Early infancy	611592	Developmental delay Seizures Hypotonia

Table 11.2 (cont.)

Metabolic disorder	Gene	Inheritance	Onset	OMIM number	Other neurological symptoms
Cerebral creatine deficiency	*GAMT* *SLC6A8*	AR XLR	Early infancy	601240 300036	Ataxia Dystonia Chorea Intellectual deficiency Seizures Spasticity Language delay Psychiatric symptoms
Mitochondrial disorders	Many different genes	mtDNA or nDNA (AR/AD)	Childhood–adulthood	NA[b]	Ataxia Dystonia Parkinsonism Chorea Myopathy Epilepsy Migraine Progressive external ophthalmoplegia

[a] AD, autosomal-dominant; AR, autosomal-recessive; XLR, X-linked recessive [b] NA: not applicable.

supranuclear gaze palsy in combination with myoclonus or another movement disorder (often ataxia or dystonia) is suggestive of Niemann–Pick disease type C (NPC), whereas a combination of a horizontal supranuclear gaze palsy and movement disorders points to Gaucher disease type 3. Furthermore, progressive external ophthalmoplegia (weakness or paralysis of the eye muscles) is a key symptom in adolescents and adults with a mitochondrial disorder [18].

Polyneuropathy

Distal and symmetrical polyneuropathy with mainly motor involvement may be secondary to an IEM. Neuropathies in IEMs may be acute, as is the case in mononeuropathies or mononeuropathy multiplex, or they have a more chronic course. In lysosomal storage disorders and mitochondrial disorders, polyneuropathy is common [19].

Strokes and Stroke-Like Episodes

Strokes, but also stroke-like episodes, have been described in metabolic disorders. Stroke-like episodes are characterized by diffuse neurological symptoms, including encephalopathy, seizures, confusion, and headache. Stroke-like episodes occur in mitochondrial disorders, in particular those caused by mutations in mtDNA, such as mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome.

Psychiatric and Cognitive Symptoms

Psychiatric symptoms are prevalent in patients with IEMs. In particular, in adolescents and adults, psychiatric symptoms can be the only feature of an IEM for years [20]. Acute psychiatric symptoms, such as delusions, agitation, confusion, and hallucinations may be triggered by intercurrent illnesses or dietary changes, for instance after high protein intake. In lysosomal storage disorders or metal storage disorders, psychiatric symptoms can also have a more insidious course. Finally, psychiatric symptoms may occur in combination with intellectual disability.

Systemic Features

Many other organs can be involved in IEMs. In particular, hepatosplenomegaly is a frequent symptom in patients with lysosomal storage disorders, although visceral symptoms tend to be much more pronounced in children than in adults. Visceral symptoms can be absent in adults with lysosomal storage diseases. Other associated features of IEMs include myopathy (in particular in mitochondrial disorders) and ocular manifestations. Kayser–Fleischer rings are a characteristic sign of Wilson disease. Cataracts, retinitis pigmentosa, and optic neuropathy may also be found in IEMs. Finally, a cherry-red spot, as a result of the accumulation of lipids in the retinal ganglion cells with sparing of the fundus, is a feature in some lysosomal disorders [21, 22].

Metabolic Disorders Associated with Myoclonus

Lysosomal Storage Disorders

Lysosomal storage disorders are a group of disorders caused by lysosomal dysfunction, leading to interference with lysosomal cargo degradation or lysosomal/endosomal transport. More than two-thirds of the lysosomal storage disorders affect the central nervous system, and common manifestations include cognitive decline and movement disorders [23]. Myoclonus and other movement disorders are not specific for certain lysosomal storage disorders.

Neuronal Ceroid Lipofuscinoses

The NCLs are characterized by the accumulation of autofluoresecent lipopigment in cells. Childhood-onset is most common with progressive neurological decline, myoclonic seizures, and visual symptoms. Late-onset forms encompass different phenotypes with some clinical overlap. In the later forms, psychiatric and cognitive symptoms tend to predominate [19].

Myoclonus is frequently seen in combination with other movement disorders, in particular in combination with ataxia. As discussed earlier, the group of NCLs form the most important group of PMEs [5].

Sialidosis Types 1 and 2

Sialidosis type 1, also called the "cherry-red spot myoclonus syndrome," is a late-onset form of sialidosis and symptoms (bilateral cherry-red spots, visual loss, and myoclonic epilepsy) are caused by neuraminidase deficiency. Myoclonus in sialidosis type 1 can be the only presenting movement disorder or can be seen in combination with ataxia. Sialidosis type 2 is a more severe form and usually presents early in life, although juvenile-onset forms are described [19].

Galactosialidosis

Galactosialidosis is caused by a combined deficiency of beta-galactosidase and neuraminidase. Early-onset symptoms include dysmorphic facial features, cherry-red spots on fundus examination, and dysostosis multiplex. Myoclonus and ataxia can be found in patients with the late-onset form of this disorder [19].

Gaucher Disease

In Gaucher disease, glucosylceramide and its derivatives accumulate in multiple organs. In particular, in Gaucher disease type 3 (the subacute neurological form), movement disorders are frequent. Patients often present with myoclonus, epilepsy, and supranuclear gaze palsy only affecting horizontal gaze [24, 25]. Atypical Gaucher disease due to saposin C deficiency shows phenotypic similarities with Gaucher disease type 3.

Tay–Sachs Disease and Sandhoff Disease

In Tay–Sachs disease and Sandhoff disease, GM2 ganglioside accumulates in the nervous system. Early-onset forms are most common. Patients show muscle weakness, spasticity, a cherry-red spot, psychomotor retardation, cognitive decline, and seizures. Symptoms in late-onset forms include movement disorders, including myoclonus, in combination with motor neuron dysfunction [19].

Niemann–Pick Disease Type C

NPC is caused by mutations in the *NPC1* or *NPC2* genes that code for proteins involved in cellular lipid transport, leading to an accumulation of unesterified cholesterol in cells. Besides visceral symptoms (e.g. hepatosplenomegaly), neurological symptoms are common. In patients with NPC, late-onset disease is characterized by movement disorders, psychiatric disorders, and cognitive decline. Vertical supranuclear gaze palsy is one of the key features. Myoclonus is common, but it can be subtle and is easily overlooked [8]. EEG–EMG polygraphic studies in patients with NPC confirm a cortical origin of the myoclonus, with short EMG burst duration, negative and positive myoclonus types, and a predominantly distal distribution [8].

Disorders of Lipid Metabolism

In disorders of lipid metabolism, the breakdown of specific lipid metabolites is impaired due to enzyme abnormalities, resulting in an accumulation of lipids.

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis is a disorder of cholesterol metabolism caused by a deficiency of the mitochondrial enzyme sterol 27-hydroxylase. A wide range of symptoms may be present, including infantile-onset with intractable diarrhea. Cataract and tendon xanthomas often present later in life. Movement disorders, including myoclonus, are also described [26].

Amino Acid Disorders and Other Organic Acid Disorders

Amino acid and organic acid disorders are caused by a deficiency of enzymes or transporters of certain amino acids, leading to an accumulation of toxic metabolites. From our personal experience we can conclude that myoclonus can be seen in a number of organic acidurias in adolescence or adulthood as well, such as glutaric aciduria type I or ketothiolase deficiency. Apparently, myoclonus can be a complication of chronic "intoxication" of the brain without any obvious metabolic decompensations.

Glycine Encephalopathy

Different types of glycine encephalopathy (nonketotic hyperglycinemia) are characterized by a deficiency of the glycine cleavage enzyme complex. As a result, glycine accumulates in several tissues and, in particular, in the central nervous system. The majority of patients present early in life with symptoms of lethargy, hypotonia, and myoclonus [27]. Prognosis is usually poor, but patients with attenuated phenotypes are described.

Disorders of Carbohydrate Metabolism

Disorders of carbohydrate metabolism are caused by mutations affecting the catabolism and anabolism of carbohydrates. Consequently, the metabolites cannot be used effectively.

GLUT1 Deficiency Syndrome

In GLUT1 deficiency syndrome, glucose transport to the brain is impaired. Symptoms include paroxysmal exercise-induced dyskinesia, epilepsy, and often developmental delay [28]. Movement disorders, including myoclonus, can be found in patients with GLUT1 deficiency. Early recognition of this disorder is important because treatment is available and often consists of the ketogenic diet.

Disorders of Mineral, Metal, or Vitamin Metabolism

Disorders of mineral, metal, or vitamin metabolism are caused by impairment of their metabolism or transport. A wide range of symptoms can be found, including myoclonus.

Neurodegenerative Syndrome Due to Cerebral Folate Transport Deficiency

Folate transport is impaired in neurodegeneration due to cerebral folate transport deficiency. Onset is usually early in life with developmental regression, movement disorders including myoclonus, myoclonic seizures, and leukodystrophy [29, 30]. Treatment is possible with folinic acid therapy.

Biotinidase Deficiency

In patients with biotinidase deficiency, there is a reduced or absent activity of biotinidase, which is necessary for multiple biotin-dependent processes, leading to energy failure and the accumulation of potentially neurotoxic and epileptogenic metabolites. Symptoms include seizures, developmental delay, hypotonia, ataxia, dermatological manifestations, and alopecia. Patients with partial biotinidase deficiency may be asymptomatic until they experience periods of illness, fever, or fasting. Seizures in biotinidase deficiency are mostly generalized tonic–clonic, but myoclonic seizures have been described [30, 31]. When treated with biotin, the prognosis is good but optic atrophy and sensorineural hearing loss, if established, persist.

Menkes Disease

Copper metabolism is impaired in Menkes disease, leading to an accumulation of copper in the kidneys and small intestine, while on the other hand copper is depleted in the brain. Symptoms include progressive neurodegeneration and also connective-tissue abnormalities, and sparse, kinky hair (known as pili torti). Seizures, with or without myoclonus, can be found [32].

Wilson Disease

Copper metabolism is also impaired in Wilson disease. The accumulation of copper in the basal ganglia may cause movement disorders. Liver disease is frequently seen in the childhood-onset form, while psychiatric symptoms and movement disorders dominate in patients with presentation later in life. In particular, parkinsonism and dystonia are frequent; however, myoclonus can be found as well [19].

Hereditary Hemochromatosis

Hereditory hemochromatosis is caused by iron accumulation due to abnormal intestinal iron absorption in the intestine. Presentation is usually in adulthood and a wide range of symptoms can be found, including an increase of skin pigmentation, arthropathy,

lethargy, and diabetes mellitus. Myoclonus may be present as well, and it is often combined with other movement disorders [33].

Pantothenate Kinase-Associated Neurodegeneration

In patients with pantothenate kinase-associated neurodegeneration (PKAN, a form of neurodegeneration with brain iron accumulation), iron accumulates particularly in the globus pallidus. Patients with early-onset forms present with gait abnormalities, usually due to dystonia and parkinsonism. Adolescent-onset forms are associated with dysarthria, psychiatric symptoms, and mild gait disturbances [19]. Myoclonus and dystonia can be found.

Adult-Onset Dystonia–Parkinsonism

Adult-onset dystonia–parkinsonism, also known as NBIA2 (neurodegeneration with brain iron accumulation 2) and PLAN (PLA2G6-related neurodegeneration), usually presents before the age of 30 years and symptoms include movement disorders and cognitive decline [19]. Besides dystonia and parkinsonism, myoclonus can be present as well.

Disorders of Neurotransmitters

Disorders of neurotransmitters are divided into those that affect synthesis, transport, or degradation. Movement disorders are frequently described in these disorders, especially dystonia in disorders affecting the dopaminergic pathway, but myoclonus can be present [19].

Pyridoxine-Related Epilepsy

The pyridoxine related epilepsies, representing various dependency states which include antiquitin and pyridox(am)ine phosphate oxidase deficiencies, present with myoclonic seizures during the first hours of life that respond to pyridoxine or pyridoxal-5-phosphate administration, respectively [34].

Aromatic L-Amino Acid Decarboxylase Deficiency

In aromatic L-amino acid decarboxylase deficiency, the production of dopamine and serotonin is reduced. Symptoms include dystonia, developmental delay, autonomic dysfunction, and oculogyric crises [19]. Affected children with seizures and myoclonus have been described [35]. Given the fact that this is a very rare disorder, myoclonus may not always be recognized.

Tyrosine Hydroxylase Deficiency

Tyrosine hydroxylase deficiency is caused by impairment of the conversion of L-tyrosine to L-dopa (levodopa). Onset is usually early in life with a progressive hypokinetic–rigid syndrome and generalized dystonia with diurnal fluctuations, encephalopathy, and autonomic disturbance. Severe subcortical myoclonus accompanied by dystonia has been described. Treatment with L-dopa improved the symptoms [36].

Energy Metabolism Disorders

Energy metabolism disorders include mitochondrial disorders, but also disorders affecting other pathways involved in energy metabolism (pyruvate oxidation and citric acid cycle). Tissues with high energy needs, including the brain, heart, retina, and skeletal muscles, are frequently affected. A wide range of clinical phenotypes can be found and onset varies widely. Myoclonus is frequently observed within a spectrum of symptoms caused by energy failure.

Mitochondrial Disorders

A wide range of symptoms can be found in mitochondrial disorders; including myopathy, migraines, stroke-like episodes, and epilepsy. Myoclonus can be present in patients with different types of mitochondrial disorders. In particular, in patients with MERRF, myoclonus is common. Myoclonus was present in one out of five patients with this disorder, while myoclonus in other mitochondriopathies is less common [37]. Other disorders of energy metabolism can give rise to myoclonus as well. POLG-related disorders, for example Alpers–Huttenlocher syndrome, present during childhood with encephalopathy, intractable myoclonic epilepsy, and hepatic failure [38]. Valproate is to be avoided in these patients because it can cause further deterioration of symptoms, including acute liver failure.

Coenzyme Q10 Deficiency

In primary coenzyme Q10 deficiency, oxidative phosphorylation is impaired. Coenzyme Q10 has an important function in the electron transfer from complex I and II to complex III of the respiratory chain. Onset is often early in life, although milder forms can present during adulthood. In the latter, movement disorders, such as myoclonus, are frequent [39].

Combined Oxidative Phosphorylation Defects

Oxidative phosphorylation is also impaired in other types of *combined* oxidative phosphorylation defects, often leading to severe symptoms during infancy or childhood. Myoclonus can be found with or without epilepsy [40, 41].

Cerebral Creatine Deficiencies

Cerebral creatine deficiencies can be caused by mutations in three different genes: *GAMT*, *AGAT*, and the transporter *SLC6A8*. Symptoms include intellectual disability, language delay, psychiatric symptoms, and movement disorders. Epileptic seizures, with or without myoclonus, are common, especially in patients with *GAMT* mutations, but also in some patients with *SLC6A8* mutations. Myoclonus in patients with *AGAT* mutations has not been described. Treatment of patients with *GAMT* mutations is possible with oral supplementation of creatine monohydrate, and results in the control of the seizures and movement disorders. No specific treatment is available for patients with *SLC6A8* mutations [30].

Treatment of Myoclonus

Treatable IEMs Associated with Myoclonus

Unfortunately, effective treatment for many IEMs is still not available and patients require symptomatic treatment of their myoclonus. A notable exception is availability of enzyme-replacement therapy, alfa-cerliponase, for CLN2 [42]. Recent translational work is leading to application of targeted therapies in these disorders, such as use of antisense oligonucleotide treatment in CLN7 [43]. An overview of IEMs causing myoclonus and their treatment is given in Table 11.3.

Symptomatic Treatment of Myoclonus in Metabolic Disorders

When disease-specific treatment is not available or not sufficient, symptomatic treatment can be started to relieve the symptoms of myoclonus. Adequate recognition of myoclonus is important because symptomatic treatment of myoclonus can improve quality of life. Even in patients with multiple neurological and non-neurological manifestations, movement disorders significantly interfere with quality of life and daily activities, irrespective of the underlying metabolic defect [44, 45]. The evidence for symptomatic treatment of myoclonus in IEM is limited. Symptomatic treatment of myoclonus in general depends on the anatomical classification. In cortical myoclonus levetiracetam and valproic acid are considered the first choice of treatment, with the latter being contraindicated in patients with POLG mutations. In other subtypes clonazepam is the first choice [3]. However, adequate treatment of myoclonus is difficult, and polytherapy is often necessary to obtain effective treatment [46].

Key Points and Clinical Pearls

- Myoclonus is frequent in metabolic disorders, but may be easily overlooked, in particular in patients with multiple movement disorders.
- Myoclonus in combination with other neurological, psychiatric, or systemic features may point to a metabolic disorder.
- Recognizing myoclonus is important because treatment is possible and may improve quality of life.

Directions for Future Research

- Myoclonus seems to be frequent in metabolic disorders, although the prevalence is still unknown. Increased recognition and accurate classification of myoclonus in patients with a metabolic disorder are needed.
- Performing EEG-EMG polygraphic studies can help in order to further define the anatomic substrate of myoclonus in different types of metabolic disorders.
- Evidence for symptomatic treatment of myoclonus in IEM is limited and more research is needed in order to define the best medical treatment.
- Targeted therapies are emerging for specific conditions based on strategies such as enzyme replacement, antisense oligonucleotides, and gene therapy.

Table 11.3 Treatment of IEMs associated with myoclonus

Metabolic disorder	Treatment
Lysosomal storage disorders	
Neuronal ceroid lipofuscinoses	Mainly symptomatic, enzyme replacement for CLN2, targeted therapies emerging (see text)
Galactosialidosis	Not available, symptomatic
Gaucher disease (mainly type 3)	Miglustat, enzyme-replacement therapy to treat accompanying visceral symptoms
Tay–Sachs disease	Not available, symptomatic
Sandhoff disease	Not available, symptomatic
Sialidosis types 1 and 2	Not available, symptomatic
Niemann-Pick type C disease	Miglustat
Atypical Gaucher disease due to saposin C deficiency	No treatment available, symptomatic
Disorders of lipid metabolism	
Cerebrotendinous xanthomatosis	Chenodeoxycholic acid
Disorders of amino acid and other organic acid metabolism	
Glycine encephalopathy	Sodium benzoate to reduce plasma glycine levels, often in combination with N-Methyl-D-aspartate antagonist (dextromethorphan or ketamine)
Disorder of carbohydrate metabolism	
GLUT1 deficiency	Ketogenic diet or modified Atkins diet
Disorders of mineral, metal, or vitamin metabolism	
Menkes disease	Early parenteral copper–histidine
Wilson disease	Penicillamine, trientine, zinc
Biotinidase deficiency	Oral biotin
Neurodegeneration due to cerebral folate transport deficiency	Oral folinic acid
Hereditary hemochromatosis	Phlebotomy
Pantothenate kinase-associated neurodegeneration (PKAN; NBIA1)	Not available, symptomatic
Adult-onset dystonia–parkinsonism (PLAN)	Not available, symptomatic
Neurotransmitter disorders	
Pyridoxine-dependent epilepsy	Oral pyridoxine, lysine/protein restriction, L-arginine
Aromatic L-amino acid decarboxylase deficiency	Pyridoxine, dopamine agonists, and MAO-inhibitors; adenoviral vector-mediated gene therapy in clinical trials
Tyrosine hydroxylase deficiency	Levodopa
Energy metabolism disorders	
Mitochondrial disorders	Not available, symptomatic
Coenzyme Q10 deficiency	Coenzyme Q10
Combined oxidative phosphorylation defect type 14 and 27	Not available, symptomatic
Cerebral creatine deficiency	*GAMT*: oral creatine monohydrate, ornithine, dietary arginine restriction *SLC6A*: not available, symptomatic

References

1. Caviness JN, Alving LI, Maraganore DM, et al. The incidence and prevalence of myoclonus in Olmsted County, Minnesota. Mayo Clin Proc. 1999;**74**(6):565–9.
2. Gouider-Khouja N, Kraoua I, Benrhouma H, Fraj N, Rouissi A. Movement disorders in neuro-metabolic diseases. Eur J Paediatr Neurol. 2010;**14**(4):304–7.
3. Zutt R, van Egmond ME, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. Nat Rev Neurol. 2015;**11**(12):687–97.
4. Apartis E, Vercueil L. To jerk or not to jerk: A clinical pathophysiology of myoclonus. Rev Neurol (Paris). 2016; **172** (8–9): 465–76.
5. Minassian BA. The progressive myoclonus epilepsies. Prog Brain Res. 2014;**213**:113–22.

6. van der Veen S, Zutt R, Elting JWJ, et al. Progressive myoclonus ataxia: Time for a new definition? Mov Disord. 2018;**33**(8):1281–6.
7. Caviness JN. Treatment of myoclonus. Neurotherapeutics. 2014;**11**(1):188–200.
8. Koens LH, Kuiper A, Coenen MA, et al. Ataxia, dystonia and myoclonus in adult patients with Niemann–Pick type C. Orphanet J Rare Dis. 2016;**11**:121.
9. Ritz K, Gerrits MC, Foncke EM, et al. Myoclonus-dystonia: Clinical and genetic evaluation of a large cohort. J Neurol Neurosurg Psychiatry. 2009;**80**(6):653–8.
10. Dreissen YE, Tijssen MA. The startle syndromes: Physiology and treatment. Epilepsia. 2012;**53** Suppl 7:3–11.
11. Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of Sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. Hum Mutat. 2013;**34**(12):1721–6.
12. van Egmond ME, Lugtenberg CHA, Brouwer OF, et al. A post hoc study on gene panel analysis for the diagnosis of dystonia. Mov Disord. 2017;**32**(4):569–75.
13. Coutelier M, Goizet C, Durr A, et al. Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia. Brain. 2015;**138**(Pt 8):2191–205.
14. Campistol J. Epilepsy in inborn errors of metabolism with therapeutic options. Semin Pediatr Neurol. 2016;**23**(4):321–31.
15. Malek N, Stewart W, Greene J. The progressive myoclonic epilepsies. Pract Neurol. 2015;**15**(3):164–71.
16. Sedel F, Gourfinkel-An I, Lyon-Caen O, et al. Epilepsy and inborn errors of metabolism in adults: A diagnostic approach. J Inherit Metab Dis. 2007;**30**(6):846–54.
17. Beal JC, Cherian K, Moshe SL. Early-onset epileptic encephalopathies: Ohtahara syndrome and early myoclonic encephalopathy. Pediatr Neurol. 2012;**47**(5):317–23.
18. Koens LH, Tijssen MAJ, Lange F, et al. Eye movement disorders and neurological symptoms in late-onset inborn errors of metabolism. Mov Disord. 2018;**33**(12):1844–56.
19. Hollak CEM, Lachman R. Inherited Metabolic Disease in Adults: A Clinical Guide. New York, NY: Oxford University Press; 2016.
20. Sedel F, Lyon-Caen O, Saudubray JM. Therapy insight: Inborn errors of metabolism in adult neurology. A clinical approach focused on treatable diseases. Nat Clin Pract Neurol. 2007;**3**(5):279–90.
21. Poll-The BT, Maillette de Buy Wenniger-Prick LJ. The eye in metabolic diseases: Clues to diagnosis. Eur J Paediatr Neurol. 2011;**15**(3):197–204.
22. Poll-The BT, Maillette de Buy Wenniger-Prick LJ, Barth PG, Duran M. The eye as a window to inborn errors of metabolism. J Inherit Metab Dis. 2003; **26**(2–3): 229–44.
23. Schultz M L, Tecedor L, Chang M, Davidson BL. Clarifying lysosomal storage diseases. Trends Neurosci. 2011;**34**(8):401–10.
24. Accardo A, Pensiero S, Ciana G, Parentin F, Bembi B. Eye movement impairment recovery in a Gaucher patient treated with miglustat. Neurol Res Int. 2010;**2010**:358534.
25. Park JK, Orvisky E, Tayebi N, et al. Myoclonic epilepsy in Gaucher disease: Genotype–phenotype insights from a rare patient subgroup. Pediatr Res. 2003;**53**(3):387–95.
26. Stelten BML, van de Warrenburg BPC, Wevers RA, Verrips A. Movement disorders in cerebrotendinous xanthomatosis. Parkinsonism Relat Disord. 2019;**58**:12–6.
27. Van Hove J, Coughlin C, II, Scharer G. Glycine encephalopathy. GeneReviews®. 2002;Nov 14 (updated Jul 11, 2013).
28. Wang D, Pascual JM, De Vivo D. Transporter type 1 deficiency syndrome. GeneReviews®. 2002;Jul 30 (updated Mar 1, 2018).
29. Toelle SP, Wille D, Schmitt B, et al. Sensory stimulus-sensitive drop attacks and basal ganglia calcification: New findings in a patient with FOLR1 deficiency. Epileptic Disord. 2014;**16**(1):88–92.
30. Mastrangelo M. Actual insights into treatable inborn errors of metabolism causing epilepsy. J Pediatr Neurosci. 2018;**13**(1):13–23.
31. Desai S, Ganesan K, Hegde A. Biotinidase deficiency: A reversible metabolic encephalopathy. Neuroimaging and MR spectroscopic findings in a series of four patients. Pediatr Radiol. 2008;**38**(8):848–56.
32. Bahi-Buisson N, Kaminska A, Nabbout R, et al. Epilepsy in Menkes disease: Analysis of clinical stages. Epilepsia. 2006;**47**(2):380–6.
33. Demarquay G, Setiey A, Morel Y, et al. Clinical report of three patients with hereditary hemochromatosis and movement disorders. Mov Disord. 2000;**15**(6):1204–9.
34. Veerapandiyan A, Winchester SA, Gallentine WB, et al. Electroencephalographic and seizure manifestations of pyridoxal 5'-phosphate-dependent epilepsy. Epilepsy Behav. 2011;**20**(3):494–501.
35. Brautigam C, Hyland K, Wevers R, et al. Clinical and laboratory findings in twins with neonatal epileptic encephalopathy mimicking aromatic L-amino acid decarboxylase deficiency. Neuropediatrics. 2002;**33**(3):113–7.

36. Stamelou M, Mencacci NE, Cordivari C, et al. Myoclonus-dystonia syndrome due to tyrosine hydroxylase deficiency. Neurology. 2012;**79**(5):435–41.

37. Mancuso M, Orsucci D, Angelini C, et al. Myoclonus in mitochondrial disorders. Mov Disord. 2014;**29**(6):722–8.

38. Cohen BH, Chinnery PF, Copeland WC. POLG-related disorders. GeneReviews®. 2010;Mar 16 (updated Mar 1, 2018).

39. Salviati L, Trevisson E, Doimo M, Navas P. Primary coenzyme Q10 deficiency. GeneReviews®. 2017;Jan 26.

40. Walker MA, Mohler KP, Hopkins KW, et al. Novel compound heterozygous mutations expand the recognized phenotypes of *FARS2*-linked disease. J Child Neurol. 2016;**31**(9):1127–37.

41. Coughlin CR, 2nd, Scharer GH, Friederich MW, et al. Mutations in the mitochondrial cysteinyl-tRNA synthase gene, *CARS2*, lead to a severe epileptic encephalopathy and complex movement disorder. J Med Genet. 2015;**52**(8):532–40.

42. Schultz A, Ajavi T, Specchio N, et al. Study of intraventricular cerliponase alfa for CLN2 disease. N Engl J Med. 2018;**378**:1898–907.

43. Kim J, Hu C, Moufawad El Achkar C, et al. Patient-customized oligonucleotide therapy for a rare genetic disease. N Engl J Med. 2019;**381**:1644–52.

44. Monbaliu E, De Cock P, Mailleux L, Dan B, Feys H. The relationship of dystonia and choreoathetosis with activity, participation and quality of life in children and youth with dyskinetic cerebral palsy. Eur J Paediatr Neurol. 2017;**21**(2):327–35.

45. Eggink H, Kuiper A, Peall KJ, et al. Rare inborn errors of metabolism with movement disorders: A case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet J Rare Dis. 2014;**9**:177.

46. Dijk JM, Tijssen MA. Management of patients with myoclonus: Available therapies and the need for an evidence-based approach. Lancet Neurol. 2010;**9**(10):1028–36.

Chapter 12

Disorders of Amino Acid Metabolism: Amino Acid Disorders, Organic Acidurias, and Urea Cycle Disorders with Movement Disorders

Stefan Kölker

Overview

Humans depend on dietary proteins as a source of amino acids; they are the metabolic basis of all functional and structural proteins in the body. Some amino acids – termed essential – cannot be synthesized by the human body, such as L-isoleucine and L-phenylalanine. Renal conservation of amino acids is extremely effective, with clearance values mostly below 1%. Stool nitrogen losses are about 1 g per day and are mostly of bacterial origin. In contrast to glucose and fatty acids, amino acids taken in excess of requirement cannot be stored but their carbon backbones are used for energy production.

Amino acid disorders, organic acidurias, and urea cycle disorders are rare inherited disorders of protein metabolism caused by deficiencies of single enzymes, cofactor metabolism, or transporters involved in the oxidative breakdown of amino acids. Biochemically, they are characterized by the accumulation of metabolites upstream of the defective enzyme (i.e. amino acids, organic acids, and/or ammonium), causing intoxication. Enzyme deficiencies in the proximal part of amino acid catabolism result in the accumulation of precursor amino acids such as L-phenylalanine or branched-chain amino acids and thus are called amino acid disorders (AADs). Amino acids can be specifically detected by the ninhydrin reaction, which became available in the late 1940s, explaining why AADs belong to the earliest identified inborn errors of metabolism (IEMs). In contrast, the definitive breakdown of many amino acids occurs mostly within the mitochondria through degradation of coenzyme A (CoA)-activated carbonic acids, so-called acyl-CoA compounds. After hydroxylation of the CoA group, so-called organic acids (i.e. water-soluble mono-, di-, or tricarboxylic acids) are released. The pathological accumulation of characteristic organic acids, but not of precursor amino acids, in body fluids is the biochemical hallmark of organic acidurias (OADs), a disease group caused by an inherited dysfunction of the distal part of amino acid degradation. OADs became detectable after the introduction of gas chromatography, particularly gas chromatography/mass spectrometry (GC/MS), in the 1960s. Thus, the historic terminology of AADs and OADs is not based on pathophysiological differences but simply reflects the development of analytical approaches. It is noteworthy that GC/MS analysis has also identified IEMs of many pathways beyond amino acid degradation, for example of cholesterol metabolism, fatty acid oxidation, carbohydrate, or mitochondrial energy metabolism.

The breakdown of amino acids results in the release of neurotoxic ammonium that is detoxified by the urea cycle. The latter takes place in periportal hepatocytes and is composed of five catalytic enzymes, two associated enzymes producing a cofactor (N-acetylglutamate) and a substrate (bicarbonate) for the formation of carbamylphosphate, and two transport proteins. The efficacy of hepatic ammonium detoxification is enhanced through the action of L-glutamine synthetase in perivenous hepatocytes, resulting in the reversible fixation of excess ammonium to L-glutamate. In the brain, enhanced L-glutamine synthesis, mostly in astrocytes, is the only way to detoxify ammonium. The biochemical hallmark of most urea cycle disorders (UCDs) is thus hyperglutaminergic hyperammonemia.

Clinically, individuals with an inherited AAD, OAD, or UCD are usually born at term after an uneventful pregnancy and delivery, and are initially asymptomatic. The onset of the first symptoms is variable, ranging from metabolic decompensation within the first days of life to the late onset of symptoms during adulthood. If the diagnosis is delayed or missed, irreversible organ damage or early death may follow [1]. In childhood, metabolic decompensations are triggered by an excess intake of protein and, most importantly, the breakdown of body protein during

Table 12.1 Examples of AADs, OADs, and UCDs presenting with movement disorders

Disease	Inheritance*	Gene (location)	Enzyme (Name, EC or TC number)	Estimated prevalence (*X* per 100,000)	MIM number
Phenylketonuria (PKU)	AR	*PAH* (12q23.2)	L-phenylalanine hydroxylase (EC 1.14.16.1)	10	#261600
Methylmalonic aciduria (MMA, mutase-deficient type)	AR	*MMUT* (6p12.3)	Methylmalonyl-CoA mutase (EC 5.4.99.2)	1	#251000
Glutaric aciduria type 1 (GA-1)	AR	*GCDH* (19p13.13)	Glutaryl-CoA dehydrogenase (EC 1.3.8.6)	1	#231670
L-2-Hydroxyglutaric aciduria (L2HGA)	AR	*L2HGDH* (14q21.3)	L-2-hydroxyglutarate dehydrogenase (EC 1.1.99.2)	<1	#236792
HHH syndrome	AR	*SLC25A15* (13q14.11)	Mitochondrial L-ornithine transporter 1 (TC 2.A.29.19.2)	<0.1	#238970

* AR, autosomal-recessive.

episodes of catabolism. The disease spectrum is broad but follows a distinct pattern in specific disorders. Despite considerable clinical variability, the central nervous system is most often affected in AADs, OADs, and UCDs [2]. Recent pathogenic concepts are based on the observation that some pathological metabolites impair key intracellular functions, such as energy metabolism, and thus may become toxic at increased concentrations, causing irreversible damage or reversible dysfunction. Other metabolites interfere with neurotransmitter pathways or interact with neurotransmitter receptors. This might explain the specific vulnerability of the brain [3].

Major therapeutic strategies aim to restrict the intake of precursor amino acids (low protein or calculated diets specifically restricting precursor amino acids), stimulate residual enzyme activity (cofactor treatment), facilitate urinary excretion (hydration, forced diuresis), enhance physiological pathways of detoxification (e.g. formation of non-toxic acylcarnitines), or open alternative routes (e.g. nitrogen scavengers, extracorporeal detoxification) [4–7]. Finally, solid organ transplantation (liver, kidney) increases the residual activity of the defective enzyme and thus attenuates or even rescues the biochemical phenotype and improves the outcome [8]. However, since irreversible organ dysfunction is already found in newborns or infants, therapies are more effective if they can be started in affected individuals while asymptomatic. Based on the seminal work of Robert Guthrie and Horst Bickel, newborn screening programs and effective therapies for many intoxication-type IEMs have been successfully developed, highlighting that such preventive programs can be disease-changing [9].

This chapter focuses on AADs, UCDs, and OADs and discusses movement disorders in these groups of disorders (Table 12.1).

The clinical spectrum of major AADs, OADs, and UCDs is discussed in detail in this chapter and is summarized in Table 12.2.

Amino Acid Disorders

Phenylketonuria

Phenylketonuria (PKU), first described in 1934, is found with an average frequency of about 1 in 10,000 newborns with large national and ethnic variability. It is caused by bi-allelic mutations in the *PAH* gene (gene locus: 12q23.2) encoding for the enzyme L-phenylalanine hydroxylase, which is expressed in liver and kidney and catalyzes the conversion of L-phenylalanine to L-tyrosine and requires tetrahydrobiopterin (BH4), iron, and molecular oxygen as cofactors. The metabolic consequences of PAH deficiency are increased plasma and cerebrospinal fluid (CSF) concentrations of L-phenylalanine and decreased L-tyrosine. Furthermore, phenylacetate, giving the urine a mousy odor, and other "phenylketones" accumulate [10]. Eighty years after its description, the molecular mechanisms of PKU are still not completely understood. L-phenylalanine competes

Table 12.2 Clinical spectrum of individuals with AADs, OADs, and UCDs

Disease	Neurological manifestations	Other manifestations
PKU	Microcephaly Severe cognitive disability Epilepsy (often starting with infantile spasms) Tremor, parkinsonism-like movements Spastic para- or tetraparesis Obsessive–compulsive disorder Autism spectrum disorder Anxiety disorders Depression	*Eyes*: Blue eyes, cataracts *Skin/hair*: pale pigmentation, eczema, blond hair
MMA (mutase-deficient type)	Microcephaly (variable) Developmental delay Cognitive disability Epilepsy Movement disorders (chorea, dystonia) following stroke-like events (mostly affecting the globus pallidus)	*Eyes*: Optic nerve atrophy *Heart*: Prolonged QT_c interval, cardiomyopathy *Kidney*: interstitial nephritis, chronic kidney disease *GI tract*: vomiting, decreased appetite, failure to thrive, pancreatitis *Blood:* Neutropenia (anemia, thrombocytopenia, pancytopenia)
GA-1	Macrocephaly Complex movement disorder with predominant dystonia (or chorea) superimposed on axial hypotonia Cognitive function is usually spared *Characteristic MRI pattern*: 1. Newborn period (reversible): Temporal hypoplasia with widening of Sylvian fissures and immature gyral pattern and delayed myelination, periventricular pseudocyst. 2. Infantile period (irreversible): Striatal necrosis spreading from the dorsolateral aspects of the putamen in a ventromedial direction, variably involving caudate and globus pallidum. 3. Adolescents/adults (unknown clinical relevance): Progression of signal alterations in periventricular white matter and gray matter (e.g. dentate nuclei, substantia nigra), subependymal nodular lesions	*Kidney*: Chronic kidney disease (adults), inconsistent
L2HGA	Macrocephaly Progressive neurological disease starting in infancy Developmental delay Cognitive disability Spastic paraparesis Cerebellar signs Extrapyramidal signs Epilepsy Malignant brain tumors (mostly of glial origin) *Characteristic MRI pattern*: subcortical white matter disease involving the U-fibers, pathological signal changes of dentate nuclei and globus pallidus, and cerebellar atrophy	*Ears*: Hearing loss *Eyes*: Strabismus, optic atrophy, nystagmus *Kidney*: Wilms tumor (single case)
HHH syndrome	Progressive spastic paraparesis Cognitive disability (variable) Myoclonic epilepsy Cerebellar signs	*Eye*: Retinal involvement such as photophobia, night blindness, tapetoretinal degeneration *GI tract*: Protein aversion, failure to thrive, episodic vomiting *Liver*: Hepatomegaly, hepatitis-like attacks, acute liver failure

with the transport of large neutral amino acids across the blood–brain barrier using L-type amino acid transporter 1. Since L-phenylalanine has the highest affinity to this transporter, increased plasma L-phenylalanine concentrations dramatically limit the transport of large neutral amino acids (LNAAs) to the brain, resulting in an overall reduced cerebral biosynthesis of proteins and neurotransmitters such as dopamine and serotonin (the so-called LNAA hypothesis) [11]. L-phenylalanine also exerts direct effects on glutamatergic signaling since it competes with L-glycine and L-glutamate at their binding sites in N-methyl-

D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, impairing synapse formation and cognitive function [3]. In addition, L-phenylalanine inhibits 3-hydroxy-3-methyglutaryl-CoA reductase, the rate-limiting step of cholesterol biosynthesis and switches forebrain oligodendrocytes to a non-myelinating state, affecting myelination. These mechanisms explain most neuropathological findings of untreated patients, i.e. significantly reduced brain weight, symmetrical reduction of periventricular and cerebellar white matter with vacuolization, and degeneration of the corticospinal tract. Neuronal cell density and even more pronounced axonal sprouting and arborization are strongly reduced and synapse formation rarified.

Newborns with PKU are asymptomatic since fetal L-phenylalanine concentrations are normalized by the mother's intact metabolism. Untreated individuals, however, almost invariably develop severe cognitive disability with an IQ below 40. The first symptom is delayed development, usually starting around age 3 months, followed by developmental arrest. Epilepsy often presents with infantile spasms. Muscular tone is increased and tendon reflexes are brisk, slowly progressing to spastic para- or tetraparesis. A parkinsonian presentation with tremor is often observed in adults. Affected individuals and their families are confronted with severe behavioral problems and neuropsychiatric comorbidities including autism spectrum disorder, aggressive behaviors, self-mutilation, and anxiety. Constitutional abnormalities such as hypopigmentation of the skin, hair (fair), and iris (blue) develop rapidly due to an impaired metabolism of melanin. Eczematous rash resembling atopic dermatitis is also found and thought to be caused by phenylacetate [10].

The first and still most important therapeutic intervention in PKU is a low L-phenylalanine diet, which should be started immediately after diagnosis, preferably after identification through newborn screening, and continued lifelong [12]. It was estimated that during infancy delayed start of therapy results in irreversible loss of one IQ point per week. There is a worldwide consensus that diet should be started if plasma L-phenylalanine rises above 600 μmol/L; however, there is still controversy about whether untreated individuals whose plasma L-phenylalanine concentrations are constantly between 360–600 μmol/L require treatment or not. Furthermore, there is uncertainty about the target L-phenylalanine levels, in particular during adulthood [7, 13]. With age, tolerance to L-phenylalanine increases, owing to the decreasing vulnerability of the brain. However, adults who do not adhere to diet might be confronted with neurocognitive dysfunction and early-onset dementia. Pregnant women require strict dietary control (L-phenylalanine target range: 120–360 μmol/L) to prevent maternal PKU, an embryofetopathy caused by the teratogenic effects of increased L-phenylalanine concentrations, partially resembling alcohol embryopathy [14]. This includes cognitive disability, microcephaly, brain malformations, congenital heart disease, limb malformation, and/or tracheoesophageal fistula. PKU patients whose PAH activity can be significantly stimulated by its cofactor BH4 should be treated with sapropterin dihydrochloride to increase their L-phenylalanine tolerance [15]. Pegvaliase, a novel enzyme substitution therapy, has recently been approved by the US Food and Drug Administration and opens new therapeutic opportunities for PKU patients.

While individuals who have been treated soon after birth and adhered to recommended therapy have an excellent outcome, late-treated individuals only partially respond to therapy. However, although cognitive disability cannot be reversed, they often show neurological and behavioral improvements, although a strict diet may be difficult to implement in older patients.

Organic Acidurias

Two groups of OADs – "classic" and "cerebral" OAD – have been delineated, based on the clinical presentation. Patients with classic OADs such as methylmalonic aciduria often present in the newborn period or infancy after a short symptom-free interval of days or weeks with life-threatening acute "sepsis-like" metabolic decompensation, including metabolic acidosis, keto- and lactic acidosis, and hyperammonemia. Such metabolic crises can occur at any age and are usually precipitated by catabolism. In contrast to classic OADs, patients with cerebral OADs present with predominant neurological symptoms, which usually develop in the absence of severe metabolic decompensation. Neurological symptoms may manifest acutely such as in glutaric aciduria type 1 or may slowly progress after a variable symptom-free period, typical of L-2-hydroxyglutaric aciduria [1].

Methylmalonic Aciduria Due to Methylmalonyl-CoA Mutase Deficiency

Methylmalonic aciduria (MMA) is the biochemical hallmark of a heterogeneous group of IEMs. This chapter focuses on mutase-deficient MMA, first described in 1967, with an estimated prevalence of 1 in 100,000 newborns. It is caused by bi-allelic mutations in the *MUT* gene (gene locus: 6p12.3) causing complete (mut^0) or partial (mut^-) deficiency of the mitochondrial enzyme methylmalonyl-CoA mutase (MUT). MUT requires 5'-deoxyadenosylcobalamin as a cofactor and hence deficient biosynthesis or transport of this cofactor, insufficient dietary intake, or impaired intestinal uptake all result in dysfunctional MUT. MUT converts L-methylmalonyl-CoA to succinyl-CoA in the final step of propionate oxidation, an important anaplerotic mechanism that helps to replenish the Krebs cycle with an important substrate. The amino acids L-isoleucine, L-threonine, L-methionine, L-valine, odd-numbered fatty acids, the side chain of cholesterol, and propionate-producing gut bacteria are major precursors of methylmalonyl-CoA. Biochemically, MUT deficiency results in intramitochondrial accumulation of propionyl-CoA and methylmalonyl-CoA. Since CoA esters cannot cross the inner mitochondrial membrane, there is a systemic accumulation of the name-giving methylmalonic acid as well as 2-methylcitric acid, 3-hydroxypropionic acid, tiglic acid, propionylcarnitine, and propionylglycine [4].

Propionyl-CoA mimics acetyl-CoA and thereby interferes with a variety of metabolic pathways including inhibition of (1) the glycine cleavage system resulting in hyperglycinemia, (2) N-acetylglutamate synthase resulting in hyperammonemia, and (3) pyruvate dehydrogenase complex resulting in lactic acidemia and hyperketosis. In addition, 2-methylcitric acid inhibits the Krebs cycle enzymes, and methylmalonate interferes with succinate transport [16–18]. Furthermore, MUT deficiency causes irreversible dysfunction of an important anaplerotic pathway. The consequence of these converging mechanisms is synergistic impairment of energy metabolism and the mitochondrial part of ureagenesis. Mitochondrial dysfunction as exemplified by the reduced potential of the inner mitochondrial membrane usually activates the PINK1–Parkin system, which then leads to degradation of damaged organelles via autophagy (mitophagy) [19]. Evidence is increasing, however, that mitochondrial quality control through mitophagy is inefficient in individuals with MMA, causing sustained mitochondrial dysfunction. This is demonstrated by a multiple deficiency of mitochondrial enzyme complexes required for oxidative phosphorylation (OXPHOS), particularly cytochrome c oxidase (complex IV), highlighting the fact that acute metabolite-induced mitochondrial dysfunction turns into metabolite-independent organelle dysfunction, with age [20, 21].

Untreated individuals with MMA, mut^0 more frequently than mut^- patients, present with severe neonatal metabolic decompensation characterized by rapidly developing multi-organ failure, which may be misinterpreted as neonatal sepsis, and biochemically by hyperammonemia, metabolic acidosis, hyperketosis, lactic acidosis, and hyperglycinemia [22]. During infancy and childhood, the brain is at particular risk for basal ganglia damage, mostly affecting the globus pallidus (termed "metabolic stroke"), during severe metabolic decompensations [23]. However, the clinical phenotype is much broader and develops with age. Failure to thrive, developmental delay and intellectual disability, axial hypotonia, extrapyramidal symptoms (mostly dystonia and chorea), seizures, microcephaly, optic atrophy, prolonged QT_c interval and cardiomyopathy, metabolic myopathy, pancreatitis, leukopenia, thrombocytopenia, anemia or pancytopenia, and chronic kidney disease all have been described [2, 4]. While hospitalizations due to impending metabolic crises are frequent in infants and children and affect neurodevelopment, these crises become less frequent or even diminish with age and are followed by a chronic progressive disease course with multiple organ dysfunction, resembling OXPHOS disorders [4, 20, 21].

Metabolic maintenance treatment aims to reduce the production of toxic metabolites by sustaining anabolism and dietary restriction of precursor amino acids (L-isoleucine, L-methionine, L-threonine, and L-valine) [4]. As significant propionate production occurs in the gut, intermittent decontamination (10–14 days per month) with oral metronidazole or colistin, as well as measures preventing constipation, are often used. L-carnitine is supplemented with the aim to stimulate physiological detoxification of propionyl-CoA via nontoxic, water-soluble propionylcarnitine and to prevent secondary carnitine depletion. Recurrent hyperammonemia, especially during infancy, may require additional pharmacotherapy with carglumic acid and sodium benzoate [24]. Hydroxy- or cyanocobalamin

do not help to stimulate residual enzyme activity in mut^0 or mut^- patients. Chronic kidney disease often progresses, necessitating hemo- or peritoneal dialysis. To prevent or stop metabolic crises, patients receive emergency treatment including an intensified supply with carbohydrates and carnitine, a transient reduction of dietary protein, and an intensified pharmacological detoxification or extracorporeal removal of toxic metabolites (ammonium, lactate, toxic organic acids) [4]. Overall, the outcome of individuals with MUT-deficient MMA is often disappointing, despite adherence to recommended metabolic therapy. Liver and/or kidney transplantation significantly improves the biochemical phenotype and protein tolerance, but does not reliably protect against neurological complications [8]. Long-term outcome studies are required to understand which patients may benefit from organ transplantation and which transplants – liver, kidney, combined liver–kidney – have favourable outcomes.

Glutaric Aciduria Type 1

Pathological accumulation of glutaric acid, a dicarboxylic acid, is the biochemical hallmark of three etiologically and clinically different IEMs termed glutaric aciduria types 1–3. This paragraph focuses on glutaric aciduria type 1 (GA-1; first described in 1975, which is commonly found with an estimated prevalence of about 1 in 100,000 newborns, but is more frequent (up to 1 in 300 newborns) in some high-risk populations such as the Amish Community in Pennsylvania, USA, and the Oji-Cree first nations in Western Ontario and Manitoba, Canada, due to founder mutations. GA-1 is caused by bi-allelic mutations in the *GCDH* gene (gene locus: 19p13.13) resulting in deficiency of flavin adenine dinucleotide (FAD)-dependent glutaryl-coenzyme A (CoA) dehydrogenase (GCDH), a mitochondrial key enzyme that catalyzes the oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA in the final catabolic pathway of L-lysine, L-hydroxylysine, and L-tryptophan. As a consequence of GCDH deficiency, glutaric, 3-hydroxyglutaric, and (inconsistently) glutaconic acids as well as of non-toxic glutarylcarnitine accumulate. Due to the limited permeability of the blood–brain barrier to dicarboxylic acids (such as glutaric acid), these strongly accumulate in the brain (so-called trapping hypothesis) [25]. Noteworthy, some of these metabolites are considered neurotoxic. This may explain why individuals with a complete loss of GCDH activity ("high excretors") have the same high risk of developing neurological disease than those with residual GCDH activity ("low excretors"). Candidate mechanisms are stimulation of excitotoxic pathways via activation of NMDA receptors, inhibition of the 2-oxoglutarate dehydrogenase complex and the dicarboxylate shuttle between astrocytes and neurons, and vascular dysfunction of the brain [16, 26, 27]. In the long run, chronic epigenetic changes caused by enhanced lysine glutarylation of metabolic enzymes and histones may result in alterations of the adaptive response to environmental changes and altered gene expression [28].

Newborns are often asymptomatic but may present with transient neurological symptoms (axial hypotonia, asymmetrical posturing) and macrocephaly, which is found in 75% of patients. Neuroimaging in newborns and infants often reveals hypoplasia of the temporal lobe with subsequently reduced opercularization and widening of the Sylvian fissure. Subependymal pseudocysts and delayed myelination are also commonly seen. All these changes can improve or completely resolve with age in individuals treated early. In addition, subdural fluid collections are occasionally found and are thought to result from increased mechanical vulnerability of bridging veins. These subdural collections can be mistaken as a consequence of non-accidental trauma [29]. The prognostically relevant event of GA-1 is irreversible striatal damage, which may be precipitated acutely by episodes of catabolism or manifest insidiously without apparent trigger. The characteristic time window of striatal injury is usually between 3 months and 36 months of age (peak: 9–10 months). Irreversible striatal injury has rarely been reported after age 6 years. Striatal lesions first manifest in the dorsolateral aspects of the putamen and then spread into a ventromedial direction. The histological hallmark is severe loss of GABAergic medium-spiny neurons, the most abundant neuronal species in the striatum [30]. The caudate and pallidum may also be involved in this process [29]. The consequence of striatal damage is a complex movement disorder with predominant generalized dystonia, superimposed on baseline axial hypotonia. With age, the dystonia tends to evolve from mobile to fixed dystonia. Orofacial dyskinesia is also a consistent finding, resulting in dys- or anarthria, speech apraxia, and impaired swallowing [31]. Less frequently, chorea is the predominant finding. The severity of the movement disorder is best predicted by the extent of striatal lesions. In

individuals with severe dystonia, life expectancy is significantly reduced. Fifty percent of severely affected patients die before adulthood due to secondary complications of their movement disorder. In individuals with the high-excretor phenotype, progressive signal changes of periventricular white matter and gray matter (e.g. substantia nigra, nucleus dentatus, and thalamus) as well as subependymal lesions with unclear clinical significance have been reported [29]. This may reflect cumulative neurotoxicity, particularly in untreated patients. Based on its apparently exclusive neurological phenotype, GA-1 had been termed a "cerebral" organic aciduria two decades ago. However, independent of the neurological phenotype, kidney function tends to decline with age and does not appear to be impacted by current therapy, and thus extends the clinical phenotype [5].

Metabolic treatment cannot reverse the neurological phenotype in symptomatic patients once striatal damage has occurred [32]. However, more than 90% of neonatally screened and presymptomatically treated patients who adhered to evidence-based recommendations remain asymptomatic, and symptomatic patients are usually less severely affected compared to the pre-screening era [33]. Recommended therapy consists of a low lysine diet until age 6 years and L-carnitine aiming to stimulate the physiological formation of non-toxic glutarylcarnitine and to prevent secondary carnitine depletion. Since a low lysine diet and carnitine supplementation do not prevent the manifestation of striatal damage during episodes of catabolism, emergency treatment with supplementation of carbohydrates, reduced protein intake, and intensified carnitine supplementation is warranted. After age 6 years, metabolic therapy is liberalized since acute or insidious striatal damage does not develop beyond this age [5]. Animal studies confirmed that these therapeutic measures reduce the accumulation of neurotoxic metabolites [34].

L-2-Hydroxyglutaric Aciduria

L-2-hydroxyglutaric aciduria (L2HGA), first described in 1980, is a rare cerebral OAD caused by bi-allelic mutations in the *L2HGDH* gene (gene locus 14q21.3) resulting in deficiency of the FAD-dependent mitochondrial enzyme L-2-hydroxyglutarate dehydrogenase (L2HGDH), which converts L-2-hydroxyglutarate to 2-oxoglutarate, a metabolite of the Krebs cycle. The metabolic consequence is the pathological accumulation of L-2-hydroxyglutarate. Furthermore, L-lysine is often normal in plasma, but modestly increased in CSF owing to the shortage of 2-oxoglutarate required for lysine oxidation [35]. L-2-hydroxyglutarate is not a normal metabolite in the metabolism of eukaryotes and eubacteria, yet mammals and bacteria have an enzyme to convert it. The metabolic proofreading hypothesis has elucidated that L-2-hydroxyglutarate can be formed as a minor side reaction of the mitochondrial enzyme L-malate dehydrogenase, a Krebs cycle enzyme, using 2-oxoglutarate as a substrate instead of its preferred substrate L-malate. Hence, L2HGDH repairs a nonsense metabolite and prevents the constant drain of 2-oxoglutarate from the Krebs cycle [36]. However, the molecular mechanisms are not yet fully understood. While L-2-hydroxyglutarate does not appear to be particularly toxic (in contrast to D-2-hydroxyglutaric acid), the chronic shortage of 2-oxoglutarate may have negative implications for energy metabolism and other pathways which require 2-oxoglutarate as a substrate [16].

Although a few individuals with L2HGA showed neonatal onset of symptoms with lethargy, epileptic encephalopathy, and cerebellar abnormalities, the majority have an insidious onset starting in infancy or childhood with subsequent chronic progression. The clinical phenotype includes developmental delay, macrocephaly, epilepsy, cerebellar ataxia, and variable extrapyramidal and pyramidal signs. By adolescence, patients are often bedridden and have severe intellectual disability. The oldest known patients are in their 40s [35, 37]. Brain MRI shows a unique and often uniform pattern with predominantly subcortical cerebral white matter abnormalities involving the U-fibres and signal alterations in the nucleus dentatus and globus pallidus. Progressive loss of myelinated arcuate fibers and a spongiform encephalopathy is the neuropathological correlate of these white matter changes on imaging. Importantly, L2HGA is a predisposing condition for the development of malignant brain tumors, mostly of glial origin, but tumorigenesis does not appear to be restricted to the brain [38, 39]. Since prolyl hydroxylases, which inactivate hypoxia-inducible factor 1-alpha, require 2-oxoglutarate as a substrate, chronic shortage of 2-oxoglutarate increases the half-life of this important factor. Furthermore, 2-oxoglutarate-dependent dioxygenases are a group of enzymes that regulate the cell's hypoxic response and epigenetic processes, particularly the demethylation of histones and DNA, acting as metabolic sensors. Dysregulation of these

processes results in altered gene expression that may facilitate tumorigenesis [16].

Currently, there is no established treatment protocol for L2HGA apart from anecdotal reports mentioning positive effects of treatment with riboflavin and/or FAD, aiming to stimulate residual enzyme activity of L2HGDH.

Urea Cycle Disorders

UCDs have a cumulative prevalence of about 1 in 35,000–50,000 newborns. The biochemical hallmark of most UCDs is hyperglutaminergic hyperammonemia due to impaired ureagenesis and concomitantly enhanced hepatic glutamine synthesis. The majority of UCDs may already manifest with life-threatening hyperammonemic encephalopathy during the newborn period following a short symptom-free interval. The presentation shares similarities with that described for MMA. Individuals with neonatal onset of UCDs are still confronted with high mortality (up to 50%) and severe neurological sequelae in those that survive the neonatal period [40]. The neurological phenotype reflects the extent of brain damage. Various movement disorders have been reported, but are less prevalent than cognitive dysfunction, epilepsy, and behavioral abnormalities. In contrast, individuals with hyperargininemia due to arginase 1 deficiency and hyperammonemia–hyperornithinemia–homocitrullinuria (HHH) syndrome due to impaired mitochondrial L-ornithine transport develop a characteristic neurological syndrome with progressive spastic paraparesis that develops independently from hyperammonemia. In the following, HHH syndrome is described in further detail.

Hyperammonemia–Hyperornithinemia–Homocitrullinuria Syndrome

HHH syndrome, first described in 1969, accounts for 1–4% of all UCDs and is likely to be less prevalent than 1 in a million newborns. However, the disease is more frequent in French Canadians, Italians, and the Japanese. Recently, a systematic literature review of all published individuals (n = 111) was reported [41]. The disease is caused by bi-allelic mutations in the *SLC25A15* gene, formerly termed *ORNT1* (gene locus: 13q14.11), encoding for the mitochondrial ornithine carrier ORC1. ORC1 transports L-ornithine, L-lysine, and L-arginine into the mitochondrial matrix. In periportal hepatocytes, it catalyzes L-ornithine–L-citrulline exchange, connecting the mitochondrial and cytosolic parts of the urea cycle. ORC1 deficiency results in hyperornithinemia in the cytosol (and plasma) but L-ornithine depletion in mitochondria, which is required as a substrate for ornithine transcarbamylase, the second enzymatic step of the urea cycle. As a consequence, ammonium and carbamylphosphate accumulate, giving rise to homocitrulline and orotic acid. Increased cytosolic L-ornithine inhibits L-arginine:L-glycine amidinotransferase, the first step of creatine synthesis, leading to secondary creatine deficiency, and increased formation of polyamines such as spermine and spermidine. Increased L-ornithine and homocitrulline may cause oxidative stress and mitochondrial dysfunction. How the above described single mechanisms synergize and result in a complex, progressive clinical phenotype is not yet understood. Two human isoforms, ORC1 and ORC2, exist. ORC2 is less active, has a lower affinity for L-ornithine and L-citrulline and is expressed to a lesser extent than ORC1; however, ORC1 deficiency activates ORC2 expression. ORC2 attenuates, but cannot rescue the biochemical and clinical consequences of ORC1 deficiency and may contribute to the broad clinical spectrum of HHH syndrome.

About 45% percent of affected individuals present during the newborn period and infancy, 45% during childhood and 10% in adolescence/adulthood. Despite early disease onset, the diagnosis is often delayed for years. Individuals with early disease onset often present with acute hyperammonemic encephalopathy, while individuals with late disease onset usually follow a slowly progressive course, characterized by protein aversion, cognitive disability, and motor dysfunction. Regardless of the disease onset, the peculiar feature of HHH syndrome is a combination of progressive spastic paraparesis, cerebellar signs (ataxia, intention tremor, nystagmus, dysdiadochokinesia, dysarthria), and myoclonic epilepsy. Not surprisingly, many patients are often initially diagnosed with infantile cerebral palsy or hereditary spastic paraparesis before the correct diagnosis is made. Cognitive impairment is often reported, with variable severity. Retinal involvement such as photophobia, night blindness, and tapetoretinal degeneration is common. In addition to the complex neurological manifestations, individuals with HHH syndrome

characteristically develop liver disease that ranges from transaminitis to hepatitis-like attacks to acute liver failure. Noteworthy, there is no apparent correlation between progressive spastic paraparesis (and liver disease) and plasma ammonium concentrations.

Emergency treatment in individuals with acute onset is similar to that for other intoxication-type IEMs, including reduction or cessation of protein intake for 24 hours, intravenous glucose infusion in combination with L-arginine (and/or L-citrulline), and nitrogen scavengers as first-line medication [6]. Metabolic maintenance treatment combines low protein diet, supplementation of L-citrulline (or L-arginine), and nitrogen scavengers (sodium benzoate, sodium or glycerol phenylbutyrate). L-Ornithine supplementation has been tried with contradictory results and is no longer recommended. Since creatine synthesis is impaired, supplementation with creatine might be considered. Conservative treatment prevents hyperammonemia and liver disease but does not prevent spasticity. Therefore, liver transplantation should be considered individually [6, 41].

The Spectrum of Movement Disorders in Inherited Diseases Affecting Amino Acid Metabolism

As discussed above, there is a shared spectrum of movement disorders in AADs, OADs, and UCDs but there are also significant differences owing to the variable age at disease onset and progression. Movement disorders in these diseases often develop acutely during or shortly after a metabolic (or encephalopathic) crisis and reflect acute "stroke-like" damage of susceptible brain regions, mostly nuclei of the basal ganglia. The preferential involvement of the basal ganglia is likely due to a high local energy demand, strong glutamatergic input and a highly vulnerable cell population, i.e. the striatal medium-spiny neurons [23, 29, 30]. Acute damage of the basal ganglia, mostly the putamen and pallidum, leads to complex movement disorders with predominant dystonia or chorea [2, 16, 33]. In contrast, spasticity in HHH syndrome [41] and L2HGA progresses chronically over years [35, 37]. This reflects the progressive dysfunction and damage of white matter, as demonstrated by delayed myelination or hypomyelination on MRI. Histological pathology confirms a spongiform myelinopathy. However, correlation of white matter changes on MRI and clinical manifestations is often poor. This is exemplified, for example, by progressive white matter changes of unclear clinical relevance in individuals with GA-1 [29]. The chronic progression of movement disorders is not well understood and is sometimes not responsive to treatment [4, 5]. Physiological changes with age, such as changes in muscular tone, need to be distinguished from true progression [31]. To solve this important question, close follow-up monitoring in a standardized setting with structured documentation is required. Irreversible movement disorders must also be separated from potentially reversible abnormalities caused by delayed myelination or intermittently disturbed neurotransmitter synthesis, i.e. reduced cerebral production of dopamine and serotonin in untreated PKU patients as a consequence of cerebral shortage of the precursor amino acids L-tyrosine and L-tryptophan [10]. Potentially reversible abnormalities usually respond well to treatment, but can become irreversible if adequate therapy is delayed. Some brain regions are more often affected (e.g. basal ganglia) in this disease group than others (e.g. cerebellum) [23, 29, 37]. Therefore, the clinical evaluation of a movement disorder should always aim to identify items that do not support the initially suspected diagnosis and may lead to another direction. This is important in order to reduce any delay in initiating specific therapy.

Treatment of Movement Disorders in Inherited Diseases Affecting Amino Acid Metabolism

Since the majority of movement disorders in this disease group reflect irreversible brain damage rather than potentially reversible dysfunction, a major goal of any therapeutic approach should be to initiate therapy in the presymptomatic state in order to prevent irreversible damage [33]. However, this is challenged by the fact that not all of these IEMs are currently included in national newborn screening programs [9] and by the fact that available therapies do not always prevent the manifestation of irreversible symptoms, e.g. the progression of spastic paraparesis in treated individuals with HHH syndrome [41]. Early organ transplantation, in particular liver transplantation, is

a therapeutic option for some, but not all diseases and individuals. While in UCDs liver transplantation rescues the inherited enzyme deficiency, this is incompletely achieved in other diseases such as in MMA owing to systemic deficiency of the MUT enzyme, or even of no benefit in GA-1 owing to the limited efflux capacity of the blood–brain barrier for toxic dicarboxylic metabolites produced in the central nervous system [4–6, 8].

For patients in whom the manifestation of a movement disorder could not be prevented, symptomatic management is often difficult. Symptomatic management often requires long and sometimes frustrating trials of several medications. Most experience exists in the therapy of movement disorders in OAD patients. The following medications (as monotherapy or in combination) are thought to be effective [4, 5]: diazepam or clonazepam (GA-1, MMA), oral or intrathecal baclofen (GA-1, MMA), trihexyiphenidyl (GA-1, MMA), and levodopa/carbidopa (MMA). For focal dystonia, botulinum A injections are used (GA-1). Other drugs have been reported to be ineffective (carbamazepine, vigabatrin, amantadine). Valproate should be avoided since it may impair mitochondrial function and foster secondary carnitine depletion. Deep brain stimulation (globus pallidus internus, nucleus subthalamicus) and pallidotomies have been reported in single OAD patients or small case series with overall unconvincing results. Recent guidelines for UCDs and PKU do not contain recommendations for pharmacotherapy of movement disorders [6, 13]. While intensification of dietary management can improve movement disorders of late diagnosed individuals with PKU, available therapies are unlikely to stop the progression of spastic paraparesis in HHH syndrome and hyperargininemia [13, 41].

Conclusions and Future Research

Movement disorders are a common but variable disease manifestation of intoxication-type IEMs caused by an inherited deficiency of amino acid degradation and ureagenesis. Despite increasing attempts to study the natural history in a structured way, using international patient registries and systematic literature review, the formal description of movement disorders in this disease group is still limited. This is particularly true for disease progression in adults where limited data exist. Since observational studies usually do not contain a multiple rater concept for the evaluation of movement disorders, it is likely that movement disorders are often incorrectly classified. Furthermore, movement disorders are often complex since multiple brain regions are acutely or chronically involved. Molecular mechanisms remain incompletely understood, limiting the development of novel targeted treatment strategies. However, novel concepts such as systemic messenger RNA therapy for MMA are currently under investigation [42]. Available drugs for the treatment of movement disorders, developed for patients with cerebral palsy, parkinsonism, or genetically defined dystonia, are often ineffective for patients with AADs, OADs, and UCDs. Secondary preventive care concepts, such as newborn screening programs in combination with evidence-based therapy, have become a disease-changing intervention for patients with PKU and GA-1. However, it remains to be elucidated whether patients with frequent neonatal metabolic decompensation (e.g. UCDs and MMA) also benefit from newborn screening.

Key Points and Clinical Pearls

- Intoxication-type metabolic diseases should always be considered in any newborn with uneventful pregnancy and delivery that who develops encephalopathy or sepsis-like decompensation after a short symptom-free interval, as well as in any individual with acute manifestations of a complex movement disorder with predominant dystonia/chorea or with progressive spasticity.
- Intoxication-type metabolic diseases often mimic other diseases (e.g. cerebral palsy), and the full clinical picture may only emerge over months or years. Neurological and non-neurological signs and symptoms are often present.
- The concentration of key metabolites in body fluids often correlates with the clinical severity of an affected individual. However, this is not necessarily true for all diseases. For instance, untreated individuals with glutaric aciduria type 1 have the same high risk of striatal lesions, regardless of the residual enzyme activity and concentrations of neurotoxic metabolites in plasma and urine.
- Intoxication-type metabolic diseases are often treatable. Since awareness is limited and only some of them are implemented into newborn screening programs, the correct diagnosis and start of targeted therapies is often delayed.

Directions for Future Research

- International patient registries are required to understand the natural history, clinical variation, and long-term outcome of affected individuals and to align recommendations for diagnosis, therapeutic management, and long-term care.
- Molecular mechanisms are incompletely understood, and well-established disease models are still rare. This hampers the development of novel targeted therapies.
- Long-term safety and efficacy of conservative treatment versus early organ transplantation needs to be carefully studied.
- Newborn screening should be expanded to enable initiation of specific therapies in the presymptomatic stage in patients with treatable diseases.

References

1. Kolker S, Garcia-Cazorla A, Valayannopoulos V, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: The initial presentation. J Inherit Metab Dis. 2015;**38**(6):1041–57.
2. Kolker S, Valayannopoulos V, Burlina AB, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: The evolving clinical phenotype. J Inherit Metab Dis. 2015;**38**(6):1059–74.
3. Kolker S, Sauer SW, Hoffmann GF, et al. Pathogenesis of CNS involvement in disorders of amino and organic acid metabolism. J Inherit Metab Dis. 2008;**31**(2):194–204.
4. Baumgartner MR, Horster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014;**9**:130.
5. Boy N, Muhlhausen C, Maier EM, et al. Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: Second revision. J Inherit Metab Dis. 2017;**40**(1):75–101.
6. Haberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012;**7**:32.
7. van Spronsen FJ, van Wegberg AM, Ahring K, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol. 2017;**5**(9):743–56.
8. Niemi AK, Kim IK, Krueger CE, et al. Treatment of methylmalonic acidemia by liver or combined liver–kidney transplantation. J Pediatr. 2015;**166**(6):1455–61 e1.
9. Lindner M, Gramer G, Haege G, et al. Efficacy and outcome of expanded newborn screening for metabolic diseases: Report of 10 years from south-west Germany. Orphanet J Rare Dis. 2011;**6**:44.
10. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010;**376**(9750):1417–27.
11. Pietz J, Kreis R, Rupp A, et al. Large neutral amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria. J Clin Invest. 1999;**103**(8):1169–78.
12. Burgard P, Schmidt E, Rupp A, Schneider W, Bremer HJ. Intellectual development of the patients of the German collaborative study of children treated for phenylketonuria. Eur J Pediatr. 1996;**155** Suppl 1:S33-8.
13. van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: Diagnosis and treatment. Orphanet J Rare Dis. 2017;**12**:162.
14. Koch R, Hanley W, Levy H, et al. The Maternal Phenylketonuria International Study: 1984–2002. Pediatrics. 2003; **112** (6 Pt 2): 1523–9.
15. Muntau AC, Roschinger W, Habich M, et al. Tetrahydrobiopterin as an alternative treatment for mild phenylketonuria. N Engl J Med. 2002;**347**(26):2122–32.
16. Kolker S, Burgard P, Sauer SW, Okun JG. Current concepts in organic acidurias: Understanding intra- and extracerebral disease manifestation. J Inherit Metab Dis. 2013;**36**(4):635–44.
17. Morath MA, Okun JG, Muller IB, et al. Neurodegeneration and chronic renal failure in methylmalonic aciduria: A pathophysiological approach. J Inherit Metab Dis. 2008;**31**(1):35–43.
18. Schwab MA, Sauer SW, Okun JG, et al. Secondary mitochondrial dysfunction in propionic aciduria: A pathogenic role for endogenous mitochondrial toxins. Biochem J. 2006;**398**(1):107–12.
19. Luciani A, Schumann A, Berquez M, et al. Impaired mitophagy links mitochondrial disease to epithelial stress in methylmalonyl-CoA mutase deficiency. Nat Commun. 2020;**11**(1):970.
20. Chandler RJ, Zerfas PM, Shanske S, et al. Mitochondrial dysfunction in MUT methylmalonic acidemia. FASEB J. 2009;**23**(4):1252–61.
21. de Keyzer Y, Valayannopoulos V, Benoist JF, et al. Multiple OXPHOS deficiency in the liver, kidney, heart, and skeletal muscle of patients with methylmalonic aciduria and propionic aciduria. Pediatr Res. 2009;**66**(1):91–5.

22. Horster F, Baumgartner MR, Viardot C, et al. Long-term outcome in methylmalonic acidurias is influenced by the underlying defect (mut^0, mut^-, cblA, cblB). Pediatr Res. 2007;**62**(2):225–30.
23. Baker EH, Sloan JL, Hauser NS, et al. MRI characteristics of globus pallidus infarcts in isolated methylmalonic acidemia. AJNR Am J Neuroradiol. 2015;**36**(1):194–201.
24. Valayannopoulos V, Baruteau J, Delgado MB, et al. Carglumic acid enhances rapid ammonia detoxification in classical organic acidurias with a favourable risk–benefit profile: A retrospective observational study. Orphanet J Rare Dis. 2016;**11**:32.
25. Sauer SW, Okun JG, Fricker G, et al. Intracerebral accumulation of glutaric and 3-hydroxyglutaric acids secondary to limited flux across the blood–brain barrier constitute a biochemical risk factor for neurodegeneration in glutaryl-CoA dehydrogenase deficiency. J Neurochem. 2006;**97**(3):899–910.
26. Sauer SW, Okun JG, Schwab MA, et al. Bioenergetics in glutaryl-coenzyme A dehydrogenase deficiency: A role for glutaryl-coenzyme A. J Biol Chem. 2005;**280**(23):21830–6.
27. Strauss KA, Donnelly P, Wintermark M. Cerebral haemodynamics in patients with glutaryl-coenzyme A dehydrogenase deficiency. Brain. 2010;**133**(Pt 1):76–92.
28. Tan M, Peng C, Anderson KA, et al. Lysine glutarylation is a protein posttranslational modification regulated by SIRT5. Cell Metab. 2014;**19**(4):605–17.
29. Harting I, Neumaier-Probst E, Seitz A, et al. Dynamic changes of striatal and extrastriatal abnormalities in glutaric aciduria type I. Brain. 2009;**132**(Pt 7):1764–82.
30. Funk CB, Prasad AN, Frosk P et al. Neuropathological, biochemical and molecular findings in a glutaric acidemia type 1 cohort. Brain. 2005;**128**(Pt 4):711–22.
31. Gitiaux C, Roze E, Kinugawa K, et al. Spectrum of movement disorders associated with glutaric aciduria type 1: A study of 16 patients. Mov Disord. 2008;**23**(16):2392–7.
32. Bjugstad KB, Goodman SI, Freed CR. Age at symptom onset predicts severity of motor impairment and clinical outcome of glutaric acidemia type 1. J Pediatr. 2000;**137**(5):681–6.
33. Boy N, Mengler K, Thimm E, et al. Newborn screening: A disease-changing intervention for glutaric aciduria type 1. Ann Neurol. 2018;**83**(5):970–9.
34. Sauer SW, Opp S, Hoffmann GF, et al. Therapeutic modulation of cerebral L-lysine metabolism in a mouse model for glutaric aciduria type I. Brain. 2011;**134**(Pt 1):157–70.
35. Topcu M, Jobard F, Halliez S, et al. L-2-Hydroxyglutaric aciduria: Identification of a mutant gene *C14orf160*, localized on chromosome 14q22.1. Hum Mol Genet. 2004;**13**(22):2803–11.
36. Van Schaftingen E, Rzem R, Marbaix A, et al. Metabolite proofreading, a neglected aspect of intermediary metabolism. J Inherit Metab Dis. 2013;**36**(3):427–34.
37. Steenweg ME, Jakobs C, Errami A, et al. An overview of L-2-hydroxyglutarate dehydrogenase gene (*L2HGDH*) variants: A genotype–phenotype study. Hum Mutat. 2010;**31**(4):380–90.
38. Moroni I, Bugiani M, D'Incerti L, et al. L-2-hydroxyglutaric aciduria and brain malignant tumors: A predisposing condition? Neurology. 2004;**62**(10):1882–4.
39. Patay Z, Mills JC, Lobel U, et al. Cerebral neoplasms in L-2 hydroxyglutaric aciduria: 3 new cases and meta-analysis of literature data. AJNR Am J Neuroradiol. 2012;**33**(5):940–3.
40. Burgard P, Kolker S, Haege G, Lindner M, Hoffmann GF. Neonatal mortality and outcome at the end of the first year of life in early onset urea cycle disorders: Review and meta-analysis of observational studies published over more than 35 years. J Inherit Metab Dis. 2016;**39**(2):219–29.
41. Martinelli D, Diodato D, Ponzi E, et al. The hyperornithinemia–hyperammonemia–homocitrullinuria syndrome. Orphanet J Rare Dis. 2015;**10**:29.
42. An D, Schneller JL, Frassetto A, et al. Systemic messenger RNA therapy as a treatment for methylmalonic acidemia. Cell Rep. 2017;**21**(12):3548–58.

Chapter

13

Disorders of Energy Metabolism: GLUT1 Deficiency Syndrome and Movement Disorders

Roser Pons, Toni S. Pearson, and Darryl C. De Vivo

Introduction

Glucose transporter type 1 (GLUT1) deficiency syndrome (GLUT1 DS) (OMIM 606777) is a disorder of brain energy metabolism caused by insufficient transport of glucose from the blood to the brain. The first patients were reported by De Vivo et al. in 1991 (hence the disorder is also referred to as De Vivo syndrome). The original patients presented with an early infantile-onset developmental encephalopathy associated with seizures, acquired microcephaly, low cerebrospinal fluid (CSF) glucose and lactate concentrations, and a decreased uptake of glucose by isolated erythrocytes in vitro [1]. This clinical presentation represents the most frequent manifestation of the condition (80–90%) and is generally referred to as the "classic phenotype" [2]. Additionally, a small proportion of patients with GLUT1 DS (10–20%) demonstrate milder clinical presentations such as benign epilepsy phenotypes, and non-epileptic phenotypes manifesting with paroxysmal and/or chronic movement disorders. These less common presentations generally are referred to as the "non-classic phenotypes" [2]. Altogether, it is apparent that GLUT1 DS may present with a wide spectrum of clinical phenotypes, each with discrete and overlapping symptoms [2–4]. Additionally, a key clinical feature of GLUT1 DS is the propensity of the neurological manifestations, mainly the motor symptoms, to worsen in the context of fasting (early morning upon awakening and before eating), exercise or environmental stress such as intercurrent illnesses, infections, anxiety, or ketogenic diet noncompliance. Furthermore, long-term follow-up of GLUT1 DS patients has helped to define the natural history and to delineate additional key features such as the presence of characteristic episodes of eye–head movements during infancy, and the evolution of the dominant clinical manifestations (seizures and movement disorders) with age and development [5–9].

Epidemiology

GLUT1 DS shows no obvious sex or racial predilection [9]. The epidemiological data are not congruent at this point. However, there is general agreement that GLUT1 DS is a rare disease. The estimated prevalence is 1 in 90,000 in Australia [10], 1 in 83,000 in Denmark [11], and 1 in 160,000 in Norway [12]. The prevalence estimate in Scotland using more rigorous techniques is 1 in 24,000 [13] suggesting that underreporting is a problem when estimating the prevalence of a rare disease. Based on reports that *SLC2A1* mutations account for several forms of idiopathic epilepsy, and based on the recognition of an expanding GLUT1 DS phenotype spectrum, it has been suggested that there may be approximately 11,000 individuals afflicted with the disorder in the USA [14]. Studies analyzing the frequency of GLUT1 DS in various forms of epilepsy have shown that GLUT1 DS is responsible for 10–12% of absence epilepsy syndromes, 0.7–1% of idiopathic generalized epilepsies, 0–5% of myoclonic astatic epilepsy, 0.6% of pediatric refractory epilepsies, and 2.7% of unselected epilepsies with intellectual disability and/or various movement disorders [11, 12, 15–18].

GLUT1 DS Pathophysiology

GLUT1 DS results from haploinsufficiency due to inactivating mutations in the *SLC2A1* gene and resulting decrease of the gene product, the GLUT1 protein. A wide spectrum of heterozygous mutations have been identified with the majority of cases representing de novo dominant mutations (about 90%). In about 10% of cases, the heterozygous mutations are transmitted as an autosomal-dominant trait, and only exceptionally (less than 1% of cases), as an autosomal-recessive trait [4, 19]. The GLUT1 protein transports glucose across the blood–brain barrier through a mechanism of facilitated diffusion. Consequently, deficiency of GLUT1

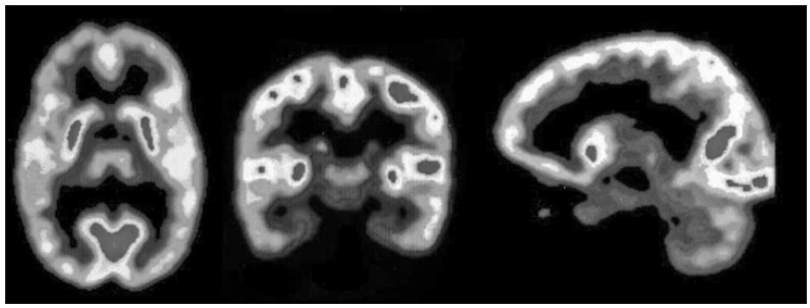

Figure 13.1 Global hypometabolism with regional vulnerability of temporal, thalamic, and cerebellar circuits in a patient with GLUT1 DS.

results in chronically reduced concentrations of glucose in the brain. We introduced the term "neuroglycopenia" to describe this metabolic state. In fact, gene dosage studies, when modeling glucose transport across the blood–brain barrier, predicted a 90% decrease in brain extracellular glucose concentration with a 50% deficiency of the *SLC2A1* gene dosage [20].

Failure to meet the increasing postnatal energy demand of the rapidly growing brain correlates with the onset of seizures in infancy [21], and probably leads to an irreversible cerebral insult and subsequently to other symptoms later in life. While it is thought that the main pathophysiological mechanism of disease in GLUT1 DS is brain energy deficiency due to the reduced availability of glucose, the precise insult to the neuronal circuitry and the effects on the developing brain are still being examined. Studies in a mouse model of GLUT1 DS demonstrated evidence of a defect in the brain microvasculature network [22]. Repletion of the GLUT1 protein in this mouse model during neonatal and early postnatal life normalized angiogenesis and prevented disease, while repletion later in life was devoid of benefit and failed to mitigate major features of the GLUT1 DS phenotype [22]. These experiments support the hypothesis of a critical developmental window when glucose availability is essential for brain growth and network formation, and its deficiency during this critical period leads to permanent brain disturbance.

Further understanding of the physiopathology of GLUT1 DS comes from ^{18}F-fluorodeoxyglucose positron emission tomographic studies in GLUT1 DS patients. These studies have shown a distinctive pattern of regional thalamocortical and cerebellar hypometabolism (Figure 13.1) [23, 24]. These findings support the notion that cerebral networks involving these regions are vulnerable to nutrient deficiency during postnatal development. It has been postulated that disturbed thalamic metabolism may influence epileptogenicity, while the disturbance of the cerebellar networks may lead to the incoordination and clumsiness that are seen, almost invariably, in GLUT1 DS. Additionally, given the role of thalamic nuclei in integrating information from different cortical association areas, it has been postulated that a disproportionate injury to thalamic metabolism correlates with the movement disorders seen in GLUT1 DS [25].

Clinical Presentation

GLUT1 DS is characterized by a spectrum of overlapping clinical phenotypes. The majority of patients present with the classic phenotype, that is a developmental encephalopathy characterized by infantile-onset refractory epilepsy, developmental delay, postnatal deceleration of head growth often leading to acquired microcephaly, variable degrees of cognitive impairment, and a complex motor disorder that includes gait ataxia, spasticity, dystonia, and paroxysmal neurological episodes [2–4, 6, 9, 26]. Within the non-classic phenotypes, clinical presentations are diverse and include: (1) benign idiopathic epilepsy syndromes resembling idiopathic epilepsies such as absence epilepsy, idiopathic generalized epilepsy, or myoclonic epilepsy; (2) neurodevelopmental disorders with highly variable motor and intellectual dysfunction; (3) paroxysmal exercise-induced dyskinesias with or without epilepsy; and (4) minimal phenotype with subtle symptoms. The latter is likely underdiagnosed and is often detected in a parent after the diagnosis of their more severely affected offspring [2, 4, 9, 12]. In such cases, the mildly affected parent may represent a mosaic state.

Given the complex spectrum of GLUT1 DS phenotypes, the overlapping clinical features, and the range of severity, a definite classification of GLUT1 DS according to clinical phenotype is not possible. Hully et al. proposed three clinical groups including: (1) classic, (2) epilepsy-dominant, and (3) movement-dominant [6]. Additionally, a useful way to

analyze the variable clinical spectrum of GLUT1 DS has been proposed by Pearson et al. by dividing the neurological symptoms of GLUT1 DS into three domains: (1) seizures, (2) movement disorders, and (3) cognitive/behavioral disturbances (Figure 13.2). The classic phenotype of GLUT1 DS is associated with symptoms involving all three domains, while the non-classic phenotypes involve only one or two domains, and symptoms may be intermittent rather than persistent [4].

Natural History

Long-term follow-up of patients with GLUT1 DS has clearly shown that the neurological manifestations evolve with age, likely illustrating the evolving regional pattern of cerebral glucose utilization throughout brain development (Figure 13.3) [5]. In the classic phenotype, onset of symptoms occurs within the first months of life in the majority of patients, while in a minority the onset is after the age of 2 years. At

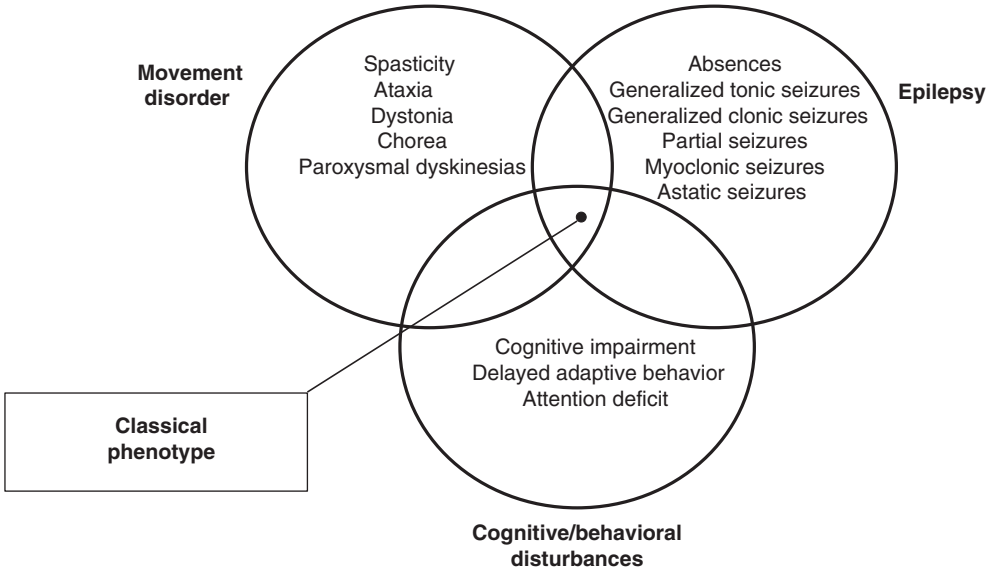

Figure 13.2 Neurological domains affected in GLUT1 DS.

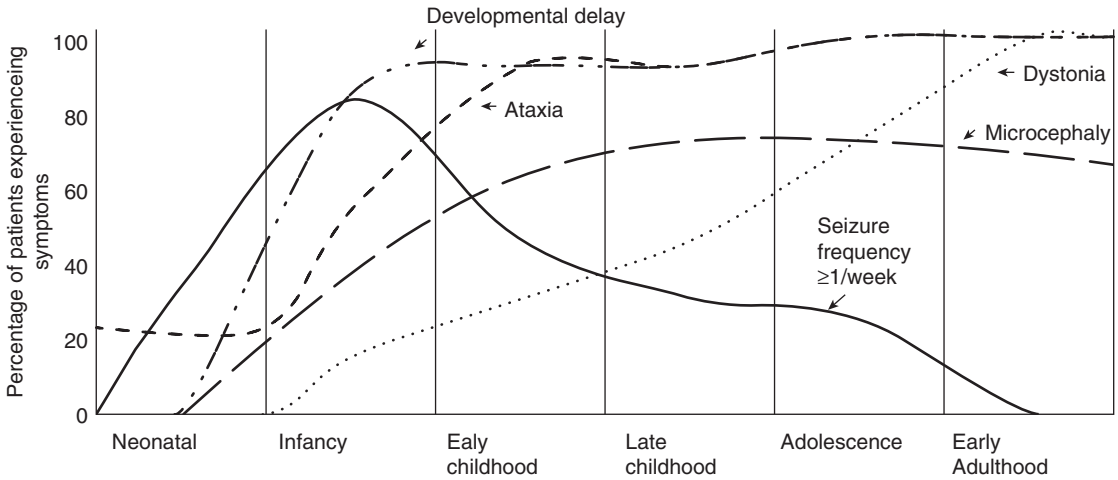

Figure 13.3 GLUT1 DS symptom prevalence by developmental epoch (Alter AS, Engelstad K, Hinton VJ, Montes J, Pearson TS, Akman CI, et al. Long-term clinical course of Glut1 deficiency syndrome. J Child Neurol. 2015;30(2):160–9.)

onset, the main clinical manifestation in two-thirds of patients is epilepsy [7]. The second most common initial clinical event in infants is a specific and characteristic type of episodic eye–head movement abnormality that is reported in more than one-third of patients [7, 8]. Recognition of these episodes may be a clue for the diagnosis (see below). Other symptoms in infancy include behavioral or autonomic changes such as paroxysmal breath-holding or episodes of disturbed alertness. After the age of 1 year, autonomic changes and eye movement abnormalities are much less common, indicating that these manifestations are dependent on the developmental state [7].

Epilepsy in GLUT1 DS reaches its peak in infancy and then wanes during childhood, with seizures becoming less frequent or even disappearing in some patients. Seizure semiology evolves over time; focal seizures are more frequent during infancy, atypical absences and myoclonic seizures start at 24 months, and generalized tonic–clonic seizures typically appear after 3 years of age [6]. Furthermore, developmental delay, ataxia, and microcephaly emerge in infancy or early childhood and remain present thereafter. Dystonia is the only symptom with continually increasing frequency throughout development, emerging by late childhood or adolescence [5]. Paroxysmal neurological events tend to start in early childhood and gradually improve as patients grow older, and in some, the events may disappear [27–31]. Additionally, through a web-based registry available to patients worldwide, it has been noted that 18% of GLUT1 DS patients report obsessive–compulsive traits that appear in childhood and tend to persist thereafter [9].

Diagnosis

Brain imaging in GLUT1 DS either is normal or shows slight brain atrophy, and in one-quarter of cases includes white matter abnormalities, including focal or diffuse supratentorial hyperintensities, prominence of perivascular Virchow–Robin spaces, and delayed myelination [2, 6, 9]. Positron emission tomography scanning is informative and shows a distinctive regional pattern of glucose hypometabolism: global reduction with enhanced regional vulnerability of thalamic, cerebellar, and mesial temporal regions. The basal ganglia often appear to have "increased metabolism" relative to the adjacent thalamic hypometabolism. This is a distinctive pattern consistent with GLUT1 DS (Figure 13.1) [23, 24]. EEG recordings may show generalized spike and wave discharges, diffuse slowing, or focal changes, and often are normal interictally [32, 33].

The distinctive biomarker of the disease is a low CSF glucose concentration (<40 mg/dL or 2.2 mmol/L) in the presence of normoglycemia, with a CSF: blood glucose ratio commonly less than 0.4. CSF glucose values of 41–52 mg/dL may be seen in milder phenotypes [2, 4]. CSF glucose values of less than 60 mg/dL (3.3 mmol/L) should be viewed as probably abnormal, and values less than 40 mg/dL are clearly abnormal. An important caveat is the importance of a simultaneous measurement of CSF lactate. On occasion, low CSF glucose values are seen in patients with mitochondrial diseases but the CSF lactate values distinguish the two "cerebral energy failure" syndromes. The CSF lactate is low normal or abnormally low in GLUT1 DS, and is elevated in mitochondrial diseases.

In our experience, about two-thirds of patients with a clinical presentation consistent with the classic phenotype and low CSF glucose and lactate values have decreased glucose uptake in vitro by isolated fresh erythrocytes [1, 2, 34]. Almost all patients with a decreased erythrocyte glucose uptake will have a disease-causing variant in the *SLC2A1* gene. Conversely, almost all patients with a normal uptake assay will have normal molecular sequencing of the *SLC2A1* gene [34].

The clinical diagnosis is confirmed with the detection of disease-causing variants in the *SLC2A1* gene. However, in approximately 10% of clinically suspected cases, molecular studies fail to detect any mutation [9, 35]. Phenotypic severity is partially explained by the genotype. Patients with missense or splice site mutations tend to have better outcomes than those with deletions or nonsense mutations [2, 3, 6, 34, 36]. The classic phenotype generally occurs de novo, while milder phenotypes are transmitted in an autosomal-dominant or, rarely, an autosomal-recessive manner [19].

Movement Disorders in GLUT1 DS

Motor symptoms are a characteristic feature of both the classic and non-classic phenotypes of GLUT1 DS. These disturbances are seen in the majority of cases, and may be a key clue to the diagnosis [2–6, 9, 13, 25, 26, 30] (Box 13.1). Movement abnormalities in GLUT1 DS are highly variable. The reported frequency of the different motor disorders in GLUT1 DS is variable,

Box 13.1 Movement disorders in Glut1 DS

Persistent movement disorders
- Gait disturbance:
  - Ataxia
  - Spastic ataxia
  - Spastic
  - Dystonic
- Dystonia
- Chorea
- Tremor
- Myoclonus
- Dyspraxia
- Tics
- Stereotypies

Paroxysmal movement disorders
- Paroxysmal events with major motor dysfunction
- Paroxysmal exercise-induced dyskinesias
- Paroxysmal eye–head movements
- Paroxysmal events with complex neurological symptoms
- Other paroxysmal events:
  - Migraines
  - Cyclic vomiting
  - Acute sleep

likely due to ascertainment bias. Patients typically have more than one motor abnormality [2–4, 25, 26, 31, 37]. The most common motor symptom is a spastic–ataxic gait disorder that usually is recognized between late infancy and early childhood, and reflects combined pyramidal-tract and cerebellar dysfunction. Variable extrapyramidal symptoms, such as dystonia and chorea, are also characteristic and emerge later in childhood or adolescence, superimposed on the chronic pyramidal-tract and cerebellar disturbances [4–6]. Additionally, GLUT1 DS patients may suffer from paroxysmal neurological symptoms that are not epileptic in nature [25]. The phenomenology of these paroxysmal events is quite variable and often involves some type of motor disturbance. In some patients, these paroxysmal events may be the only obvious clinical manifestation [38]. Motor disturbances in GLUT1 DS can be divided into two major categories: (1) persistent movement disorders and (2) paroxysmal movement disorders (Box 13.1).

Persistent Movement Disorders

The most frequent persistent movement disorders seen in patients with GLUT1 DS are gait disturbances followed by dystonia, chorea, and tremor. These occur in all GLUT1 DS phenotypes. Severity is variable and ranges from non-specific clumsiness to major motor dysfunction. In general, the severity of the movement disorder correlates with the severity of the overall phenotype. A specific characteristic of GLUT1 DS-associated movement disorders that serves as an important diagnostic clue is their tendency to fluctuate in severity, worsening during fasting, exercise, or with other environmental stressors such as intercurrent illness, infection, fever, anxiety, and ketogenic diet non-compliance. Occasionally, a precipitating trigger cannot be detected [4, 6, 14, 25, 31, 35, 37].

Gait Disturbances

Achievement of independent walking is often delayed in patients with GLUT1 DS patients, and the most severely affected patients may never achieve the ability to walk [4, 6, 12, 30, 31, 37, 39, 40]. The most typical gait disturbance in GLUT1 DS is ataxia [3, 6, 9, 25, 26, 31]. Often, patients have coexisting spasticity and a resulting spastic–ataxic gait that is characterized by unsteadiness, leg stiffness, shortened stride length and decreased heel strike, together with a wide base (in contrast to the "scissoring" gait of spastic diplegia in cerebral palsy) [25, 41]. Some patients have dystonic posturing of the upper limbs when walking, while others have overflow chorea [25]. Other less common gait disorders seen in severe GLUT1 DS phenotypes include a pure spastic gait and a primarily dystonic gait [3, 25, 42]. Intermittent worsening of gait during exercise or fasting is characteristic. Some authors have described an inability to stand late in the day due to ataxia which is relieved by food intake [4, 25]. This fluctuating gait disturbance is reminiscent of other genetic disorders like Segawa disease and suggests the possibility of a common disease mechanism such as synaptic dysfunction. GLUT1 DS is not considered a neurodegenerative disorder, but progression of spasticity, and less often of ataxia, during puberty or adolescence may occur. This worsening may be transient. Some patients may become wheelchair-dependent [5, 6, 30, 43].

Dystonia

Dystonia is the second most frequent chronic movement disorder in GLUT1 DS. Dystonia is reported to

occur in 20–86% of patients with the classic phenotype and in 13% with the non-classic phenotypes. This large variability in the reported frequency of dystonia in GLUT1 DS may reflect under-recognition of subtle dystonic posturing in the milder phenotypes [3, 6, 9, 16, 25, 31, 44]. The severity of dystonia in GLUT1 DS is variable and mainly presents as postural or action dystonia involving the limbs distally, more often the upper extremities. Task-specific dystonia and dystonic tremor have been reported in some patients [6, 29, 37–39, 42, 43, 45].

Chorea

Chorea is reported in 3–75% in different series, again likely reflecting ascertainment bias [3, 6, 25, 46]. Chorea is often mild and involves the face and the upper limbs distally. In a smaller number of patients, chorea may be prominent [6, 26, 37, 40, 42].

Tremor

Tremor is reported in upwards of 70% of GLUT1 DS patients with the classic phenotype [25]. It is characterized as a terminal action tremor and is associated with ataxia, dysarthria, dyssynergia, truncal incoordination, and ocular dyspraxia, reflecting the prominence of cerebellar dysfunction in this disorder [25, 36, 40]. Other types of tremor including postural and dystonic tremor have also been reported in some patients. Features of parkinsonism have been described infrequently in GLUT1 DS; but resting tremor, as part of a parkinsonian syndrome, has not been reported [18, 27, 42, 45].

Myoclonus

Myoclonus in GLUT1 DS is generally of epileptic origin. However, non-epileptic myoclonus also has been reported in individual patients, including startle, action, and postural myoclonus [15, 25, 26].

Dyspraxia

Dyspraxia, characterized by motor planning difficulties affecting specific motor tasks is often seen in GLUT1 DS patients. Ocular and oro-buccal dyspraxia have been reported in up to 20% of patients with the classic phenotype [25]. Poor eye–hand coordination, poor fine motor skills, and clumsiness are often reported in these patients [6, 12, 46].

Stereotypies and Tics

Stereotypies and tics have both been noted in some patients with GLUT1 DS [25], but are not considered to be disease-specific features, given the high prevalence of these benign movement disorders in the general population.

Paroxysmal Movement Disorders

Paroxysmal non-epileptic intermittent neurological symptoms, often with prominent motor manifestations, occur throughout the whole phenotypic spectrum in GLUT1 DS. In the literature, these events may also be referred to as intermittent or episodic. The frequency of paroxysmal events in GLUT1 DS ranges from 30% to 59% of cases [3, 25, 26, 31]. Although paroxysmal events occur throughout the severity spectrum, it is generally accepted that these signs constitute the main clinical signature of the milder GLUT1 DS forms [28, 38].

Insufficient energy supply to meet demand, possibly leading to synaptic dysfunction, is a proposed mechanism underlying paroxysmal events in GLUT1 DS. Consistent with this hypothesis, precipitating factors of paroxysmal events in GLUT1 DS include conditions with increased energy demand, such as the post-absorptive state (upon awakening, or before meals), fasting, exercise, and vigorous physical activity. Other frequent factors are emotional stress, fever, fatigue, or poor ketogenic diet compliance. Sleep deprivation, temperature changes, and drug-associated factors (e.g. phenobarbital, clonazepam, theophylline) have also been reported. Occasionally, no precipitants are recognized. The most frequent mitigating factors are eating, carbohydrate intake, and resting [3, 6, 9, 15, 25, 26, 28, 29, 31, 38, 42].

The clinical manifestations of GLUT1 DS-associated paroxysmal events are very variable. However, they tend to be stereotyped in each patient. Nosologically, they do not appear to be epileptic in nature. Some patients may experience prominent dysphoria and emotional lability during the events, while others experience confusion or somnolence. The possibility that these episodes may represent a type of focal seizure that is not detectable by scalp EEG has been considered, but factors that argue against this possibility include preserved alertness, the absence of other typical clinical manifestations of seizures, and a normal ictal EEG [25]. Non-motor paroxysmal events may also occur. Examples include migraine headaches, episodes of behavioral and emotional disturbances, cyclical vomiting, or acute sleep episodes [9, 12, 25, 26, 30, 31].

Episodes may start gradually or explosively. When gradual, the episodes present with prominent worsening of the baseline neurological status. In general, patients with the classic phenotype tend to manifest multiple types of paroxysmal events, whereas in non-classic phenotypes patients tend to manifest 1 or 2 types. The duration of episodes ranges from minutes to hours and occasionally days, with the more explosive events being shorter in duration. The frequency ranges from daily, to weekly, to monthly or every few months [6, 9, 25–28, 31, 38, 39, 42, 43, 46, 47].

In the classic phenotype, paroxysmal movement disorders tend to develop later in childhood or during adolescence, as the seizures become less prominent or disappear. In the non-classic phenotypes episodes tend to start in the early or late childhood ages. In general, patients exhibit gradual improvement as they get older, and in some cases, the events may disappear entirely, regardless of whether the patient adheres to the ketogenic diet [5, 6, 9, 26–31, 38, 39, 42, 45]. Paroxysmal events in GLUT1 DS may be categorized in five main types based on their clinical presentation: (1) paroxysmal events with major motor dysfunction; (2) paroxysmal exercised-induced dyskinesia (PED); (3) paroxysmal eye–head movements; (4) paroxysmal events with complex neurological symptoms, and (5) other paroxysmal events

Paroxysmal Events with Major Motor Dysfunction

This group of paroxysmal events includes intermittent episodes of weakness, episodes of ataxia, and episodes of non-kinesigenic dyskinesias. Intermittent episodes of weakness, manifesting as paraparesis, tetraparesis, hemiparesis, or monoparesis, are reported in 29–50% of GLUT1 DS patients [6, 9, 26, 46, 48]. Sudden total body paralysis mimicking periodic paralysis can also occur [15, 25, 31, 38]. The underlying pathophysiology for these episodes of transient neurological symptoms is not certain. Imaging abnormalities are consistent with focal cerebral hypoperfusion [48]. Two mechanisms for this phenomenon have been proposed: hypometabolism related to insufficient glucose supply in the central nervous system, and cerebral blood vessel dysfunction and susceptibility to transient vasospasm. The latter is supported by the known abundance of GLUT1 transporters in cerebral endothelial cells, the developmental impairment of cerebral angiogenesis, and the resulting diminution of brain microvasculature in a mouse model of *SLC1A2* haploinsufficiency [22].

Occasionally the pattern of hemiplegic episodes and accompanying clinical features in patients with GLUT1 DS can mimic the syndrome of alternating hemiplegia of childhood [9, 49, 50]. However, in contrast to classic alternating hemiplegia of childhood, the age of presentation of the atypical GLUT1 DS-associated attacks is generally older, there is no associated prominent autonomic or bulbar dysfunction during the attacks, and the episodes are often precipitated by fasting or exercise and mitigated by food, especially carbohydrates. Paroxysmal non-kinesigenic dyskinesia episodes in GLUT1 DS manifest either with chorea or dystonia often involving the limbs, and at times the axial or the orofacial musculature [12, 25, 26, 30, 31]. Paroxysmal episodes of ataxia can also occur, and in some, the episodes may be reminiscent of episodic ataxia [2, 3, 15, 27, 51].

Paroxysmal Exercise-Induced Dyskinesias

This group of paroxysmal events also manifests with major motor dysfunction. The main trigger is exercise. These episodes are described separately from the previous group of paroxysmal events because PED constitutes the main clinical manifestation in a number of patients with GLUT1 DS [4, 38]. In fact, PED is considered the most characteristic movement disorder type in GLUT1 DS [26], and for this reason this phenotype is presented in more detail in this section.

PED due to mutations in *SLC2A1* is designated as DYT18 in the catalogue of genetic dystonia syndromes. It can occur with or without associated epilepsy. Patients often have normal interictal neurological examinations, but mild movement disorders and/or learning disabilities can also occur. Some patients may also have other types of paroxysmal events such as migraines [12, 15, 16, 27, 29, 38, 42, 43, 45]. PED generally starts during childhood, but it can also start later in adolescence or early adulthood. The paroxysms are characterized by involuntary movements typically precipitated by prolonged exertion. Patients usually have choreoathetosis or dystonia. Less often, ballismus may occur, alone or in combination. Patients may experience premonitory sensations such as tingling and impending weakness. The involuntary movements can be bilateral or unilateral. The lower limbs are most commonly affected, but the arms, face, and trunk may also be involved. When severe, the involuntary movements may make walking impossible. These episodes are sometimes

misinterpreted as epileptic events, and in mild cases may be dismissed as non-specific symptoms. Some patients experience associated autonomic features including sweating, pallor, hypoventilation, rising epigastric sensation, or anxiety [15, 27, 29, 30, 38, 39, 42, 43, 45].

Sustained walking (10–30 minutes) or running are the most common precipitating factors, although other factors such as stress, fasting, and sleep deprivation can precipitate the events. Occasionally, episodes may occur with mild motor activity. The duration of the events ranges from a few minutes to 3 hours, although episodes typically resolve within 30 minutes. Frequency is variable from several times a week to yearly. The events tend to improve with age, although in some cases can worsen during adolescence or adulthood. Prolonged writing can precipitate upper limb dystonia [5, 15, 27, 29, 30, 38, 39, 43, 45].

Patients with PED associated with progressive spastic paraparesis due to *SCL2A1* mutations have been reported and were previously designated as DYT9 in the catalogue of genetic dystonia syndromes [29].

Paroxysmal Eye–Head Movements

Abnormal eye movements in GLUT1 DS are reported with a frequency of 23–75% of cases [6, 7, 9]. The description of these movements is highly variable and includes reports of intermittent involuntary gaze movements, paroxysmal rotatory or disorganized eye movements, and even opsoclonus [6, 7, 9, 52]. Recently a retrospective review of a large series of patients with GLUT1 DS helped characterize these episodes, which have subsequently been considered to be a disease-specific feature of GLUT1 DS in early infancy [8]. The eye movement episodes consist of repeated multidirectional saccades occurring at a frequency of one to two per second. The eye movements are often accompanied by head movements in the same direction, creating the impression that the infant is trying to visually follow a darting object. Video analysis indicated that the events were most consistent with saccadic eye–head gaze shifts, which are characterized by the presence of inter-saccadic intervals, aligned direction of the eye and head movement, and the optional presence of the head component. The pathophysiological mechanism underlying paroxysmal eye–head gaze saccades in GLUT1 DS is unknown. It is presumed that the movements are triggered by abnormal neuronal activity in the immature oculomotor circuit for gaze control, as a result of glucose deficiency. Consistent with this hypothesis, these episodes are precipitated by fatigue, excitement, or fasting, and respond favorably to the ketogenic diet in some patients. As has been described with other features in GLUT1 DS, these episodes evolve over time. They almost always emerge before age 6 months, decrease in frequency by late infancy, and tend to disappear in childhood. Thus, these episodes represent an age-dependent manifestation of the disease that is likely related to a specific stage of brain development [8].

Paroxysmal Events with Complex Neurological Symptoms

These episodes are characterized by multiple symptoms occurring during a spell, which appear simultaneously or sequentially. These events often occur in patients with the classic phenotype, and tend to start more gradually and last longer than paroxysmal dyskinesia episodes. They are characterized by the variable association of some type of gait disturbance (often ataxia), weakness (hemiparesis, quadriparesis, or sudden paralysis), and parkinsonian features or involuntary movements (chorea, dystonia, myoclonus). Autonomic features such as vomiting or pallor, and prominent dysphoria with variable combinations of irritability, inconsolable crying, or even screaming may also occur [25, 46].

Some examples of complex paroxysmal episodes described in the literature include: episodes of irregular myoclonic jerks involving head and shoulder associated with dystonia of the upper limbs and inability to walk [39]; episodes of ataxia associated with dystonia [42]; episodes of headaches, screaming, ataxia, and uncontrollable behavior [42]; episodes of slow psychomotor ability associated with dysarthria, ataxia, and orolingual dyskinesias [40]; episodes of unsteady gait, hemiparesis, fatigue, and vomiting [28]; episodes of acute cerebellar ataxia, vomiting, and abnormal eye movements [53]; episodes of sweating and yawning, combined with generalized weakness and impaired consciousness [30]; episodes of dysarthria associated with PED [30]; episodes with overlapping features of alternating hemiplegia of childhood and hemiplegic migraine [50]; and variable combinations of migraine, autonomic symptoms, confusion, dysphoria, intermittent ataxia, and mono-/hemi-/quadriplegia [46].

Other Paroxysmal Events

GLUT1 DS patients may experience headaches that often are indistinguishable from migraine, and can occur with or without aura. They are reported in 6–23 % of GLUT1 DS patients [26, 31]. Sometimes headaches can be complicated, either with hemiparesis, dysphasia, aphasia, somnolence, or confusion. The severity is variable and, at times, headaches can become the major burden of the disease. The causal relationship of headaches with GLUT1 DS is supported by their resolution after the patient is treated with a ketogenic diet [25, 27, 31, 45, 51, 54].

Cyclical vomiting also has been recognized as another type of paroxysmal event in GLUT1 DS. In the series from Japan, it occurred in up to 45% of patients [31].

Paroxysmal episodes of behavioral disturbance can occur in some patients with irritability, aggressive outbursts, somnolence, lethargy, or confusion [15, 18, 25, 28, 37]. More often, these behavioral disturbances occur in association with other types of paroxysms, as mentioned before.

Some adult patients may develop other paroxysmal events, such as paroxysms of action myoclonus, or paroxysmal painful cramps in the legs, occurring during the night [30]. Finally, sudden sleep episodes have also been reported, and again the causal relationship of these episodes with GLUT1 DS is supported by their resolution after the patient is treated with a ketogenic diet [12].

Treatment

The ketogenic diet is the mainstay of treatment in GLUT1 DS. This diet is composed of a high-fat, carbohydrate-restricted diet and provides ketone bodies as an alternative brain fuel. Ketone bodies support normal brain function and growth, which is particularly vital in the first decade of life. Early introduction of the diet is the most effective intervention, leading to the control of seizures in the majority of patients. The beneficial effect on cognitive and motor function, however, is less clear [3–6, 9, 30, 44, 55, 56]. Despite this, we believe that early diagnosis and treatment of GLUT1 DS with a ketogenic diet is neuroprotective and improves outcome by mitigating neurological signs and symptoms. This belief is supported by a retrospective study demonstrating that timing of ketogenic diet introduction has a predictive value for cognitive outcome [57]; and by an observational study showing that an advanced age at initiation of ketogenic diet therapy is a risk factor for ineffectiveness of the diet [58].

In some cases, the ketogenic diet cannot be implemented because of difficulty with compliance or because of concerns about the dietary restrictions. The use of a regular diet with frequent meals and carbohydrate-containing snacks can be effective in patients with milder phenotypes [18, 30]. Compliance remains a challenge when starting a ketogenic diet even though the dietary alternatives represent inferior substitutes. Brain extraction of ketone bodies is influenced by the degree of ketonemia because the transport of ketone bodies across the blood–brain barrier, like glucose, represents facilitated diffusion. Diffusion across membranes is determined by the concentration gradient. Adaptations in the form of a modified Atkins diet, a medium chain triglycerides–ketogenic diet, and a low glycemic index diet have been used in GLUT1 DS but the blood levels of ketone bodies are lower than the levels achieved by the classic ketogenic diet. As a result, the concentration gradient across the blood–brain barrier is less. In practice, there appears to be no major difference in efficacy [56]. However, the long-term outcome is determined by many factors, including the phenotypic severity, the nature of the pathogenic mutation, the age when first treated, the degree and continuity of ketonemia, dietary compliance, etc. Not controlling for these variables will obscure the outcome of a clinical trial and fail to show superiority of one dietary regimen compared to another. As a result, choosing a more palatable diet may be falsely reassuring and result in the selection of a less effective treatment regimen.

The effectiveness of the ketogenic diet on gait disturbances and chronic movement disorders is generally not as striking as it is on seizures. Beneficial effects are variable and range from mild to significant. Patients with favorable responses report improvements in gait stability, motor skills, and energy levels. Standardized testing demonstrates improvements in visuomotor skills and motor development [4, 6, 28, 30, 31, 37, 40, 44, 55, 56]. The effect of the ketogenic diet on the fluctuation of motor symptoms and on the paroxysmal disorders is generally remarkable, leading to a dramatic reduction in frequency and intensity, and even complete disappearance in many patients.

Patients with PED are able to walk and even run long distances after treatment. The response to the ketogenic diet may be immediate when reaching ketosis, or it may take days to weeks. Suboptimal compliance with the ketogenic diet and loss of ketosis leads to a recurrence of symptoms [15, 18, 26, 31, 37, 45, 46].

Acetazolamide has been used for the treatment of paroxysmal ataxia and dyskinesia with benefits in several patients with Glut1 DS [59]. Acetazolamide inhibits carbonic anhydrase but its exact mechanism of action is unknown. It has been postulated that it reduces neuronal excitability through the lowering of intracellular pH. Another postulated mechanism of action is membrane stabilization through a direct action on ion channels.

Triheptanoin (C7 oil) is a naturally occurring fat that is readily synthesized from castor bean oil. It is an odd-chain triglyceride with anapleurotic properties. C7 oil is metabolized to acetyl-coenzyme A (CoA) and propionyl-CoA, and the latter ultimately is metabolized to oxaloacetate. Acetyl-CoA and oxaloacetate condense to form citric acid and replenish the pool of metabolic intermediaries in the Krebs cycle. Triheptanoin has been tested in an open-label trial in patients with GLUT1 DS who were not on a ketogenic diet [60]. Significant improvements in seizure control and vocabulary performance were demonstrated after 3 months of treatment. The C7 oil was safe, metabolically neutral, and well tolerated except for gastrointestinal discomfort in some patients [60]. Triheptanoin has also been studied for the management of non-epileptic paroxysmal manifestations in patients with GLUT1 DS [47]. An open-label pilot study in patients with GLUT1 DS who were not on a ketogenic diet reported significant improvement in the frequency and duration of the non-epileptic paroxysmal events and normalization of the functional MRI bioenergetic profile during brain activation [47]. Extension of this study confirmed the dramatic (97%) and sustained reduction of motor and non-motor paroxysmal events over 3 years. Furthermore, the magnitude and duration of the favorable response supported the therapeutic benefit of triheptanoin [61]. Further studies utilizing randomized, double-blinded, placebo-controlled trials will be necessary to clarify the effect of the C7 oil on the different manifestations of GLUT1 DS.

Experimental studies in GLUT1 DS model mice also show promise for molecular therapies based on gene transfer. Administration of AAV9-based vectors expressing the *SLC2A1* gene leads to repletion of the GLUT1 protein, prevention or mitigation of the clinical phenotype, and improvement of the CSF glucose levels [22, 62]. These results are encouraging and, after choosing the timing, the best injection route, and the optimal dosing, gene therapy could be a promising approach for the treatment of GLUT1 DS patients [22, 62]. Newborn screening for GLUT1 DS would facilitate the treatment of patients in the pre-symptomatic phase, when the developing brain is remarkably vulnerable to neurodevelopmental disorders like GLUT1 DS.

Antiepileptic drug treatment of seizures has been the conventional approach historically, and phenobarbital has been the specific drug of choice in the newborn–infantile period. This traditional approach is problematic as we have learned more about GLUT1 DS as a cause of epilepsy in this vulnerable age group. Biomarkers such as hypoglycorrhachia should be investigated as soon as possible, and the genetic basis for the epileptic condition determined quickly, to select the appropriate treatment. The ketogenic diet clearly is the correct treatment for GLUT1 DS. Phenobarbital, in this case, can worsen the disease process by inhibiting the residual activity of the GLUT1 transporter [55]. Other medications also can produce side effects that are counterproductive in the long-term management of these patients.

In summary, GLUT1 DS is a complex disorder and the pathophysiological mechanisms are still far from completely understood. Clearly, the energy demands of the developing brain increase dramatically after birth, and remain elevated for most of the first postnatal decade [21]. GLUT1 deficiency causes cerebral energy failure during this period, and likely interferes with the structural development and subsequent functioning of the maturing brain [22]. Acquired microcephaly and diminished brain microvasculature are two clear consequences of energy failure and emphasize the need for early diagnosis and treatment. Movement disorders are a major symptom domain with varied and complex symptomatology influenced by the status of brain development. It is important to recognize the clinical signatures of GLUT1 DS, as they may be the key diagnostic clues for this treatable disorder. Early diagnosis, most importantly, leads to the avoidance of unnecessary medications, immediate initiation of a ketogenic diet, and a better long-term outcome. Gene therapy remains a realistic hope for permanent treatment in the future.

Key Points and Clinical Pearls

- Movement disorders are a characteristic feature of glucose transporter type 1 (GLUT1) deficiency syndrome (GLUT1 DS).
- Most patients experience a combination of persistent and paroxysmal motor symptoms that typically evolve with age and brain development.
- The severity of motor symptoms ranges widely, from minimal to severe.
- A key feature of many movement disorders in GLUT1 DS is their propensity to worsen in the context of fasting, exercise, ketogenic diet non-compliance, or intercurrent illnesses.

Directions for Future Research

- Further studies on the development of animal models of GLUT1 DS, to understand the impact of chronic hypoglycorrhachia on postnatal brain development and circuit maturation.
- The development of more effective, durable, disease-modifying treatments.
- Gene therapy as a permanent treatment.

References

1. De Vivo DC, Trifiletti RR, Jacobson RI, et al. Defective glucose transport across the blood–brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N Engl J Med. 1991;**325**(10):703–9.
2. Wang D, Pascual JM, Yang H, et al. Glut-1 deficiency syndrome: Clinical, genetic, and therapeutic aspects. Ann Neurol. 2005;**57**(1):111–8.
3. Leen WG, Klepper J, Verbeek MM, et al. Glucose transporter-1 deficiency syndrome: The expanding clinical and genetic spectrum of a treatable disorder. Brain. 2010;**133**(Pt 3):655–70.
4. Pearson TS, Akman C, Hinton VJ, Engelstad K, De Vivo DC. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep. 2013;**13**(4):342.
5. Alter AS, Engelstad K, Hinton VJ, et al. Long-term clinical course of Glut1 deficiency syndrome. J Child Neurol. 2015;**30**(2):160–9.
6. Hully M, Vuillaumier-Barrot S, Le Bizec C, et al. From splitting GLUT1 deficiency syndromes to overlapping phenotypes. Eur J Med Genet. 2015;**58**(9):443–54.
7. Akman CI, Yu J, Alter A, Engelstad K, De Vivo DC. Diagnosing glucose transporter 1 deficiency at initial presentation facilitates early treatment. J Pediatr. 2016;**171**:220–6.
8. Pearson TS, Pons R, Engelstad K, et al. Paroxysmal eye-head movements in Glut1 deficiency syndrome. Neurology. 2017;**88**(17):1666–73.
9. Hao J, Kelly DI, Su J, Pascual JM. Clinical aspects of glucose transporter type 1 deficiency: Information from a global registry. JAMA Neurol. 2017;**74**(6):727–32.
10. Coman DJ, Sinclair KG, Burke CJ, et al. Seizures, ataxia, developmental delay and the general paediatrician: Glucose transporter 1 deficiency syndrome. J Paediatr Child Health. 2006;**42**(5):263–7.
11. Larsen J, Johannesen KM, Ek J, et al. The role of *SLC2A1* mutations in myoclonic astatic epilepsy and absence epilepsy, and the estimated frequency of GLUT1 deficiency syndrome. Epilepsia. 2015;**56**(12):e203-8.
12. Ramm-Pettersen A, Nakken KO, Haavardsholm KC, Selmer KK. GLUT1-deficiency syndrome: Report of a four-generation Norwegian family with a mild phenotype. Epilepsy Behav. 2017;**70**(Pt A):1–4.
13. Symonds JD, Zuberi SM, Stewart K, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: A prospective population-based national cohort. Brain. 2019;**142**:2303–18.
14. Brockmann K. The expanding phenotype of GLUT1-deficiency syndrome. Brain Dev. 2009;**31**(7):545–52.
15. Suls A, Dedeken P, Goffin K, et al. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in *SLC2A1*, encoding the glucose transporter GLUT1. Brain. 2008;**131**(Pt 7):1831–44.
16. Arsov T, Mullen SA, Rogers S, et al. Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. Ann Neurol. 2012;**72**(5):807–15.
17. Ivanova N, Peycheva V, Kamenarova K, et al. Three novel *SLC2A1* mutations in Bulgarian patients with different forms of genetic generalized epilepsy reflecting the clinical and genetic diversity of GLUT1-deficiency syndrome. Seizure. 2018;**54**:41–4.
18. Liu Y, Bao X, Wang D, et al. Allelic variations of Glut-1 deficiency syndrome: The Chinese experience. Pediatr Neurol. 2012;**47**(1):30–4.
19. Rotstein M, Engelstad K, Yang H, et al. Glut1 deficiency: Inheritance pattern determined by haploinsufficiency. Ann Neurol. 2010;**68**(6):955–8.
20. Barros LF, Bittner CX, Loaiza A, Porras OH. A quantitative overview of glucose dynamics in the gliovascular unit. Glia. 2007;**55**(12):1222–37.

21. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann Neurol. 1987;**22**(4):487–97.
22. Tang M, Gao G, Rueda CB, et al. Brain microvasculature defects and Glut1 deficiency syndrome averted by early repletion of the glucose transporter-1 protein. Nat Commun. 2017;**8**:14152.
23. Pascual JM, Van Heertum RL, Wang D, Engelstad K, De Vivo DC. Imaging the metabolic footprint of Glut1 deficiency on the brain. Ann Neurol. 2002;**52**(4):458–64.
24. Akman CI, Provenzano F, Wang D, et al. Topography of brain glucose hypometabolism and epileptic network in glucose transporter 1 deficiency. Epilepsy Res. 2015;**110**:206–15.
25. Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in Glut-1 deficiency. Mov Disord. 2010;**25**(3):275–81.
26. De Giorgis V, Teutonico F, Cereda C, et al. Sporadic and familial Glut1 DS Italian patients: A wide clinical variability. Seizure. 2015;**24**:28–32.
27. Schneider SA, Paisan-Ruiz C, Garcia-Gorostiaga I, et al. GLUT1 gene mutations cause sporadic paroxysmal exercise-induced dyskinesias. Mov Disord. 2009;**24**(11):1684–8.
28. Koy A, Assmann B, Klepper J, Mayatepek E. Glucose transporter type 1 deficiency syndrome with carbohydrate-responsive symptoms but without epilepsy. Dev Med Child Neurol. 2011;**53**(12):1154–6.
29. Weber YG, Kamm C, Suls A, et al. Paroxysmal choreoathetosis/spasticity (DYT9) is caused by a GLUT1 defect. Neurology. 2011;**77**(10):959–64.
30. Leen WG, Taher M, Verbeek MM, et al. GLUT1 deficiency syndrome into adulthood: A follow-up study. J Neurol. 2014;**261**(3):589–99.
31. Ito Y, Takahashi S, Kagitani-Shimono K, et al. Nationwide survey of glucose transporter-1 deficiency syndrome (GLUT-1DS) in Japan. Brain Dev. 2015;**37**(8):780–9.
32. Leary LD, Wang D, Nordli DR, Jr., Engelstad K, De Vivo DC. Seizure characterization and electroencephalographic features in Glut-1 deficiency syndrome. Epilepsia. 2003;**44**(5):701–7.
33. Pong AW, Geary BR, Engelstad KM, et al. Glucose transporter type I deficiency syndrome: Epilepsy phenotypes and outcomes. Epilepsia. 2012;**53**(9):1503–10.
34. Yang H, Wang D, Engelstad K, et al. Glut1 deficiency syndrome and erythrocyte glucose uptake assay. Ann Neurol. 2011;**70**(6):996–1005.
35. Willemsen MA, Vissers LE, Verbeek MM, et al. Upstream *SLC2A1* translation initiation causes GLUT1 deficiency syndrome. Eur J Hum Genet. 2017;**25**(6):771–4.
36. Levy B, Wang D, Ullner PM, et al. Uncovering microdeletions in patients with severe Glut-1 deficiency syndrome using SNP oligonucleotide microarray analysis. Mol Genet Metab. 2010;**100**(2):129–35.
37. Friedman JR, Thiele EA, Wang D, et al. Atypical GLUT1 deficiency with prominent movement disorder responsive to ketogenic diet. Mov Disord. 2006;**21**(2):241–5.
38. Weber YG, Storch A, Wuttke TV, et al. GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak. J Clin Invest. 2008;**118**(6):2157–68.
39. Zorzi G, Castellotti B, Zibordi F, Gellera C, Nardocci N. Paroxysmal movement disorders in GLUT1 deficiency syndrome. Neurology. 2008;**71**(2):146–8.
40. Perez-Duenas B, Prior C, Ma Q, et al. Childhood chorea with cerebral hypotrophy: A treatable GLUT1 energy failure syndrome. Arch Neurol. 2009;**66**(11):1410–4.
41. Blumenschine M, Montes J, Rao AK, Engelstad K, De Vivo DC. Analysis of gait disturbance in Glut 1 deficiency syndrome. J Child Neurol. 2016;**31**(13):1483–8.
42. Anand G, Padeniya A, Hanrahan D, et al. Milder phenotypes of glucose transporter type 1 deficiency syndrome. Dev Med Child Neurol. 2011;**53**(7):664–8.
43. Roubergue A, Apartis E, Mesnage V, et al. Dystonic tremor caused by mutation of the glucose transporter gene GLUT1. J Inherit Metab Dis. 2011;**34**(2):483–8.
44. Gumus H, Bayram AK, Kardas F, et al. The effects of ketogenic diet on seizures, cognitive functions, and other neurological disorders in classical phenotype of glucose transporter 1 deficiency syndrome. Neuropediatrics. 2015;**46**(5):313–20.
45. Urbizu A, Cuenca-Leon E, Raspall-Chaure M, et al. Paroxysmal exercise-induced dyskinesia, writer's cramp, migraine with aura and absence epilepsy in twin brothers with a novel *SLC2A1* missense mutation. J Neurol Sci. 2010;**295**(1–2):110–3.
46. Pellegrin S, Cantalupo G, Opri R, Dalla Bernardina B, Darra F. EEG findings during "paroxysmal hemiplegia" in a patient with GLUT1-deficiency. Eur J Paediatr Neurol. 2017;**21**(3):580–2.
47. Mochel F, Hainque E, Gras D, et al. Triheptanoin dramatically reduces paroxysmal motor disorder in patients with GLUT1 deficiency. J Neurol Neurosurg Psychiatry. 2016;**87**(5):550–3.

48. Almuqbil M, Rivkin MJ, Takeoka M, Yang E, Rodan LH. Transient regional cerebral hypoperfusion during a paroxysmal hemiplegic event in GLUT1 deficiency syndrome. Eur J Paediatr Neurol. 2018;**22**(3):544–7.

49. Rotstein M, Doran J, Yang H, et al. Glut1 deficiency and alternating hemiplegia of childhood. Neurology. 2009;**73**(23):2042–4.

50. Weller CM, Leen WG, Neville BG, et al. A novel *SLC2A1* mutation linking hemiplegic migraine with alternating hemiplegia of childhood. Cephalalgia. 2015;**35**(1):10–5.

51. Mohammad SS, Coman D, Calvert S. Glucose transporter 1 deficiency syndrome and hemiplegic migraines as a dominant presenting clinical feature. J Paediatr Child Health. 2014;**50**(12):1025–6.

52. Appavu B, Mangum T, Obeid M. Glucose transporter 1 deficiency: A treatable cause of opsoclonus and epileptic myoclonus. Pediatr Neurol. 2015;**53**(4):364–6.

53. Ohshiro-Sasaki A, Shimbo H, Takano K, Wada T, Osaka H. A three-year-old boy with glucose transporter type 1 deficiency syndrome presenting with episodic ataxia. Pediatr Neurol. 2014;**50**(1):99–100.

54. Posar A, Santucci M. Unusual phenotype of glucose transport protein type 1 deficiency syndrome: A case report and literature review. J Pediatr Neurosci. 2014;**9**(1):36–8.

55. Klepper J, Scheffer H, Leiendecker B, et al. Seizure control and acceptance of the ketogenic diet in GLUT1 deficiency syndrome: A 2- to 5-year follow-up of 15 children enrolled prospectively. Neuropediatrics. 2005;**36**(5):302–8.

56. Oguni H, Ito Y, Otani Y, Nagata S. Questionnaire survey on the current status of ketogenic diet therapy in patients with glucose transporter 1 deficiency syndrome (GLUT1DS) in Japan. Eur J Paediatr Neurol. 2018;**22**(3):482–7.

57. De Giorgis V, Masnada S, Varesio C, et al. Overall cognitive profiles in patients with GLUT1 deficiency syndrome. Brain Behav. 2019;**9**(3):e01224.

58. Bekker YAC, Lambrechts DA, Verhoeven JS, et al. Failure of ketogenic diet therapy in GLUT1 deficiency syndrome. Eur J Paediatr Neurol. 2019;doi:10.1016/j.ejpn.2019.02.012.

59. Tchapyjnikov D, Mikati MA. Acetazolamide-responsive episodic ataxia without baseline deficits or seizures secondary to GLUT1 deficiency: A case report and review of the literature. Neurologist. 2018;**23**(1):17–8.

60. Pascual JM, Liu P, Mao D, et al. Triheptanoin for glucose transporter type 1 deficiency (G1D): Modulation of human ictogenesis, cerebral metabolic rate, and cognitive indices by a food supplement. JAMA Neurol. 2014;**71**(10):1255–65.

61. Hainque E, Gras D, Meneret A, et al. Long-term follow-up in an open-label trial of triheptanoin in GLUT1 deficiency syndrome: A sustained dramatic effect. J Neurol Neurosurg Psychiatry. 2019; doi:10.1136/jnnp-2018-320283.

62. Nakamura S, Muramatsu SI, Takino N, et al. Gene therapy for Glut1-deficient mouse using an adeno-associated virus vector with the human intrinsic GLUT1 promoter. J Gene Med. 2018;**20**(4):e3013.

Chapter 14

Lysosomal Storage Disorders: Niemann–Pick Disease Type C and Movement Disorders

Marc C. Patterson

Introduction

Niemann–Pick disease type C (NPC) is an atypical, ultra-rare, lysosomal storage disease [1]. In contrast to classic lysosomal storage diseases [2], the lysosomal storage of macromolecules is not caused by an enzyme deficiency, but rather by a deficiency of the protein products of two distinct genes, *NPC1* and *NPC2* [3, 4]. These two proteins are highly conserved across species; despite intense study for many years, their basic functions and the sequence of pathogenic events remains uncertain. It is apparent that NPC1 and NPC2 are intimately involved in endosomal–lysosomal trafficking of macromolecules, and a deficiency of either one is associated with lysosomal storage of cholesterol, glycosphingolipids, and a variety of other molecules, as part of a cascade of events that includes inflammation, synaptic and neuronal dysfunction, and eventually cell death by apoptosis [5].

The tissues contain an abundance of maldistributed free cholesterol, particularly in the liver and spleen, and there is also an increase in the mass of glycosphingolipids, including glucosylceramide and GM2 ganglioside, which is more pronounced in the central nervous system than in peripheral tissues [6]. At a light microscopic level, involved neurons are swollen, and show both ectopic dendritogenesis and the presence of axonal spheroids. The most severely affected neurons are the Purkinje cells [7], which may show abnormal storage even before birth [8]. There is a stereotyped pattern of cell loss [9]. Neurons in the brainstem [10], basal ganglia, diencephalon, and cortex are also involved [11], as are dorsal root ganglion cells, although peripheral neuropathy is only rarely clinically apparent in humans [12, 13] or mice with NPC [14].

The disease may present at any age, from fetal life to maturity [15]. Fetal or neonatal organomegaly, with or without ascites, may be associated with pulmonary infiltration and a significant morbidity and mortality. Although the liver, and more frequently the spleen, may be enlarged, the course of the disease beyond infancy is largely characterized by progressive neurodegeneration. All levels of the central nervous system are involved in NPC, accounting for its diverse manifestations (see Table 14.1). Given the widespread involvement of the nervous system in NPC, it is not surprising that movement disorders are frequent manifestations of the disease. Of note, one (retrospective) study of movement disorders in children with lysosomal diseases found that NPC was the disorder most frequently associated with movement disorders [16] and that ataxia was the most frequent manifestation in NPC, as in other lysosomal diseases, consistent with the high burden of disease in Purkinje cells.

Eye Movements

Vertical supranuclear saccadic palsy (VSSP) (also, but somewhat less accurately, known as vertical supranuclear gaze palsy or VSGP), is a hallmark of NPC [17]; the pathology is exquisitely localized to the rostral interstitial nucleus of the medial longitudinal fasciculus [18]. The evolution of the gaze palsy has been observed in a relatively small number of patients. It first manifests as increased saccadic latency, most often in down gaze, followed by a progressive loss of speed and amplitude of vertical saccades. Impairment of horizontal saccades (HSSP) follows that of vertical saccades. Patients who survive long enough lose all saccadic eye movements. Parents of children with VSSP will sometimes recognize characteristic head thrusting, with or without eye blinking, which represents an adaptive response to the saccadic impairment. Eye blinking breaks fixation, and the subsequent head thrust generates a vestibulo-ocular reflex that initiates a saccade in the same plane. Reading may also be impaired by VSSP (and HSSP), which causes difficulty moving from the end of one line of text to the next, as well as in scanning texts. In

Table 14.1 Neuroanatomy and neurological manifestations of NPC

Locus	Cortex	Basal ganglia	Diencephalon	Brainstem	Cerebellum	Peripheral nerves
Manifestations	Cognitive dysfunction, psychiatric manifestations, epilepsy, myoclonus	Dystonia	Gelastic cataplexy, sleep inversion	Saccadic palsies, dysphagia	Ataxia, dysarthria, dysphagia	Sensory neuropathy (rare)

adults, a "round the houses" sign has been observed in NPC, demonstrating that this finding is not specific for progressive supranuclear palsy [19].

The clinician must systematically examine saccades to recognize this sign, which is often overlooked, even when present in full-blown form. This author believes that reports on the clinical manifestations of NPC that describe older children or adults who lack this finding must be treated with skepticism, unless a formal assessment of eye movements has been performed in a systematic fashion by experienced clinicians or using neurophysiological measurements of saccades, or both.

Various measurements of saccadic eye movements have been used as biomarkers in NPC. Horizontal eye movement saccadic velocity was selected as the primary outcome measure in a study of miglustat in NPC (most participants had complete, or near-complete, VSSP at entry) [20]. The relationship between saccadic eye movements and the clinical manifestations of NPC had not been formally assessed at the time, but this has been explored in later studies [21, 22].

Ataxia

Ataxia is almost universal in NPC, manifesting beyond infancy. It manifests most commonly as clumsiness in the first decade of life, and insidiously progresses to ataxia of gait and limb movement. Over a period of years, sometimes decades, patients become dependent on walking aids, and eventually require a wheelchair for mobility. This disease progression is paralleled by gradual atrophy of the cerebellum, which has been quantitated, and which is a promising surrogate marker of disease progression [22].

Ataxia also correlates closely with a loss of Purkinje cells in the murine and feline models of the disease [7, 23]. As might be anticipated, there is substantial Purkinje cell involvement in animal models before the presumed symptomatic threshold is crossed, and symptoms and signs appear. This has clear implications for therapy – a substantial proportion of Purkinje cells are dysfunctional or dead by the time symptoms and signs are detectable, thus limiting the scope of disease-modifying therapies, and challenging symptomatic treatments. Physical and occupational therapies have an important place in the management of ataxia in NPC, although their role has not been systematically studied in this disease; rehabilitation is recommended by the American Academy of Neurology as part of the treatment of cerebellar motor dysfunction, based on limited data [24]. Indeed, it is difficult to imagine how such a study might be ethically pursued. Clinical experience suggests that such interventions are of benefit, and expert opinion supports their use [25]; their cessation is often accompanied by a clear regression in function.

Many drugs (alcohol, antiseizure drugs, benzodiazepines, and others) can provoke or exacerbate ataxia through their effects on Purkinje cells, but few, if any, agents improve ataxia. N-acetyl-DL-leucine has been studied in patients with NPC. The drug has been used to treat acute vertigo in France since 1957, and one study found that it partially normalized the abnormal transmembrane potential in deafferented vestibular neurons [26]. Based on similarities between vestibular and cerebellar neurons [27], it was hypothesized that N-acetyl-DL-leucine might be effective in ataxia. An open-label study showed improvement in the Scale for the Assessment and Rating of Ataxia (SARA) and the Spinocerebellar Ataxia Functional Index (SCAFI) in 12 out of 13 patients with a variety of degenerative cerebellar ataxias exposed to the tablet form of N-acetyl-DL-leucine [28]. In contrast, a study of the liquid form of this agent in somewhat older patients with different degenerative cerebellar ataxias, assessed by blinded evaluation of video recordings, found no evidence of benefit on objective measures, although seven out of ten patients reported a subjective benefit [29]. A multicenter, multinational, randomized, double-blinded, placebo-controlled, crossover phase III trial of N-acetyl-DL-leucine in 108 patients with adult-onset cerebellar ataxia is currently in progress, and should provide a clearer picture of the role of this

agent in adult-onset ataxias. Twelve patients with NPC were given N-acetyl-DL-leucine in a dose of 3 g per day for 1 week, followed by 5 g per day for 3 weeks, followed by a washout period of 1 month. They were assessed using the SARA, SCAFI, modified Disability Rating Scale (mDRS), EuroQol 5Q-5D-5L, and the visual analog scale (VAS) at baseline, after 4 weeks exposure to the experimental drug, and after the washout period. All measures showed evidence of benefit; the mean SARA score fell from the baseline value of 10.8 at baseline to 7.0 following 4 weeks of N-acetyl-DL-leucine, returning to 10.5 after a month of washout [30]. Further studies of this agent in NPC are planned.

Dystonia

Dystonia is frequent in NPC. It often begins as action or stress dystonia, appearing in one foot while walking, or in the feet and/or hands during activities such as heel walking. Axial and bulbar muscles may also be involved, including those of facial expression. For example, one report described a 29-year-old woman who exhibited bibrachial and facial dystonia with grimacing [19], accompanied by hyperreflexia and vertical gaze palsy. Another patient began to exhibit slowed running at 8 years, and finger dystonia 2 years later [31].

A few studies have quantitated the frequency or character of dystonia. A French study of five adolescents and adults with NPC found that all had movement disorders [32]. Dystonia was reported in two out of five patients, all of whom had ataxia.

Myoclonus

Myoclonus occurs frequently in NPC. In one series of five juvenile onset patients, all exhibited fragmentary myoclonus [33]. All of the subjects had disrupted sleep and one had cataplexy as well. Stimulus-sensitive myoclonus has been observed [34]. Myoclonus was present in three out of five late (adolescent and adult) cases in a French series [32], and was found in five out of eight late-onset Dutch cases [35]. It was the presenting finding in three subjects. EEG–EMG coherence analysis showed that the myoclonus was of cortical origin in this series. No study has formally evaluated the management of myoclonus in NPC. In the experience of this author, both levetiracetam and clonazepam may be helpful in ameliorating this symptom when it is troubling to the patient.

Spasticity

Spasticity often coexists with dystonia in NPC, and the contribution of each to a patient's function may be difficult to disentangle at the bedside. Patients are often hyperreflexic, but usually have flexor plantar responses.

Tremor

Fifteen patients with NPC were studied with accelerometry and surface electromyography of the upper extremities [36]. Almost half of these exhibited postural tremor, which was usually bilateral. The frequencies ranged between 0.3 Hz and 3 Hz, with an average amplitude of 1.2±0.98 mm. Just fewer than 90% of patients had bilateral action tremor, whose frequencies ranged between 2 Hz and 3.7 Hz, with an average amplitude of 5.25±3.76 mm. The surface EMG recordings revealed long but variable duration, variable-amplitude muscle burst discharges during action in some patients, as well as short, high-frequency, irregularly timed bursts in others. The findings on accelerometry were most strongly correlated with cerebellar outflow tremor. The surface EMG findings were mixed, being most consistent with dystonic, myoclonic, and choreiform movements, including dystonic tremor.

A later study assessed 14 subjects with NPC and 14 age-matched controls using spiral analysis [37]. The spirals drawn by the patients were abnormal, exhibiting lines which were wavy, crossing, and with irregularly spaced loops. The spirals were drawn more slowly and were more tremulous than in controls. The NPC patients tended to use a constant elevated pressure when drawing. The fluctuation in loop width was thought to be analogous to cerebellar ataxia, and was in keeping with the previous studies using accelerometry and surface EMG. The increased pressure and slow speed of drawing were suggestive of focal dystonia, and the slow speed together with diminished acceleration was more suggestive of parkinsonism, although the absence of micrographia would not be typical.

Management

There are no controlled studies on the management of movement disorders in NPC, although one open-label study has suggested that ataxia may be improved by the administration of N-acetyl-DL-leucine; controlled studies of this agent for the management of ataxia in NPC are currently being planned. Thus, patients should be offered standard physical and pharmacological therapies for these movement disorders [1, 25].

There is currently no approved therapy in the United States for NPC. Miglustat, an iminosugar that inhibits glucosylceramide synthase, has shown survival benefit in animal models of NPC [23]. There is evidence that miglustat may have beneficial effects on eye movements in human NPC as well as on disease progression [20] [38–45], particularly swallowing and ataxia. Preclinical studies of 2-hydroxypropyl-β-cyclodextrin (cyclodextrin) in mice and cats have shown evidence of improved survival [46–48], and a report of NPC subjects treated through (uncontrolled) expanded access programs suggested benefits in slowing disease progression [49], but the preliminary results of a double-blinded, randomized clinical trial of intrathecal cyclodextrin in NPC (NCT02534844) showed no difference in the primary endpoint between controls and patients receiving the active agent. Complete data from this study are yet to be released or published at the time of writing (November, 2018).

Conclusions

NPC is an atypical lysosomal disease characterized by progressive neurodegeneration. Ataxia, vertical supranuclear gaze palsy, and a variety of other involuntary movements, including dystonia, myoclonus, spasticity, and tremor, complicate the course of the illness. Disease-modifying therapies are currently being investigated. In the meantime, the consensus of expert opinion is that standard approaches to the management of these movement disorders, including the use of physical, occupational, and speech therapy, symptomatic pharmacotherapy, and, in selected cases, botulinum toxin, is most appropriate.

Key Points and Clinical Pearls

- Ataxia is almost universal in Niemann–Pick disease type C (NPC), accounts for a substantial part of the morbidity and often indicates disease progression.
- Dystonia and myoclonus are also common though less well studied movement disorders in NPC.
- There are no controlled studies on the management of movement disorders in NPC.
- Several disease-modifying therapies are currently being investigated. Their impact on the incidence and progression of movement disorders in NPC remains to be defined.

Directions for Future Research

- A systematic characterization of movement disorders across the age spectrum in NPC.
- Development and use of standardized rating scales that allow the inclusion of movement disorders as outcome parameters in clinical trials for NPC.
- Evaluation of the impact of novel disease-modifying therapies on movement disorders in NPC.

References

1. Patterson MC, Clayton P, Gissen P, et al. Recommendations for the detection and diagnosis of Niemann–Pick disease type C: An update. Neurol Clin Pract. 2017;**7**(6):499–511.
2. Hers HG. Inborn lysosomal diseases. Gastroenterology. 1965;**48**:625–33.
3. Carstea ED, Morris JA, Coleman KG, et al. Niemann–Pick C1 disease gene: Homology to mediators of cholesterol homeostasis. Science. 1997;**277**(5323):228–31.
4. Naureckiene S, Sleat DE, Lackland H, et al. Identification of *HE1* as the second gene of Niemann–Pick C disease. Science. 2000;**290**(5500):2298–301.
5. Lloyd-Evans E, Platt FM. Lipids on trial: The search for the offending metabolite in Niemann–Pick type C disease. Traffic. 2010;**11**(4):419–28.
6. Vanier MT. Complex lipid trafficking in Niemann–Pick disease type C. J Inherit Metab Dis. 2015;**38**(1):187–99.
7. Higashi Y, Murayama S, Pentchev PG, Suzuki K. Cerebellar degeneration in the Niemann–Pick type C mouse. Acta Neuropathol. 1993;**85**(2):175–84.
8. Vanier MT. Prenatal diagnosis of Niemann–Pick diseases types A, B and C. Prenat Diagn. 2002;**22**(7):630–2.
9. Sarna JR, Larouche M, Marzban H, et al. Patterned Purkinje cell degeneration in mouse models of Niemann–Pick type C disease. J Comp Neurol. 2003;**456**(3):279–91.
10. Luan Z, Saito Y, Miyata H, et al. Brainstem neuropathology in a mouse model of Niemann–Pick disease type C. J Neurol Sci. 2008;**268**(1–2):108–16.
11. Paul CA, Boegle AK, Maue RA. Before the loss: Neuronal dysfunction in Niemann–Pick type C disease. Biochim Biophys Acta. 2004;**1685**(1–3):63–76.

12. Zafeiriou DI, Triantafyllou P, Gombakis NP, et al. Niemann–Pick type C disease associated with peripheral neuropathy. Pediatr Neurol. 2003;**29** (3):242–4.

13. Chien YH, Lee NC, Tsai LK, et al. Treatment of Niemann–Pick disease type C in two children with miglustat: Initial responses and maintenance of effects over 1 year. J Inherit Metab Dis. 2007;**30**(5):826.

14. Bagel JH, Sikora TU, Prociuk M, et al. Electrodiagnostic testing and histopathologic changes confirm peripheral nervous system myelin abnormalities in the feline model of Niemann–Pick disease type C. J Neuropathol Exp Neurol. 2013;**72** (3):256–62.

15. Vanier MT. Niemann–Pick disease type C. Orphanet J Rare Dis. 2010;**5**:16.

16. Ebrahimi-Fakhari D, Hildebrandt C, Davis PE, et al. The spectrum of movement disorders in childhood-onset lysosomal storage diseases. Mov Disord Clin Pract. 2018;**5**(2):149–55.

17. Salsano E, Umeh C, Rufa A, Pareyson D, Zee DS. Vertical supranuclear gaze palsy in Niemann–Pick type C disease. Neurol Sci. 2012;**33**(6):1225–32.

18. Solomon D, Winkelman AC, Zee DS, Gray L, Buttner-Ennever J. Niemann–Pick type C disease in two affected sisters: Ocular motor recordings and brain-stem neuropathology. Ann N Y Acad Sci. 2005;**1039**:436–45.

19. Crespi J, Brathen G, Quist-Paulsen P, Pagonabarraga J, Roig-Arnall C. Facial dystonia with facial grimacing and vertical gaze palsy with "round the houses" sign in a 29-year-old woman. Neuroophthalmology. 2016;**40** (1):31–4.

20. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann–Pick C disease: A randomised controlled study. Lancet Neurol. 2007;**6** (9):765–72.

21. Abel LA, Walterfang M, Fietz M, Bowman EA, Velakoulis D. Saccades in adult Niemann–Pick disease type C reflect frontal, brainstem, and biochemical deficits. Neurology. 2009;**72**(12):1083–6.

22. Abel LA, Bowman EA, Velakoulis D, et al. Saccadic eye movement characteristics in adult Niemann–Pick Type C disease: Relationships with disease severity and brain structural measures. PLoS One. 2012;**7**(11): e50947.

23. Stein VM, Crooks A, Ding W, et al. Miglustat improves Purkinje cell survival and alters microglial phenotype in feline Niemann–Pick disease type C. J Neuropathol Exp Neurol. 2012;**71**(5):434–48.

24. Zesiewicz TA, Wilmot G, Kuo SH, et al. Comprehensive systematic review summary: Treatment of cerebellar motor dysfunction and ataxia. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;**90** (10):464–71.

25. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann–Pick disease type C. Orphanet J Rare Dis. 2018;**13**:50.

26. Ferber-Viart C, Dubreuil C, Vidal PP. Effects of acetyl-DL-leucine in vestibular patients: A clinical study following neurotomy and labyrinthectomy. Audiol Neurootol. 2009;**14**(1):17–25.

27. Highstein SM, Holstein GR. The anatomy of the vestibular nuclei. Prog Brain Res. 2006;**151**:157–203.

28. Strupp M, Teufel J, Habs M, Feuerecker R, Muth C, van de Warrenburg BP, et al. Effects of acetyl-DL-leucine in patients with cerebellar ataxia: A case series. J Neurol. 2013;**260**(10):2556–61.

29. Pelz JO, Fricke C, Saur D, Classen J. Failure to confirm benefit of acetyl-DL-leucine in degenerative cerebellar ataxia: A case series. J Neurol. 2015;**262**(5):1373–5.

30. Bremova T, Malinova V, Amraoui Y, et al. Acetyl-DL-leucine in Niemann–Pick type C: A case series. Neurology. 2015;**85**(16):1368–75.

31. Abe K, Sakai N. Patient with Niemann–Pick disease type C: Over 20 years' follow-up. BMJ Case Rep. **2017**;2017.

32. Anheim M, Lagha-Boukbiza O, Fleury-Lesaunier MC, et al. Heterogeneity and frequency of movement disorders in juvenile and adult-onset Niemann–Pick C disease. J Neurol. 2014;**261**(1):174–9.

33. Vankova J, Stepanova I, Jech R, et al. Sleep disturbances and hypocretin deficiency in Niemann–Pick disease type C. Sleep. 2003;**26**(4):427–30.

34. Josephs KA, Van Gerpen MW, Van Gerpen JA. Adult onset Niemann–Pick disease type C presenting with psychosis. J Neurol Neurosurg Psychiatry. 2003;**74** (4):528–9.

35. Koens LH, Kuiper A, Coenen MA, et al. Ataxia, dystonia and myoclonus in adult patients with Niemann–Pick type C. Orphanet J Rare Dis. 2016;**11**:121.

36. Floyd AG, Yu QP, Piboolnurak P, et al. Kinematic analysis of motor dysfunction in Niemann–Pick type C. Clin Neurophysiol. 2007;**118**(5):1010–8.

37. Hsu AW, Piboolnurak PA, Floyd AG, et al. Spiral analysis in Niemann–Pick disease type C. Mov Disord. 2009;**24**(13):1984–90.

38. Pineda M, Wraith JE, Mengel E, et al. Miglustat in patients with Niemann–Pick disease type C (NP–C): A multicenter observational retrospective cohort study. Mol Genet Metab. 2009;**98**(3):243–9.

39. Patterson MC, Vecchio D, Jacklin E, et al. Long-term miglustat therapy in children with Niemann–Pick disease type C. J Child Neurol. 2010;**25**(3):300–5.

40. Scheel M, Abegg M, Lanyon LJ, Mattman A, Barton JJ. Eye movement and diffusion tensor imaging analysis of treatment effects in a Niemann–Pick type C patient. Mol Genet Metab. 2010;**99**(3):291–5.

41. Wraith JE, Vecchio D, Jacklin E, et al. Miglustat in adult and juvenile patients with Niemann–Pick disease type C: Long-term data from a clinical trial. Mol Genet Metab. 2010;**99**(4):351–7.

42. Heron B, Valayannopoulos V, Baruteau J, et al. Miglustat therapy in the French cohort of paediatric patients with Niemann–Pick disease type C. Orphanet J Rare Dis. 2012;**7**:36.

43. Abel LA, Walterfang M, Stainer MJ, Bowman EA, Velakoulis D. Longitudinal assessment of reflexive and volitional saccades in Niemann–Pick type C disease during treatment with miglustat. Orphanet J Rare Dis. 2015;**10**:160.

44. Patterson MC, Mengel E, Vanier MT, et al. Stable or improved neurological manifestations during miglustat therapy in patients from the international disease registry for Niemann–Pick disease type C: An observational cohort study. Orphanet J Rare Dis. 2015;**10**:65.

45. Sedel F, Chabrol B, Audoin B, et al. Normalisation of brain spectroscopy findings in Niemann–Pick disease type C patients treated with miglustat. J Neurol. 2016;**263**(5):927–36.

46. Liu B, Turley SD, Burns DK, et al. Reversal of defective lysosomal transport in NPC disease ameliorates liver dysfunction and neurodegeneration in the NPC1-/- mouse. Proc Natl Acad Sci USA. 2009;**106**(7):2377–82.

47. Davidson CD, Ali NF, Micsenyi MC, et al. Chronic cyclodextrin treatment of murine Niemann–Pick C disease ameliorates neuronal cholesterol and glycosphingolipid storage and disease progression. PLoS One. 2009;**4**(9):e6951.

48. Vite CH, Bagel JH, Swain GP, et al. Intracisternal cyclodextrin prevents cerebellar dysfunction and Purkinje cell death in feline Niemann–Pick type C1 disease. Sci Transl Med. 2015;**7**(276):276ra26.

49. Berry-Kravis E, Chin J, Hoffmann A, et al. Long-term treatment of Niemann–Pick type C1 disease with intrathecal 2-hydroxypropyl-beta-cyclodextrin. Pediatr Neurol. 2018;**80**:24–34.

Chapter

15

Lysosomal Storage Disorders: Neuronal Ceroid Lipofuscinoses and Movement Disorders

Jennifer Vermilion, Jonathan W. Mink, and Erika F. Augustine

Introduction

The neuronal ceroid lipofuscinoses (NCLs) are rare, inherited, neurodegenerative, fatal lysosomal diseases of childhood caused by mutations in various genes. Although NCLs comprise more than 10 distinct diseases, they share core signs and symptoms: vision loss, epilepsy, dementia, and movement disorders [1–3]. Pathologically, NCLs are characterized by lysosomal accumulation of autofluorescent ceroid lipopigments [2]. These accumulations result in different ultrastructural inclusion patterns on electron microscopy in the various NCL forms. Most NCL genes encode for proteins involved in lysosomal or secretory cellular pathways [4].

Prior to the identification of causative genes, NCLs were classified by age at onset and ultrastructural electron microscopy findings [3] and were categorized as infantile (INCL), late-infantile (LINCL), juvenile (JNCL), or adult (ANCL). The genes causing classic forms of INCL (*CLN1*), LINCL (*CLN2*), and JNCL (*CLN3*) were the first to be discovered [4]. These are the most extensively described NCLs in the literature to date. However, through improved and more efficient modes of genetic testing and gene discovery, several additional NCL-causing genes have been discovered in recent years [4]. The discovery of the causative NCL genes has highlighted the phenotypic variability and overlap within and between the NCLs. However, commonly used terminology still refers to age at onset (infantile, late-infantile, juvenile, adult) as part of the description of phenotypic variants related to specific genes [4]. For example, although CLN1 (ceroid lipofuscinosis, neuronal, type 1) disease classically presents with symptom onset in infancy, late-infantile, juvenile, and adult-onset forms of CLN1 disease have all been described [2].

In classic CLN1 disease, there is rapid developmental regression, movement disorders, epilepsy, and vision loss by 2 years of age [5]. However, certain *CLN1* mutations lead to later onset of disease and slower decline [6–10]. Compared to CLN1 disease, CLN2 disease is more homogeneous. *CLN2* mutations cause classic LINCL, with symptom onset prior to 6 years. The disorder is characterized by a developmental plateau or regression, refractory epilepsy, movement disorders, vision loss, and eventual spastic quadraparesis [11]. Many other genes are implicated in variants of LINCL, including *CLN5*, *CLN6*, *CLN7*, and *CLN8* [4]. These variants were initially named based on the geographic location of the original patients described (i.e. "Finnish variant" for LINCL secondary to *CLN5* mutations). However, because these mutations have now been observed in other populations, this form of naming is no longer favored. Due to the confusion regarding the naming of NCLs, NCL experts now recommend combining both affected gene and clinical phenotype for classification (i.e. CLN2 disease, late-infantile phenotype) [3]. Although most individuals with NCLs will have ophthalmological and neurological manifestations, it is worth noting that both CLN3 disease and CLN7 disease have each been described as also having an isolated retinal dystrophy phenotype in addition to the traditionally recognized forms [12, 13]. On the other hand, classic ANCL does not have retinal involvement [14, 15]. In some NCLs, clinical heterogeneity of disease features and severity are noted within a single pedigree, where affected individuals possess the same gene mutations [16]. Reasons underlying these differences are not well understood.

It has been suggested that each form of NCL may have a characteristic movement disorder, potentially localizing to different anatomic regions or functional circuits within the nervous system. For example, myoclonus, a prominent feature of CLN2 disease, typically arises from dysfunction of the cerebral cortex, brainstem, or spinal cord [17]. Parkinsonism, a prominent feature of CLN3 disease, typically arises from dysfunction in the basal ganglia, including effects of

Table 15.1 NCL genetic classification

NCL type[a]	Gene name	Gene locus	Protein name	Protein type	Inheritance pattern[b]
CLN1	*PPT1*	1p32	Palmitoyl-protein thioesterase (PPT1)	Soluble lysosomal enzyme	AR
CLN2	*TPP1*	11p15	Tripeptidyl peptidase (TPP1)	Soluble lysosomal enzyme	AR
CLN3	*CLN3*	16p12	Battenin	Transmembrane protein	AR
CLN4	*DNAJC5*	20q13	Cysteine string protein alpha (CSPα)	Membrane-associated protein of synaptic vesicles	AD
CLN5	*CLN5*	13q22	CLN5 protein	Soluble lysosomal matrix protein	AR
CLN6	*CLN6*	15q21	CLN6 protein	Transmembrane protein of endoplasmic reticulum	AR
CLN7	*MFSD8*	4q28	Major facilitator superfamily domain containing 8 (MFSD8)	Lysosomal membrane protein	AR
CLN8	*CLN8*	8p23	CLN8 protein	Transmembrane protein of endoplasmic reticulum	AR
CLN10	*CTSD*	1p15.5	Cathepsin D (CTSD)	Soluble lysosomal enzyme	AR
CLN11	*GRN*	17q	Progranulin (PGRN)	Autocrine growth factor	AR
CLN12	*ATP13A2*	1p36	ATPase cation transporting 13A2 (ATP13A2)	ATPase	AR
CLN13	*CTSF*	11q13	Cathepsin F (CTSF)	Soluble lysosomal enzyme	AR

[a] Note – CLN9 and CLN14 have not been confirmed as NCL disorders and thus are not included. [b] AD, autosomal-dominant; AR, autosomal-recessive.

nigrostriatal dopamine deficiency [18, 19]. The different types of movement disorder within and across NCL types suggest that there may be preferential vulnerability of different neuron populations in relation to different mutations. Therefore, understanding the specific characteristic movement disorders may inform the understanding of pathobiology and treatment targets.

In the following sections, we describe the key movement disorders occurring in NCL disorders, by NCL type, and then discuss specific therapies for NCL-related movement disorders. For a comprehensive discussion of approaches to diagnosis and the full clinical spectrum of NCL disorders, we refer readers to recent reviews [2–4, 14, 20], and to the NCL Mutation and Patient Database (www.ucl.ac.uk/ncl-disease/mutation-and-patient-database) for detailed description of the gene mutation spectrum and genotype–phenotype correlations for each NCL type. Table 15.1 shows each recognized NCL disorder and its causative gene. Table 15.2 provides a summary of movement disorders that occur across the full disease spectrum of each NCL.

Clinical Features of the NCLs

The genomic era of NCL disorders, where NCL diseases were recognized to represent distinct entities due to unique gene mutations began in the mid-1990s with first discoveries of NCL-causing genes (CLN1, *PPT1*; CLN3, *CLN3*) [21, 22]. The most recent NCL gene was confirmed in 2013 (CLN13, *CTSF*) [23]. Prior to the genomic era, diagnoses were based on ultrastructural pathology and age at onset, neither of which is highly specific for a particular NCL genetic mutation. Thus, while older reports may provide useful phenotypic descriptions, in many cases it cannot be concluded with certainty which form(s) of NCL are being described. With respect to movement disorders, specificity is further limited by the variable use of standard definitions and consensus terminology, making comparison across reports a challenge. Furthermore, distinctions between epileptic and non-epileptic myoclonus can be challenging. These factors limit our complete understanding of the movement disorder spectrum of NCL disorders. In the current era of next-generation sequencing, an unbiased

Table 15.2 Movement disorders reported in the NCLs

	Ataxia	Dystonia	Myoclonus	Parkinsonism	Tremor	Chorea	Stereotypy
CLN1	+ (LI, A)*		+ (I)*	+ (A)		+	
CLN2	+*	+	+*	+		+	
CLN3		+	+	+*		+	
CLN4	+*	+	+*	+			
CLN5	+*		+*		+		
CLN6	+ (LI, A)*		+				+ (LI)
CLN7	+*	+	+*		+		+
CLN8	+ (LI)*		+*				
CLN10	+ (J)				+ (C)*		
CLN11	+*		+				
CLN12	+		+*	+*	+		
CLN13	+*		+	+	+*		

A: adult onset; C: congenital; I: infantile onset; J: juvenile onset; LI: late-infantile onset; + denotes presence of the movement disorder; *denotes predominant movement disorder type. Note – CLN14 has not been confirmed as a NCL disorder and thus is not included.

approach to diagnosis, the confirmation of an NCL disorder seems to occur earlier in the disease (personal experience) which, over time, may contribute to a better understanding of the full spectrum of NCL diseases and a knowledge of associated movement disorders.

CLN1 Disease (*PPT1*)

Infants with the classic form of CLN1 disease often demonstrate typical development until 6–12 months of age, when deceleration of head growth, hypotonia, myoclonus, refractory epilepsy, and vision loss develop. Early in the disease, MRI T2-weighted sequences demonstrate hypointense signal changes in the thalamus and basal ganglia and hyperintense periventricular signal changes [24, 25]. Progressive, generalized cerebral atrophy is noted until approximately 4 years of age, after which further MRI changes are minimal [24]. Across all presentations of CLN1 disease, prominent cerebellar volume loss is a key imaging feature. Prominent epileptic and non-epileptic myoclonus, starting between 12 months and 24 months of age, occurs almost universally in the classic infantile-onset form [26]. Additional movement disorders in early-onset forms, including chorea [27], are less commonly described. Death occurs in the late first or early second decade.

In addition to the classic infantile-onset form, CLN1 disease can present with later-onset forms, including a juvenile NCL-like form that begins with vision loss, as seen in CLN3 disease [28]. Myoclonus tends to be less prominent in these patients. This form is sometimes referred to as juvenile NCL with GRODS (granular osmiophilic deposits), based on the pattern of inclusions observed on electron microscopy.

CLN2 Disease (*TPP1*)

Prior to the onset of definitive symptoms, children with the classic form of CLN2 disease can demonstrate relatively typical development until age 2–4 years. Language delay may represent a prodromal symptom [29]. Following onset of refractory epilepsy, there is rapid deterioration of cognitive, motor, and visual skills, followed by a protracted period of markedly impaired motor and cognitive function, culminating in death at a median age of 10 years [30].

In the classic late-infantile-onset form of CLN2 disease, myoclonus and cerebellar ataxia represent the predominant movement phenotype [31]. Myoclonus may be epileptic or non-epileptic in nature, which can be challenging to distinguish on a clinical basis. Additional movement disorders, beyond myoclonus and ataxia, have been described in the classic disease as well as childhood onset forms of atypical or protracted forms CLN2 disease, including: dystonia [31], tremor [31], chorea [32], and parkinsonism/dystonia–parkinsonism, including freezing of gait [33], and

akathisia [33]. There is a report of an exacerbation of the complex movement disorder phenotype in CLN2 disease in the setting of the administration of valproate in children, commonly used in the management of epilepsy. Two children presented acutely with worsening of the existing movement disorder, encephalopathy, hyperthermia, and elevated creatine kinase levels. All symptoms improved within 24 hours of withdrawal of the valproate therapy and there were no other suspected etiologies of the decompensation in the context of a thorough evaluation [34].

Recently, it has been recognized that bi-allelic missense mutations in *TPP1* may also result in an adult-onset, predominantly ataxic, phenotype – spinocerebellar ataxia recessive type 7 (SCAR7). Vision loss, epilepsy, and overt cognitive dysfunction are not observed in this phenotype and storage-material findings can be absent [35]. A similar phenotype can present in childhood as reported by Dy et al., where bi-allelic *TPP1* mutations resulted in progressive cerebellar dysfunction and static below-average cognitive skills in a 10-year-old girl [36].

CLN3 Disease (*CLN3*)

CLN3 disease is the most prevalent form of NCL and has the most uniform phenotype of the NCL disease spectrum [1]. Disease onset is typically at 4–8 years of age, with rapidly progressive vision loss representing the most common initial symptom [37]. Over the course of multiple years, children develop seizures, behavioral difficulties, cognitive changes, and motor impairment. Motor symptoms emerge around 11 years of age with loss of independent ambulation by late adolescence to early adulthood [38]. Initial motor abnormalities include rigidity, bradykinesia, and a shuffling gait (parkinsonism) [39]. As motor skills decline, speech impairment progresses until children become non-verbal. Prior to the loss of speech, the speech pattern in CLN3 disease is unintelligible and characterized by frequent stuttering and dysfluency. In late adolescence, cardiac conduction abnormalities emerge, manifesting primarily with bradyarrhythmias [40]. Hyperkinetic involuntary movements are less commonly described but may occur, including chorea, tics, stereotypies, and myoclonus [39, 41, 42]. Rarely, emergent movement disorder crises occur in CLN3 disease. Elkay et al. described two sisters with CLN3 disease who developed abnormal movements. One developed chorea at age 9 years and progressive gait difficulties leading to loss of ambulation at age 12 years when she developed progressive generalized dystonia. Despite treatment, she developed dystonic storm with hyperthermia and elevated creatinine kinase. The other sister developed progressive generalized dystonia at age 17 years, and eventually severe dystonic storm [41].

Parkinsonism, the most common motor abnormality in CLN3 disease, is thought to arise from dopamine dysfunction in the striatum. Single-photon emission CT images in patients with juvenile NCL and parkinsonism demonstrate decreased striatal dopamine transporter density, and positron emission tomography demonstrates reduced striatal dopamine D1 receptor binding [43, 44].

CLN4 Disease (*DNAJC5*)

CLN4 disease is the only currently known autosomal-dominant form of NCL [45]. Symptom onset is typically a presentation with cerebellar dysfunction around 30 years of age with later development of epilepsy, myoclonus, and dementia [46–48]. Visual function is preserved. Alternate presentations have been described, including cranial and neck dystonia without myoclonus [46], and syndromes of myoclonus epilepsy with parkinsonism [48].

CLN5 Disease (*CLN5*)

The classic CLN5 disease phenotype is often described as a variant late-infantile type of NCL (vLINCL). Juvenile-onset and adult-onset forms have also been described. Symptoms commence between 2 years and 7 years of age, with motor clumsiness or delay and inattention, followed by progressive vision loss, cognitive and motor regression, ataxia, myoclonus, and epilepsy, then premature death in early adulthood (second to fourth decade) [49]. The initial course is slow, evolving to the development of severe neuropsychiatric symptoms in the second decade, with most of a cohort of 15 reported children being bedridden within a decade of recognized onset [49]. In addition to ataxia and myoclonus, stereotypies may also occur.

More recently, an adult-onset CLN5 disease phenotype was described as an autosomal-recessive cerebellar ataxia syndrome with dementia [50]. This report contrasts with typical teaching of associating autosomal-dominant cerebellar ataxias with adult-onset and autosomal-recessive cerebellar ataxias with primarily childhood onset.

CLN6 Disease (*CLN6*)

CLN6 disease was initially classified as a variant of late-infantile NCL and presents between 18 months and 5 years of age [51]. It was later linked to teenage- and adult-onset (Kufs disease) forms as well [52–54]. Though adult-onset NCLs were initially attributed to CLN4 disease, *CLN6* mutations are now recognized as the cause of the majority of adult-onset NCLs [3].

Although the phenotype of CLN6 disease is widely variable, a common early childhood presentation is with epilepsy in pre-school years, followed by the development of vision loss and ataxia along with cognitive regression [55, 56]. Hand-wringing stereotypies occur in a subset of patients [56]. Cerebral and cerebellar atrophy is characteristic. In early childhood-onset forms, death typically occurs in the second decade of life.

Mutations in *CLN6* are responsible for the majority of autosomal-recessive Kufs disease. Unlike childhood-onset NCLs, Kufs disease does not typically include retinal involvement. Kufs disease has been traditionally divided into two forms, type A and type B. Type A Kufs disease is characterized by progressive myoclonic epilepsy. Type B Kufs disease is characterized by adult-onset dementia with co-occurring motor dysfunction. However, there is often an overlap between the type A and type B phenotypes. For example, patients with type A Kufs phenotype often have evidence of cognitive or motor dysfunction prior to the onset of seizures [52, 53]. Both action and epileptic myoclonus are common in these patients. Overall, prominent action myoclonus and ataxia represent the predominant movement disorders in adult-onset Kufs disease of both types (A and B). These features contribute to a slowly progressive loss of mobility in affected patients. Additional movement disorders have been described and present later, including dystonia and tremor [52].

Canafoglia et al. described the clinical and electrographic features of 11 patients with CLN6 disease [54]. Seven presented with a late-infantile phenotype; symptoms began between 3 years and 6 years of age. One child had a later onset at 8 years of age, and three had symptom onset in the second or third decade of life. All children demonstrated a constellation of cognitive abnormalities plus ataxia and refractory epilepsy, and cerebellar atrophy was common (n = 7). Cognitive symptoms were the most common first symptom for children in this cohort (n = 6). Other presentations included ataxia (n = 1) and extrapyramidal signs that were not fully described (n = 1). Within months of disease onset, all children had motor abnormalities, and these findings were followed by epilepsy and vision loss. Multifocal action myoclonus began at variable times in the course of disease. Of the five with extended follow-up, loss of ambulation occurred on average 3.5 years after disease onset. Three patients in this series had the type A Kufs phenotype, consistent with progressive myoclonus epilepsy [54]. Cortical myoclonus progressed over time and caused significant motor impairment. One patient, with onset of learning difficulties at 12 years and seizures at 17 years, was bedridden by age 26 years due to continuous myoclonus. Two patients demonstrated ataxia in the intermediate stage of the disease and two patients showed both pyramidal and extrapyramidal signs in the later disease stages. Loss of ambulation occurred several years after disease onset in two of the three patients. Cognitive decline, in contrast, was relatively slow. All adults had normal vision.

Another series reported a similar progression of symptoms in adult-onset CLN6 disease (Kufs disease), including onset in early adulthood, action or stimulus-induced myoclonus, and a severe functional impact of myoclonus combined with dementia [57]. Eyelid myoclonia can be a component of the refractory epilepsy phenotype, and the disease in adults may also manifest with progressive ataxia [58].

CLN7 Disease (*MFSD8*)

Also originally categorized within the group Turkish variant LINCL (vLINCL), CLN7 disease is now recognized as a distinct entity, as is true for CLN6 and CLN8. Classic CLN7 disease begins in early childhood, between 3 years and 7 years of age, primarily presenting with developmental delay or regression and refractory epilepsy with polymorphic seizures [59–61]. Both cerebral and cerebellar atrophy are evident on brain imaging, although cerebellar atrophy is more prominent and progressive [59]. Ataxia and myoclonus represent the predominant movement disorders, appearing early in the disease course. In some series, loss of ambulation occurs within 2 years of ataxia onset [59, 62]. As with other NCLs, myoclonus may be epileptic or non-epileptic in nature. Stereotyped hand movements akin to those observed in Rett syndrome as well as dystonia have been reported [60, 62].

CLN8 Disease (*CLN8*)

There are two distinct phenotypes of CLN8 disease: (1) progressive epilepsy with intellectual disability

(Northern epilepsy syndrome) and (2) variant late-infantile NCL (vLINCL). The vLINCL form of CLN8 disease is characterized by early-childhood onset and rapid, severe symptomatic progression. Initial presentation is typically with developmental delay and refractory myoclonic epilepsy in the toddler to preschool years, combined with ataxia. Subsequently, vision loss progressing to blindness develops [63–65]. In one child, following a period of early-onset retinal dystrophy and possible seizures, parkinsonism developed, characterized by shuffling gait and problems initiating voluntary movements. Within 2 years, ambulation was lost and disabling dyskinesias developed [66]. In some, stereotyped hand movements occur, similar to those that may occur in CLN6 and CLN7 diseases [63]. Cerebral and cerebellar atrophy and diffuse white matter hyperintensity are also evident [63, 65–68].

CLN9 Disease

CLN9 disease has been proposed although not confirmed as a distinct entity.

CLN10 Disease (*CTSD*)

Mutations in *CTSD* that lead to cathepsin D deficiency may manifest as CLN10 disease [69], as either a congenital-onset or juvenile-onset NCL. In addition to the features described below, at least two cases of CLN10 disease, one with infantile onset and one with juvenile onset, have been reported to have associated hypertrophic cardiomyopathy [70].

In the congenital disease, presentation is characterized by microcephaly with severe brain atrophy, respiratory insufficiency, hypertonia, neonatal seizures, and jitteriness. Age at death ranges between hours and weeks of life. Although the concept of a congenital NCL was first described decades ago [71–76], only rare cases have been reported since then [77, 78]. Siintola et al. first described congenital NCL secondary to *CTSD* mutations in three siblings born to consanguineous parents, and one unrelated child without family history of consanguinity [79]. The affected infants were born at term with significant microcephaly, intractable epilepsy, and spasticity. One infant was reported to have jerky movements in utero, attributed to myoclonic seizures. Postnatal apnea was severe, and death occurred within 1–10 days of delivery. Dysmorphic features such as low-set ears were described. Prior to the identification of the gene, Sandbank described two siblings born with microcephaly and abnormal movements who progressed to death 24–48 hours after delivery [76]. These infants presented with hyperkinesis and tremors in the hands and legs. While these patients did not have a genetic diagnosis, CLN10 is likely based on the congenital onset of an NCL. Abnormal movements have not been reported in other cases of congenital NCL [71, 72, 75]. Congenital-onset CLN10 disease is presumed to be related to complete inactivation of CTSD enzyme activity.

One case of early-infantile NCL secondary to *CTSD* mutations has been described [70]. This patient presented with early acquired microcephaly and cerebral atrophy and a progressive intractable epilepsy. Hypertrophic cardiomyopathy developed in this child. Of note, abnormal movements were not described.

Juvenile NCL secondary to *CTSD* mutations presents with ataxia and retinitis pigmentosa. Steinfeld et al. described the first case of juvenile CLN10 disease in which the patient presented in early childhood with ataxia and vision changes [69]. Over the course of years, dementia, loss of speech, and retinal atrophy emerged. She was wheelchair-bound by 17 years of age and had significant intellectual disability. Hersheson et al. later described two consanguineous families with juvenile-onset symptoms secondary to homozygous *CTSD* mutations [80]. All affected individuals had ataxia, retinitis pigmentosa, and cognitive decline. In the first family, symptom onset was at 15 years of age for multiple family members, with ataxia as the presenting sign. In the second family, age of onset was 8 years. Sensory peripheral neuropathy and hypertrophic cardiomyopathy were also described in some individuals. On neuroimaging, cerebellar atrophy is a characteristic finding across congenital and juvenile ages at onset [80].

CLN11 Disease (*GRN*)

While heterozygous mutations in the progranulin gene (*GRN)* are a cause of frontotemporal dementia, homozygous loss-of-function mutations in *GRN* are a cause of adult-onset NCL. As seen in most childhood-onset NCLs, rapidly progressive vision loss is a key component of the disease phenotype in CLN11 disease, and epilepsy is variably present. The predominant movement disorder is mild to moderate ataxia, and myoclonus, palinopsia, and mild cognitive impairment are also present [81–83].

CLN12 Disease (*ATP13A2*)

Mutations in *ATP13A2* are typically associated with a form of juvenile Parkinson disease associated with dementia (Kufor–Rakeb syndrome) [84] or hereditary spastic paraplegia (SPG78) [85]. *ATP13A2* loss-of-function mutations have also been implicated in CLN12 disease [86]. Vacuolated lymphocytes may be seen in cases due to *ATP13A2* mutations as they are in CLN3 disease, with ultrastructural findings similar to those observed in other forms of NCL. Rigidity and akinesia are the predominant movement disorders in this form of NCL, with some also demonstrating resting tremor, which is uncommon in CLN3 disease, the other NCL typically manifesting parkinsonism. Transient response to levodopa, at times with the development of dyskinesias has been reported [86]. In addition, uncommon with the parkinsonism observed in CLN3 disease, coexisting myoclonus and ataxia have been seen.

CLN13 Disease (*CTSF*)

While type A Kufs disease (adult-onset NCL) has been attributed to CLN4 or CLN6 disease, more recently, type B Kufs disease has been associated with mutations in *CTSF*, which encodes cathepsin F, a lysosomal enzyme [23, 87]. In cases reported to date, symptom onset is in the third or fourth decade of life. Ataxia and tremor along with other cerebellar symptoms such as dysarthria are common. These symptoms are followed by the development of dementia, although in some cases, cognitive symptoms or seizures are the presenting sign [23, 87]. Additional involuntary movements described in isolated cases include segmental myoclonus and perioral dyskinesias that are not further specified [23, 87]. The epilepsy of CLN13 disease is less refractory than in other NCL forms. Vision loss has not been reported. MRI brain scans are non-specific but may demonstrate diffuse cerebral and cerebellar atrophy [88].

CLN14 Disease (*KCTD7*)

Mutations in *KCTD7* have previously been linked to progressive myoclonic epilepsy [89, 90]. CLN14 disease has been proposed [91], but has not been confirmed as an NCL. In addition to the progressive myoclonic epilepsy phenotype, there are patients reported with childhood onset of refractory epilepsy, developmental regression, non-epileptic myoclonus, ataxia, and vision loss, as typically seen in NCL disorders. Lysosomal storage, however, has been only variably present in tissue specimens [91, 92], raising questions around classification as an NCL disorder [14, 92, 93].

Treatment

Treatment approaches to movement disorders associated with an NCL are almost exclusively symptomatic and based on the specific movement disorder phenomenology. Little is known about whether movement disorders respond differently in different forms of NCL. There are some reports of response to movement disorder treatment in a small number of patients that will be reviewed here. With the recent emergence of enzyme-replacement therapy for CLN2 disease, there may be information forthcoming about how the movement disorders in that form of NCL are affected by this treatment. Similarly, with gene therapy in trials for CLN3 disease (ClinicalTrials.gov NCT03770572) and CLN6 disease (ClinicalTrials.gov NCT02725580) at the time of this publication, the landscape of movement disorders associated with those NCLs is undergoing rapid change.

Symptomatic Treatments

A comprehensive review of symptomatic movement disorder treatment is beyond the scope of this chapter; recent reviews are available [94, 95]. Although no systematic studies are available, the following case reports or small series contain information that may be helpful in guiding treatment decisions.

Parkinsonism

Parkinsonism is the most prevalent movement disorder in CLN3 disease and has also been reported in other forms. In CLN3 disease, there is good evidence for degeneration of the nigrostriatal dopamine neurons [96] and some evidence for reduction of D1, but not D2, receptor binding [44]. These observations in addition to the parkinsonian symptoms suggest that treatment with levodopa or a dopamine agonist may provide symptomatic benefit. In a study of 21 individuals with CLN3 disease, carbidopa/levodopa improved the parkinsonian syndrome in comparison to treatment with selegiline or no treatment. Selegiline-treated patients did not improve compared to controls [97]. However, a previous study of five patients with JNCL (genetically unconfirmed) treated with levodopa plus benserazide did not report improvements in walking or sitting down [98]. A report of drug-induced

dystonia in a patient with JNCL [99], and a separate report of neuroleptic malignant syndrome in a patient with CLN3 disease [100] following treatment with dopamine-blocking antipsychotic medication, also support the idea that dopamine deficiency occurs in this disorder and dopamine-blocking medications should be used with caution.

Two patients with CLN2 disease have been described with documented biopterin and dopamine deficiency [101, 102]. One had symptomatic improvement with carbidopa/levodopa treatment [102] and the other did not [101]. Reasons for the difference in response to treatment cannot be determined from the available information.

Dystonia

There is little published information about the treatment of dystonia in patients with any form of NCL. Trihexyphenidyl and baclofen are the mainstays of symptomatic treatment for dystonia in children, but it is not known to what extent dystonia responds to those treatments in the NCLs. There is reason to be cautious about the use of anticholinergic medications in patients with dementia as this may contribute to impaired cognition [103].

There is a report of dystonia treatment with pallidotomy, globus pallidus deep brain stimulation (DBS), or both in two sisters with CLN3 disease and progressive dystonia resulting in dystonic storm [41]. One of the sisters also had marked chorea that improved along with the dystonia following DBS. There is a single report of benefit from pallidal DBS for hemidystonia in a patient with genetically unconfirmed adult NCL [104].

Chorea

Symptomatic treatment of chorea is unsatisfying in many patients. Benzodiazepines, dopamine-receptor blockers, and dopamine-depleting medications are the most consistently effective, but in some disorders, antiseizure medications may be beneficial. There are no published reports to guide selection from among these medication classes in patients with NCLs. As noted above, there is a single report of improved chorea in a patient treated with pallidotomy followed by pallidal DBS [41].

Myoclonus

There is scant literature addressing the treatment of non-epileptic myoclonus in the NCLs. Many forms of NCL are associated with both epileptic and non-epileptic myoclonus, and it difficult to discern from reports in the literature whether reported improvements of myoclonus are due to improvement of epilepsy or of non-epileptic myoclonus. Non-epileptic myoclonus may respond to piracetam, levetiracetam, valproic acid, benzodiazepines, or other antiseizure medications. One report of a valproate-induced complex movement disorder with severe dystonia and myoclonus, in a child with advanced CLN2 disease, suggests that valproic acid derivatives should be used with caution in patients with that form of NCL [34].

Other Movement Disorders

There is insufficient literature to inform disease-specific selection of treatments for ataxia, tremor, tics, or stereotypy in the NCLs.

Disease-Modifying Treatments

With the advent of an approved disease-modifying enzyme-replacement therapy for CLN2 disease (TPP1 deficiency, cerliponase alfa) [105], there is hope that slowing disease progression with this therapy will result in less severe movement disorders or may even prevent them. However, as of this writing, there are no data available to address this question. Enzyme-replacement therapy does slow the loss of motor function, related to overall slowing of neurodegeneration and not to the prevention of specific movement disorders. Vision loss, when present, appears to persist despite enzyme-replacement therapy. Recent translation of antisense oligonucleotide therapy with improvement in myoclonic seizure activity in a child with CLN7 shows the promise of individualized, targeted therapy based on next generation genomics and gene editing [106].

At the time of this writing, several gene therapies are in development or in early-stage clinical trials for the NCLs. The reader is referred to the ClinicalTrials.gov website for the current status on these trials. It is hoped that disease modification will be the most effective approach to reducing or preventing disabling movement disorders in the NCLs. However, until that information becomes available, symptomatic treatment will have an important role in patients with an NCL that has an impairing movement disorder.

Conclusions

Movement disorders are a core part of the symptomatology in NCL disorders. Virtually every category of movement disorder has been described in the NCLs

across all of the known monogenic forms and across all age-based phenotypes. Within NCLs as a group, two main groups of movement disorders emerge as predominant: (1) ataxia with and without myoclonus, and (2) parkinsonism. Dystonia, stereotypies, chorea, and tremor can occur in NCL disorders, but manifest less consistently across genotypes and phenotypes.

Therapy for movement disorders in the NCLs is largely based on the specific movement disorder type and the severity. Mild movement disorders not causing impairment of function or comfort may not necessitate treatment. When treatment is indicated, the most effective treatment is more likely to depend on the movement disorder type than on the NCL type. As knowledge about the NCLs increases, disease-specific treatments may emerge as important strategies for treating or preventing movement disorders.

Key Points and Clinical Pearls

- The neuronal ceroid lipofuscinoses (NCLs) demonstrate genetic heterogeneity and phenotypic pleiotropy
- Movement disorders are a core feature of NCLs
- There are two groups of predominant movement disorders in NCL disorders:
  - Ataxia with or without myoclonus
  - Parkinsonism
- The treatment of movement disorders in NCLs is based on a symptomatic approach

Directions for Future Research

- Determine to what degree symptomatic treatment of movement disorders in the NCLs improves function and quality of life.
- Improve natural history knowledge of the various NCLs to enhance understanding of the associated movement disorders and disease courses.
- Determine whether or not central nervous system-directed enzyme-replacement therapy for CLN2 disease modifies the movement disorder associated with this disorder.
- Evaluate the impact of novel, disease-specific therapies on the development of movement disorders and overall disease course in specific NCLs.

References

1. Mole SE, Williams RE. Neuronal ceroid-lipofuscinoses. GeneReviews®. 2001;Oct 10 (updated Aug 1, 2013).
2. Nita DA, Mole SE, Minassian BA. Neuronal ceroid lipofuscinoses. Epileptic Disord. 2016;**18**(S2):73–88.
3. Mink JW, Augustine EF, Adams HR, Marshall FJ, Kwon JM. Classification and natural history of the neuronal ceroid lipofuscinoses. J Child Neurol. 2013;**28**(9):1101–5.
4. Mole SE, Cotman SL. Genetics of the neuronal ceroid lipofuscinoses (Batten disease). Biochim Biophys Acta. 2015;**1852**(10 Pt B):2237–41.
5. Santavuori P, Haltia M, Rapola J. Infantile type of so-called neuronal ceroid-lipofuscinosis. Dev Med Child Neurol. 1974;**16**(5):644–53.
6. Becker K, Goebel HH, Svennerholm L, Wendel U, Bremer HJ. Clinical, morphological, and biochemical investigations on a patient with an unusual form of neuronal ceroid-lipofuscinosis. Eur J Pediatr. 1979;**132**(3):197–206.
7. Das AK, Becerra CH, Yi W, et al. Molecular genetics of palmitoyl-protein thioesterase deficiency in the U.S. J Clin Invest. 1998;**102**(2):361–70.
8. Ramadan H, Al-Din AS, Ismail A, et al. Adult neuronal ceroid lipofuscinosis caused by deficiency in palmitoyl protein thioesterase 1. Neurology. 2007;**68**(5):387–8.
9. van Diggelen OP, Thobois S, Tilikete C, et al. Adult neuronal ceroid lipofuscinosis with palmitoyl-protein thioesterase deficiency: First adult-onset patients of a childhood disease. Ann Neurol. 2001;**50**(2):269–72.
10. Wisniewski KE, Connell F, Kaczmarski W, et al. Palmitoyl-protein thioesterase deficiency in a novel granular variant of LINCL. Pediatr Neurol. 1998;**18**(2):119–23.
11. Steinfeld R, Heim P, von Gregory H, et al. Late infantile neuronal ceroid lipofuscinosis: Quantitative description of the clinical course in patients with *CLN2* mutations. Am J Med Genet. 2002;**112**(4):347–54.
12. Ku CA, Hull S, Arno G, et al. Detailed clinical phenotype and molecular genetic findings in *CLN3*-associated isolated retinal degeneration. JAMA Ophthalmol. 2017;**135**(7):749–60.
13. Khan KN, El-Asrag ME, Ku CA, et al. Specific alleles of CLN7/MFSD8, a protein that localizes to photoreceptor synaptic terminals, cause a spectrum of nonsyndromic retinal dystrophy. Invest Ophthalmol Vis Sci. 2017;**58**(7):2906–14.
14. Mole SE, Anderson G, Band HA, et al. Clinical challenges and future therapeutic approaches for

neuronal ceroid lipofuscinosis. Lancet Neurol. 2019;**18** (1):107–16.

15. Berkovic SF, Staropoli JF, Carpenter S, et al. Diagnosis and misdiagnosis of adult neuronal ceroid lipofuscinosis (Kufs disease). Neurology. 2016;**87** (6):579–84.
16. Mahajnah M, Zelnik N. Phenotypic heterogeneity in consanguineous patients with a common *CLN8* mutation. Pediatr Neurol. 2012;**47**(4):303–5.
17. Cassim F, Houdayer E. Neurophysiology of myoclonus. Neurophysiol Clin. 2006; **36** (5-6): 281–91.
18. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science. 1990;**249**(4975):1436–8.
19. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 1990;**13** (7):281–5.
20. Schulz A, Kohlschutter A, Mink J, Simonati A, Williams R. NCL diseases: Clinical perspectives. Biochim Biophys Acta. 2013;**1832**(11):1801–6.
21. Vesa J, Hellsten E, Verkruyse LA, et al. Mutations in the palmitoyl protein thioesterase gene causing infantile neuronal ceroid lipofuscinosis. Nature. 1995;**376**(6541):584–7.
22. Lerner TJ, Boustany R-MN, Anderson JW, et al. Isolation of a novel gene underlying Batten disease, *CLN3*. Cell. 1995;**82**(6):949–57.
23. Smith KR, Dahl HH, Canafoglia L, et al. Cathepsin F mutations cause type B Kufs disease, an adult-onset neuronal ceroid lipofuscinosis. Hum Mol Genet. 2013;**22**(7):1417–23.
24. Vanhanen SL, Puranen J, Autti T, et al. Neuroradiological findings (MRS, MRI, SPECT) in infantile neuronal ceroid-lipofuscinosis (infantile CLN1) at different stages of the disease. Neuropediatrics. 2004;**35**(1):27–35.
25. Riikonen R, Vanhanen SL, Tyynela J, Santavuori P, Turpeinen U. CSF insulin-like growth factor-1 in infantile neuronal ceroid lipofuscinosis. Neurology. 2000;**54**(9):1828–32.
26. Levin SW, Baker EH, Zein WM, et al. Oral cysteamine bitartrate and N-acetylcysteine for patients with infantile neuronal ceroid lipofuscinosis: A pilot study. Lancet Neurol. 2014;**13**(8):777–87.
27. Confort-Gouny S, Chabrol B, Vion-Dury J, Mancini J, Cozzone PJ.MRI and localized proton MRS in early infantile form of neuronal ceroid-lipofuscinosis. Pediatr Neurol. 1993;**9**(1):57–60.
28. Metelitsina TI, Waggoner DJ, Grassi MA. Batten disease caused by a novel mutation in the *PPT1* gene. Retin Cases Brief Rep. 2016;**10**(3):211–3.
29. Nickel M, Schulz A, Kohlschütter A, et al. PP03.8 – 2898: Late language acquisition and unexplained epilepsy are indicators of easily detectable CLN2 disease. *Eur J Paediatr Neuro*. 2015;**19**:S38.
30. Nickel M, Simonati A, Jacoby D, et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. Lancet Child Adolesc Health. 2018;**2**(8):582–90.
31. Williams RE, Adams HR, Blohm M, et al. Management strategies for CLN2 disease. Pediatr Neurol. 2017;**69**:102–12.
32. Saini AG, Sankhyan N, Singhi P. Chorea in late-infantile neuronal ceroid lipofuscinosis: An atypical presentation. *Pediatr Neurol*. 2016;**60**:75–8.
33. Di Giacopo R, Cianetti L, Caputo V, et al. Protracted late infantile ceroid lipofuscinosis due to *TPP1* mutations: Clinical, molecular and biochemical characterization in three sibs. J Neurol Sci . 2015;**356**(1):65–71.
34. Johannsen J, Nickel M, Schulz A, Denecke J. Considering valproate as a risk factor for rapid exacerbation of complex movement disorder in progressed stages of late-infantile CLN2 disease. Neuropediatrics. 2016;**47**(3):194–6.
35. Sun Y, Almomani R, Breedveld GJ, et al. Autosomal recessive spinocerebellar ataxia 7 (SCAR7) is caused by variants in *TPP1*, the gene involved in classic late-infantile neuronal ceroid lipofuscinosis 2 disease (CLN2 disease). Hum Mutat. 2013;**34** (5):706–13.
36. Dy ME, Sims KB, Friedman J. TPP1 deficiency: Rare cause of isolated childhood-onset progressive ataxia. Neurology. 2015;**85**(14):1259–61.
37. Marshall FJ, de Blieck EA, Mink JW, et al. A clinical rating scale for Batten disease: Reliable and relevant for clinical trials. Neurology. 2005;**65**(2):275–9.
38. Cialone J, Adams H, Augustine EF, et al. Females experience a more severe disease course in Batten disease. J Inherit Metab Dis. 2012;**35**(3):549–55.
39. Ostergaard JR. Juvenile neuronal ceroid lipofuscinosis (Batten disease): Current insights. Degener Neurol Neuromuscul Dis. 2016;**6**:73–83.
40. Ostergaard JR, Rasmussen TB, Molgaard H. Cardiac involvement in juvenile neuronal ceroid lipofuscinosis (Batten disease). Neurology. 2011;**76**(14):1245–51.
41. Elkay M, Silver K, Penn RD, Dalvi A. Dystonic storm due to Batten's disease treated with pallidotomy and deep brain stimulation. Mov Disord. 2009;**24** (7):1048–53.
42. Hofman IL. Observations in institutionalized neuronal ceroid-lipofuscinosis patients with special reference to

involuntary movements. J Inherit Metab Dis. 1993;**16** (2):249–51.

43. Aberg L, Liewendahl K, Nikkinen P, et al. Decreased striatal dopamine transporter density in JNCL patients with parkinsonian symptoms. Neurology. 2000;**54** (5):1069–74.
44. Rinne JO, Ruottinen HM, Nagren K, Aberg LE, Santavuori P. Positron emission tomography shows reduced striatal dopamine D1 but not D2 receptors in juvenile neuronal ceroid lipofuscinosis. Neuropediatrics. 2002;**33**(3):138–41.
45. Boehme DH, Cottrell JC, Leonberg SC, Zeman W. A dominant form of neuronal ceroid-lipofuscinosis. Brain. 1971;**94**(4):745–60.
46. Ferrer I, Arbizu T, Pena J, Serra JP. A golgi and ultrastructural study of a dominant form of Kufs' disease. J Neurol. 1980;**222**(3):183–90.
47. Josephson SA, Schmidt RE, Millsap P, McManus DQ, Morris JC. Autosomal dominant Kufs' disease: A cause of early onset dementia. J Neurol Sci. 2001; **188** (1-2): 51–60.
48. Burneo JG, Arnold T, Palmer CA, et al. Adult-onset neuronal ceroid lipofuscinosis (Kufs disease) with autosomal dominant inheritance in Alabama. Epilepsia. 2003;**44**(6):841–6.
49. Simonati A, Williams RE, Nardocci N, et al. Phenotype and natural history of variant late infantile ceroid-lipofuscinosis 5. Dev Med Child Neurol. 2017;**59**(8):815–21.
50. Mancini C, Nassani S, Guo Y, et al. Adult-onset autosomal recessive ataxia associated with neuronal ceroid lipofuscinosis type 5 gene (*CLN5*) mutations. J Neurol. 2015;**262**(1):173–8.
51. Sharp JD, Wheeler RB, Lake BD, et al. Loci for classical and a variant late infantile neuronal ceroid lipofuscinosis map to chromosomes 11p15 and 15q21-23. Hum Mol Genet. 1997;**6**(4):591–5.
52. Berkovic SF, Oliver KL, Canafoglia L, et al. Kufs disease due to mutation of *CLN6*: Clinical, pathological and molecular genetic features. Brain. 2019;**142**(1):59–69.
53. Arsov T, Smith KR, Damiano J, et al. Kufs disease, the major adult form of neuronal ceroid lipofuscinosis, caused by mutations in *CLN6*. Am J Hum Genet. 2011;**88**(5):566–73.
54. Canafoglia L, Gilioli I, Invernizzi F, et al. Electroclinical spectrum of the neuronal ceroid lipofuscinoses associated with *CLN6* mutations. Neurology. 2015;**85**(4):316–24.
55. Siintola E, Topcu M, Kohlschutter A, et al. Two novel *CLN6* mutations in variant late-infantile neuronal ceroid lipofuscinosis patients of Turkish origin. Clin Genet. 2005;**68**(2):167–73.
56. Guerreiro R, Bras JT, Vieira M, et al. CLN6 disease caused by the same mutation originating in Pakistan has varying pathology. Eur J Paediatr Neurol. 2013;**17**(6):657–60.
57. Andrade DM, Paton T, Turnbull J, et al. Mutation of the *CLN6* gene in teenage-onset progressive myoclonus epilepsy. Pediatr Neurol. 2012;**47**(3):205–8.
58. Ozkara C, Gunduz A, Coskun T, et al. Long-term follow-up of two siblings with adult-onset neuronal ceroid lipofuscinosis, Kufs type A. Epileptic Disord. 2017;**19**(2):147–51.
59. Topcu M, Tan H, Yalnizoglu D, et al. Evaluation of 36 patients from Turkey with neuronal ceroid lipofuscinosis: Clinical, neurophysiological, neuroradiological and histopathologic studies. Turkish J Pediatr. 2004;**46**(1):1–10.
60. Siintola E, Topcu M, Aula N, et al. The novel neuronal ceroid lipofuscinosis gene *MFSD8* encodes a putative lysosomal transporter. Am J Hum Genet. 2007;**81** (1):136-46.
61. Mandel H, Cohen Katsanelson K, Khayat M, et al. Clinico-pathological manifestations of variant late infantile neuronal ceroid lipofuscinosis (vLINCL) caused by a novel mutation in *MFSD8* gene. Eur J Med Genet. 2014;**57**(11-12):607–12.
62. Craiu D, Dragostin O, Dica A, et al. Rett-like onset in late-infantile neuronal ceroid lipofuscinosis (CLN7) caused by compound heterozygous mutation in the *MFSD8* gene and review of the literature data on clinical onset signs. Eur J Paediatr Neuro. 2015;**19** (1):78–86.
63. Striano P, Specchio N, Biancheri R, et al. Clinical and electrophysiological features of epilepsy in Italian patients with CLN8 mutations. Epilepsy Behav. 2007;**10**(1):187–91.
64. Katata Y, Uematsu M, Sato H, et al. Novel missense mutation in *CLN8* in late infantile neuronal ceroid lipofuscinosis: The first report of a *CLN8* mutation in Japan. Brain Dev-JPN. 2016;**38**(3):341–5.
65. Reinhardt K, Grapp M, Schlachter K, et al. Novel *CLN8* mutations confirm the clinical and ethnic diversity of late infantile neuronal ceroid lipofuscinosis. Clin Genet. 2010;**77**(1):79–85.
66. Beesley C, Guerreiro RJ, Bras JT, et al. CLN8 disease caused by large genomic deletions. Mol Genet Genomic Med. 2017;**5**(1):85–91.
67. Gao Z, Xie H, Jiang Q, et al. Identification of two novel null variants in *CLN8* by targeted next-generation sequencing: First report of a Chinese patient with neuronal ceroid lipofuscinosis due to *CLN8* variants. BMC Med Genet. 2018;**19**(1):21.
68. Allen NM, O'hIci B, Anderson G, et al. Variant late-infantile neuronal ceroid lipofuscinosis due to

a novel heterozygous *CLN8* mutation and de novo 8p23.3 deletion. Clinical Genetics. 2012;**81** (6):602–4.

69. Steinfeld R, Reinhardt K, Schreiber K, et al. Cathepsin D deficiency is associated with a human neurodegenerative disorder. Am J Hum Genet. 2006;**78**(6):988–98.
70. Doccini S, Sartori S, Maeser S, et al. Early infantile neuronal ceroid lipofuscinosis (CLN10 disease) associated with a novel mutation in *CTSD*. J Neurol. 2016;**263**(5):1029–32.
71. Norman RM, Wood N. A congenital form of amaurotic family idiocy. J Neurol Psychiatry. 1941; **4** (3-4): 175–90.
72. Barohn RJ, Dowd DC, Kagan-Hallet KS. Congenital ceroid-lipofuscinosis. Pediatr Neurol. 1992;**8**(1):54–9.
73. Brown NJ, Corner BD, Dodgson MC. A second case in the same family of congenital familial cerebral lipoidosis resembling amaurotic family idiocy. Arch Dis Child. 1954;**29**(143):48–54.
74. Garborg I, Torvik A, Hals J, Tangsrud SE, Lindemann R. Congenital neuronal ceroid lipofuscinosis. A case report. Acta Pathol Microbiol Immunol Scand A. 1987;**95**(3):119–25.
75. Humphreys S, Lake BD, Scholtz CL. Congenital amaurotic idiocy: Pathological, histochemical, biochemical and ultrastructural study. Neuropathol Appl Neurobiol. 1985;**11**(6):475–84.
76. Sandbank U. Congenital amaurotic idiocy. Pathol Eur. 1968;**3**(2):226–9.
77. Fritchie K, Siintola E, Armao D, et al. Novel mutation and the first prenatal screening of cathepsin D deficiency (CLN10). Acta Neuropathol. 2009;**117** (2):201–8.
78. Varvagiannis K, Hanquinet S, Billieux MH, et al. Congenital neuronal ceroid lipofuscinosis with a novel *CTSD* gene mutation: A rare cause of neonatal-onset neurodegenerative disorder. Neuropediatrics. 2018;**49** (2):150–3.
79. Siintola E, Partanen S, Stromme P, et al. Cathepsin D deficiency underlies congenital human neuronal ceroid-lipofuscinosis. Brain. 2006;**129** (Pt 6):1438–45.
80. Hersheson J, Burke D, Clayton R, et al. Cathepsin D deficiency causes juvenile-onset ataxia and distinctive muscle pathology. Neurology. 2014;**83** (20):1873–5.
81. Canafoglia L, Morbin M, Scaioli V, et al. Recurrent generalized seizures, visual loss, and palinopsia as phenotypic features of neuronal ceroid lipofuscinosis due to progranulin gene mutation. Epilepsia. 2014;**55** (6):e56–9.
82. Almeida MR, Macario MC, Ramos L, et al. Portuguese family with the co-occurrence of frontotemporal lobar degeneration and neuronal ceroid lipofuscinosis phenotypes due to progranulin gene mutation. Neurobiol Aging. 2016;**41**:200.e1–5.
83. Smith Katherine R, Damiano J, Franceschetti S, et al. Strikingly different clinicopathological phenotypes determined by progranulin-mutation dosage. Am J Hum Genet . 2012;**90**(6):1102-7.
84. Ramirez A, Heimbach A, Grundemann J, et al. Hereditary parkinsonism with dementia is caused by mutations in *ATP13A2*, encoding a lysosomal type 5 P-type ATPase. Nat Genet. 2006;**38** (10):1184–91.
85. Estrada-Cuzcano A, Martin S, Chamova T, et al. Loss-of-function mutations in the *ATP13A2/PARK9* gene cause complicated hereditary spastic paraplegia (SPG78). Brain. 2017;**140**(2):287–305.
86. Bras J, Verloes A, Schneider SA, Mole SE, Guerreiro RJ. Mutation of the parkinsonism gene *ATP13A2* causes neuronal ceroid-lipofuscinosis. Hum Mol Genet. 2012;**21**(12):2646–50.
87. Di Fabio R, Moro F, Pestillo L, et al. Pseudo-dominant inheritance of a novel *CTSF* mutation associated with type B Kufs disease. Neurology. 2014;**83**(19):1769–70.
88. Di Fabio R, Colonnese C, Santorelli FM, Pestillo L, Pierelli F. Brain imaging in Kufs disease type B: Case reports. BMC Neurol. 2015;**15**:102.
89. Van Bogaert P, Azizieh R, Desir J, et al. Mutation of a potassium channel-related gene in progressive myoclonic epilepsy. Ann Neurol. 2007;**61**(6):579–86.
90. Farhan SM, Murphy LM, Robinson JF, et al. Linkage analysis and exome sequencing identify a novel mutation in *KCTD7* in patients with progressive myoclonus epilepsy with ataxia. Epilepsia. 2014;**55**(9): e106–11.
91. Staropoli JF, Karaa A, Lim ET, et al. A homozygous mutation in *KCTD7* links neuronal ceroid lipofuscinosis to the ubiquitin-proteasome system. Am J Hum Genet. 2012;**91**(1):202–8.
92. Mastrangelo M, Sartori S, Simonati A, et al. Progressive myoclonus epilepsy and ceroidolipofuscinosis 14: The multifaceted phenotypic spectrum of *KCTD7*-related disorders. Eur J Med Genet. 2019;**62**(12):103591. doi:10.1016/j.
93. Metz KA, Teng X, Coppens I, et al. KCTD7 deficiency defines a distinct neurodegenerative disorder with a conserved autophagy-lysosome defect. Ann Neurol. 2018;**84**(5):766-80.
94. Koy A, Lin JP, Sanger TD, et al. Advances in management of movement disorders in children. Lancet Neurol. 2016;**15**(7):719–35.

95. Singer HS, Mink JW, Glibert DL, Jankovic J. Movement Disorders in Childhood, 2nd edn. Philadelphia, PA: Academic Press; 2015.
96. Åberg L, Liewendahl K, Nikkinen P, et al. Decreased striatal dopamine transporter density in JNCL patients with parkinsonian symptoms. Neurology. 2000;**54**(5):1069-74.
97. Åberg LE, Rinne JO, Rajantie I, Santavuori P. A favorable response to anitparkinsonian treatment in juvenile neuronal ceroid lipofucinosis. Neurology. 2001;**56**(9):1236-9.
98. Zweije-Hofman IL, van der Zee HJ, van Nieuwenhuizen O. Anti-parkinson drugs in the Batten–Spielmeyer–Vogt syndrome: A pilot trial. Clin Neurol Neurosurg. 1982;**84**(2):101–5.
99. Gospe SM, Jr., Jankovic J. Drug-induced dystonia in neuronal ceroid-lipofuscinosis. Pediatr Neurol. 1986;**2**(4):236–7.
100. Vercammen L, Buyse GM, Proost JE, Van Hove JL. Neuroleptic malignant syndrome in juvenile neuronal ceroid lipofuscinosis associated with low-dose risperidone therapy. J Inherit Metab Dis. 2003;**26**(6):611–2.
101. Barisic N, Logan P, Pikija S, Skarpa D, Blau N. *R208X* mutation in *CLN2* gene associated with reduced cerebrospinal fluid pterins in a girl with classic late infantile neuronal ceroid lipofuscinosis. Croat Med J. 2003;**44**(4):489–93.
102. Le NM, Parikh S. Late infantile neuronal ceroid lipofuscinosis and dopamine deficiency. J Child Neurol. 2012;**27**(2):234–7.
103. Cialone J, Blackburn J, Mink J. Trihexyphenidyl has cognitive side effects in children with DYT1 dystonia (IN10-2.003). Neurology. 2012;**78**(1Supplement): P02.177.
104. Hasegawa H, Alkufri F, Munro N, et al. GPi deep brain stimulation for palliation of hemidystonia and hemibody jerking in a patient with suspected adult onset neuronal ceroid lipofuscinosis. J Neurol Sci. 2016;**362**:228–9.
105. Schulz A, Ajayi T, Specchio N, et al. Study of intraventricular cerliponase alfa for CLN2 disease. N Engl J Med. 2018;**378**(20):1898–907.
106. Kim J, Hu C, Moufawad El Achkar C, et al. Patient-customized oligonucleotide therapy for a rare genetic disease. N Engl J Med 2019;**381**:1644–52.

Chapter 16

Syndromes of Neurodegeneration with Brain Iron Accumulation

Susanne A. Schneider, Carmen Espinós, and Belén Pérez-Dueñas

Introduction to NBIA Disorders

The syndromes of neurodegeneration with brain iron accumulation (NBIA) are a group of disorders defined by progressive hypo- and/or hyperkinetic movement disorders and excessive iron deposition in the brain [1]. Iron predominantly accumulates in (and around) the basal ganglia, mainly the globus pallidus, and can be detected as hypointensity on T2-weighted images due to shortening effects on relaxation time. Brain pathology demonstrates degeneration of neurons and astrocytes. Eosinophilic, roundish swellings containing degenerate organelles (i.e. spheroid bodies) are also common in many subtypes of NBIA. Several genes associated with NBIA disorders have been identified (including *PANK2*, *PLA2G6*, *WDR45*, *C19orf12*, *FA2H*, *ATP13A2*, *COASY*, *FTL1*, *CP*, and *DCAF17*). These genes and their proteins play a role in mitochondrial function, lipid metabolism, and autophagy. The terminology of the syndromes associated with these genes follows a pattern in that the first word(s) (or letters in the abbreviated name) refer to the molecular substrate and the last two words read "associated neurodegeneration," e.g. pantothenate kinase-associated neurodegeneration (PKAN), *PLA2G6*-associated neurodegeneration (PLAN), and so on. The recognized clinical spectrum (which is often age-dependent) and molecular understanding continue to evolve and the first controlled clinical treatment trials are underway. Here we present the main clinical features including useful clinical rating scales, genetic mechanisms, biomarkers, pathology, and therapeutic approaches of the most prevalent forms of NBIA (Table 16.1).

Clinical Phenotypes

Common Clinical Features of NBIA Syndromes

NBIA disorders are complex multisystem disorders, making the diagnosis challenging. Symptoms may be non-specific in early disease phases and consist, for example, of global development delay or delayed motor development, prior to onset of more specific signs.

Pyramidal and extrapyramidal features are core symptoms. Movement disorders manifest mainly with dystonia and parkinsonian signs (rigidity and loss of postural reflexes), but also chorea. Furthermore, cognitive decline is a core feature of these disorders. Psychiatric features such as obsessive–compulsive disorder and behavioral disturbances may be present. Autonomic involvement is also common. Notably, for some of the disorders an age-dependent phenotype has been recognized (see below).

The disease course is invariably progressive and patients lose the ability to walk usually within 10–15 years after onset. Premature death usually occurs from secondary complications or due to episodes of status dystonicus.

In most forms, NBIA disorders have an early onset and their inheritance is autosomal-recessive. Exceptions (e.g. neuroferritinopathy and aceruloplasminemia) are outlined below.

Specific Features of NBIA Syndromes

Pantothenate Kinase-Associated Neurodegeneration Caused by *PANK2* Mutations (NBIA type 1)

The most common among the NBIA disorders is pantothenate kinase-associated neurodegeneration (PKAN), due to mutations in the *PANK2* gene. The worldwide prevalence has been estimated at 1 in 1,000,000. The **classic** presentation is relatively homogeneous, with onset usually before age 6 years of a gait disorder due to dystonia and rigidity of legs [2, 3]. Oromandibular dystonia is often prominent. Pigmentary retinal degeneration, often detected by electroretinography, is almost invariably present in classic PKAN [4]. There is a well-known correlation

Table 16.1 Overview of NBIA syndromes and genes

Condition (Acronym)	Synonym	Gene	Chromosomal position	LB pathology	Childhood-onset variant		Late-onset variant	
					Age of onset	Clinical presentation	Age of onset	Clinical presentation
PKAN	NBIA1	*PANK2*	20p13	No	Early childhood, around age 3 years	Typical PKAN	Teens or early adulthood	Atypical PKAN
PLAN	NBIA2, PARK14	*PLA2G6*	22q12	√	Infancy	Infantile neuroaxonal dystrophy	Teens or early adulthood	Dystonia parkinsonism
FAHN	SPG35	*FA2H*	16q23	Not known	Childhood	Leukodystrophy, hereditary spastic paraplegia		
MPAN	–	*C19orf12*	19q12	√	11 (range, 4–30 years)	Pyramidal extrapyramidal syndrome		
Kufor–Rakeb syndrome	PARK9	*ATP13A2*	1p36	(√)	Childhood-teenage	Parkinsonism, pyramidal-tract signs, eye movement disorder		
BPAN	SENDA syndrome	*WDR45*	Xp11.23	Not known	Childhood	Encephalopathy with psychomotor regression, then static	Then: 20s to 30s	Sudden onset progressive dystonia parkinsonism
Aceruloplasminemia	–	*CP*	3q23	No	–	–	50s (range, 16–70 years)	Extrapyramidal, diabetes, dementia
Neuroferritinopathy	–	*FTL1*	19q13	No	–	–	40s	Chorea, dystonia, dementia
Idiopathic late-onset cases	–	Probably heterogeneous	Probably heterogeneous	Heterogeneous	–	–	Heterogeneous	Parkinsonism, in some resembling idiopathic PD

Abbreviations: BPAN, beta-propeller protein-associated neurodegeneration; CP, ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FTL1 ferritin light chain 1; MPAN, mitochondrial membrane-associated neurodegeneration; PANK2, pantothenate kinase 2; PKAN, pantothenate kinase-associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, *PLA2G6*-associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SPG, spastic paraplegia; √ = present.

between the age of onset and the rate of disease progression. Onset may, however, also occur late, i.e. in early adulthood, as **atypical late-onset PKAN**. Here, cognitive decline and psychiatric features are often the leading symptoms whereas motor involvement tends to be less severe. Movement disorders often present as unilateral dystonic tremor or focal arm dystonia [2, 5–11].

PLA2G6-Associated Neurodegeneration Caused by *PLA2G6* Mutations (NBIA Type 2)

The second core NBIA syndrome is *PLA2G6*-associated neurodegeneration (PLAN) due to *PLA2G6* gene mutations (NBIA type 2). The **classic** form begins early, between 6 months and 2 years of age as infantile neuroaxonal dystrophy (INAD). Progressive motor deterioration often leads to spastic or hypotonic tetraparesis with marked truncal hypotonia. Optic atrophy causes vision impairment. Seizures may occur at later stages of the disease, and dystonia has been reported in patients with long disease duration [12]. Denervation on EMG and fast rhythms on EEG are the typical electrophysiological findings that may facilitate early diagnosis [13]. In patients with later disease onset the phenotype may be **atypical** (atypical neuroaxonal dystrophy) and includes dystonia–parkinsonism combined with pyramidal signs, cerebellar ataxia, eye movement abnormalities, cognitive decline, and psychiatric features. Parkinsonism is characterized by the presence of tremor, i.e. a typical pill-rolling resting tremor, rigidity, and severe bradykinesia with a good response to levodopa. The latter may be in line with the finding of Lewy body pathology [14–16]. Early development of dyskinesias occurs. Development of Parkinson disease in siblings with heterozygous *PLA2G6* mutations has been reported.

Beta-Propeller Protein-Associated Neurodegeneration Caused by *WDR45* Mutations

Mutations in *WDR45* cause beta-propeller protein-associated neurodegeneration (BPAN). The clinical presentation was initially summarized under the term "static encephalopathy (of childhood) with neurodegeneration in adulthood" (SENDA syndrome) [17–19]. Onset is in early childhood, with developmental delay and intellectual disability, which remain relatively static until adulthood. In early adulthood, affected individuals usually develop sudden-onset progressive dystonia–parkinsonism and dementia. The clinical spectrum further includes seizures, ataxia, and behavioral problems that are often similar to autism spectrum disorder. Seizure types are diverse and include focal and generalized seizures (absence, tonic, atonic, tonic–clonic, and myoclonic), infantile spasms, and epileptic encephalopathies consistent with Lennox Gastaut syndrome. Overall, seizures tend to resolve or become less prominent with age, whereas cognitive decline and movement disorders (progressive parkinsonism and dystonia) emerge as characteristic findings. Additional features include eye movement abnormalities, sleep disorders, frontal release signs, and dysautonomia.

Mitochondrial Membrane Protein-Associated Neurodegeneration Caused by *C19orf12* Mutations

Mutations in *C19orf12* at chromosome 19q12 cause mitochondrial membrane protein-associated neurodegeneration (MPAN) [20]. Due to a founder effect, MPAN is more common in the Polish community. Onset is in childhood to early adulthood (age range 4–30 years), with a mean of 11 years. Spastic para- or tetraparesis with muscle atrophy are typical for MPAN. Dysarthria, parkinsonism, and dystonia are very common but not present in all cases. Optic atrophy, cognitive decline, and psychiatric symptoms may occur [20–27]. Notably, a mild phenotype resembling idiopathic Parkinson disease has been reported.

Other NBIA Genes (*FA2H*, *ATP13A2*, *COASY*, *FTL1*, *CP*, *DCAF17*, *SCP2*, and *GTPBP2*)

FA2H mutations were recently identified as another cause of NBIA, **FAHN** [28]. The clinical spectrum overlaps with leukodystrophies and the hereditary spastic paraplegias. The clinical phenotype of FAHN is characterized by childhood-onset gait impairment, spastic quadriparesis, severe ataxia, and dystonia. Seizures and divergent strabismus may also be present and overlap with the clinical features of PLAN.

Mutations in *ATP13A2* located on chromosome 1p cause **Kufor–Rakeb syndrome**. The clinical phenotype comprises levodopa-sensitive parkinsonism, pyramidal-tract signs, eye movement abnormalities with incomplete supranuclear upgaze palsy, facial-faucial (i.e. tonsillar)-finger mini-myoclonus, autonomic dysfunction, psychiatric features, and dementia. Disease onset is usually in adolescence [29–31].

COASY-associated neurodegeneration (**CoPAN**) due to mutations in the coenzyme A (CoA) synthase (*COASY*) gene is a form of NBIA metabolically closely related to PKAN [32]. It also presents with early-onset

gait difficulty and learning disabilities, followed in puberty by bradykinesia, generalized dystonia, and spastic–dystonic tetraparesis with distal areflexia due to motor axonal neuropathy. Notably, there is no retinopathy, in contrast to PKAN and some of the other NBIA syndromes.

Neuroferritinopathy due to *FTL1* gene mutations is often thought of as one of the Huntington-like disorders because of adult-onset chorea, psychiatric features, and cognitive decline. Inheritance is autosomal-dominant. However, other features such as orolingual–mandibular dyskinesia, blepharospasm, cerebellar ataxia, and parkinsonism (even at onset) may be present. As in Huntington disease, pyramidal involvement is usually absent.

Aceruloplasminemia also presents in adulthood. Core neurological features are cognitive impairment, cerebellar ataxia, and craniofacial dyskinesia. Notably, a recent case series involving 55 cases revealed that diabetes was the first symptom in almost 70% of patients, manifesting at a median age of 38 years, often accompanied by microcytic or normocytic anemia. The combination preceded neurological symptoms in almost 90% of the neurologically symptomatic patients by more than ten years [33]. Ophthalmological examination often reveals peripheral retinal degeneration secondary to iron accumulation and photoreceptor cell loss. Systemic iron accumulation also leads to increased liver iron content (without cirrhosis).

Mutations in the *DCAF17* gene cause **Woodhouse–Sakati syndrome**, a rare autosomal-recessive multisystem neuroendocrine disorder characterized by hypogonadism, childhood-onset hair thinning that often progresses to alopecia totalis, diabetes mellitus, deafness, cognitive decline, and extrapyramidal features. Seizures, polyneuropathy, thyroid dysfunction, keratoconus, and syndactyly of hands or feet may also be present [34]. Some 30 families have been described, mostly from Middle Eastern countries. Insulin-like growth factor 1 is usually low; ECG may be abnormal, albeit patients are usually asymptomatic.

Bi-allelic **mutations in *SCP2***, encoding the peroxisomal enzyme sterol carrier protein x (SCPx), have recently been described to cause NBIA in two unrelated patients [35, 36] The first patient presented with torticollis and dystonic head tremor, mild cerebellar signs, hyposmia, and azoospermia with motor neuropathy, with onset in late childhood. The other presented with adult-onset spinocerebellar ataxia and deafness, with brain MRI characteristic of NBIA, in the absence of movement disorders or myopathy. Abnormal pristanic acid and phytanic acid levels may be a clue. Dietary therapy, similar to the diet recommended for Refsum disease, led to improvement.

Finally, there is a recent report of ***GTPBP2* mutations associated with NBIA** [37] in a consanguineous family with three affected children. All had delayed early developmental milestones with moderate intellectual disability. Upon presentation at ages 34, 30, and 29 years, respectively, there was dystonia, mild to moderate ataxia, and autonomic dysfunction including skin thickening, mottling, and loss of hair on the legs. Investigations demonstrated chronic motor neuronopathy and abnormal electroretinography.

Clinical Rating Scales

International validated rating scales, mainly for dystonia and parkinsonism, have been used in case series of PKAN patients in an attempt to capture clinical improvement after deep brain stimulation or iron chelating therapy. The scales used in these studies were the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS), Unified Parkinson Disease Rating Scale (UPDRS), International Cooperative Ataxia Rating Scale (ICARS), and Unified Dystonia Rating Scale (UDRS). However, PKAN patients show an overlapping dystonia–parkinsonism syndrome that cannot be easily differentiated, as well as other motor abnormalities (i.e. chorea, pyramidal signs, or abnormal ocular movements) and neuropsychiatric disturbances (cognitive decline, behavioral abnormalities) that are not always recorded in the previously mentioned scales. As a consequence, there is a lack of specific validated instruments to measure the functional impairment and the rate of disease progression in a multidimensional and comparable manner, and we do not know yet which symptoms contribute the most to functional disability in PKAN.

A pilot study for a disease-specific clinical rating scale – the PKAN diseases rating scale (PKAN-DRS) – was recently developed for patients with PKAN [38]. The scale included 34 items (maximal score, 135) encompassing six subscales for cognition, behavior, disability, parkinsonism, dystonia, and other neurological signs. Forty-seven patients aged 6–77 years were examined with the PKAN-DRS. Dystonia and parkinsonism, core features of PKAN, were present in

all cases and had a significant impact on the patients' ability to perform activities of daily living. Disability, dystonia, and other neurological signs were more severe in patients with earlier onset of disease, whereas parkinsonian features were more common in older patients with longer disease duration.

The disability questionnaire of the scale also showed that dysarthria and dysphagia impaired or prevented speech and swallowing in most patients, and half of PKAN patients either could not walk at all or needed a walking device or assistance. The disease also showed a strong impact on school attendance and academic abilities in childhood, and later prevented patients from engaging in employment in adulthood. Finally, the analysis of the properties of the scale itself demonstrated that the PKAN-DRS is a reliable and valid instrument for the assessment of pediatric and adult patients with PKAN.

More recently, the PKAN-activity of daily living (PKAN-ADL) rating scale has been developed as a novel patient-reported clinical outcomes measure. It assesses 12 domains of ADLs using single-item questions about difficulty with speech, drooling, swallowing, writing, eating tasks, dressing, personal-hygiene tasks, turning or changing position in bed, sitting, falling, walking, and discomfort or pain [39]. The PKAN-ADL scale was developed as the primary efficacy outcome in the recently completed phase 3 trial, randomized, double-blinded, placebo-controlled pivotal trial of fosmetpantotenate in adult and pediatric patients with PKAN (NCT03041116). For other forms of NBIA, no clinical scales capable of monitoring disease progression have been developed.

Neuroimaging

MRI Techniques

Brain MRI imaging is often the key diagnostic test toward a diagnosis of an NBIA disorder [40]. T2*-weighted and susceptibility-weighted imaging (SWI) images are particularly sensitive to detect iron and confirm the distribution of iron on histological studies with the presence of both antiferromagnetic iron (ferritin) and ferrimagnetic iron.

Iron accumulation characteristically affects the globus pallidus. It may also extend to adjacent areas, which may be somewhat helpful during the work-up. However, it may not be possible to come to a final diagnosis based on imaging patterns alone as there is radiological overlap and radiological variability. Furthermore, the development of MRI findings in NBIA patients appears to be a dynamic process [3, 41]; imaging abnormalities may precede the development of clinical signs (i.e. in asymptomatic carriers of homozygous mutations), while in others iron may be absent in early disease stages or may alter over time. Thus, if the initial MRI is unremarkable, repeated MRI may be useful. Furthermore, the areas affected by iron deposition do not necessarily correlate with the clinical syndrome. Nevertheless, for some NBIA subforms, distinct imaging patterns have been recognized.

Specific MRI Patterns of NBIA Genes

Imaging Findings in PKAN

MRI [42, 43] with appropriate iron sensitive T2*-weighted or SWI sequences detects the characteristic "eye of the tiger" sign, corresponding to a hyperintensity surrounded by an hypointense rim. The latter is produced by iron accumulation in the anterior-medial part of the globus pallidus, sometimes extending into the knee of the internal capsule, subthalamic nucleus, and substantia nigra [41, 44]. Additional calcifications in the basal ganglia have been described in some cases. As mentioned above, the development of the MRI alterations may be dynamic, in some preceding the development of clinical signs, or it may rarely be absent despite clinical signs in others [6, 41, 45, 46].

Using diffusion tensor imaging, increased fractional anisotropy along with abnormal mean diffusivity was demonstrated in the globus pallidus and substantia nigra of PKAN patients, probably due to iron deposits disturbing the local magnetic field [41, 47]. Proton MRS is not consistent but sometimes shows markedly decreased N-acetylaspartate in the globus pallidus, reflecting neuronal damage. Dopamine transporter single-photon emission CT imaging, a measure of striatal dopamine function, is generally normal in PKAN, although abnormal findings have been reported in line with the clinical experience that PKAN may manifest as parkinsonism. Cardiac ^{123}I-meta-iodobenzylguanidine imaging, which is used to assess postganglionic neuronal function of the sympathetic nervous system, was also normal in PKAN, in contrast to Parkinson disease and other Lewy body disorders, where uptake is typically reduced. Transcranial sonography demonstrates bilateral hyperechogenicity in the substantia nigra

and lenticular nucleus. It was thus suggested that transcranial sonography may be used as an inexpensive and simple screening method for the diagnosis of NBIA disorders.

Imaging Findings in PLAN

Neuroimaging in the *PLA2G6*-associated form (PLAN, NBIA2) shows cerebellar atrophy occurring in the early stages of INAD, but this was absent in late-onset disease. Although half of INAD patients may lack signs of iron accumulation early in the disease course [13], they usually develop globus pallidus hypointensities reflecting iron as the disease progresses [12]. Notably, in contrast to the pattern seen in PKAN there is no central hyperintensity. Additional iron deposits in the substantia nigra may be present [14]. Contrary to PKAN, iron accumulation is not a universal feature of PLAN. Late-onset cases may lack signs of iron accumulation and MRI may even be completely normal. Others may show cortical atrophy or white matter changes. Thus, not all forms of *PLA2G6*-related neurodegeneration fall into the group of NBIA disorders but there is neuroradiological variability.

Imaging Findings in BPAN (*WDR45*-Associated NBIA)

Imaging features highly characteristic of BPAN are (a) iron deposition is more marked in the substantia nigra than in the globus pallidus in T2-weighted images, and (b) the hypointensity of the substantia nigra is surrounded by a halo of hyperintensity in T1-weighted images [17, 48]. Furthermore, cerebral and milder cerebellar atrophy may be seen.

Imaging Findings in MPAN (*C19orf12*-Associated NBIA)

In MPAN, iron deposition extends beyond the pallidal region involving the substantia nigra. Hyperintense streaking of the medial medullary lamina between the globus pallidus interna and externa (which may resemble the eye of the tiger sign) may be present in 20% of patients. Generalized brain atrophy or cerebellar atrophy may be present. Transcranial sonography in MPAN patients demonstrates bilateral hyperechogenicity of the lenticular nucleus in the absence of nigral abnormalities.

Imaging Findings in Other NBIA forms (*FA2H*, *ATP13A2*, *COASY*, *FTL1*, *CP*, and *DCAF17*)

In **FAHN**, MRI features include progressive leukoencephalopathy with cortical, cerebellar, and brainstem atrophy – in addition to pallidal iron accumulation. Not all patients with FAHN, however, show iron accumulation. Corpus callosum thinning may be a diagnostic clue.

Brain imaging in patients with **Kufor–Rakeb syndrome** may show diffuse moderate generalized atrophy, with iron accumulation affecting the putamen and sometimes the caudate.

Brain imaging in **CoPAN** revealed bilateral hyperintensity and swelling of the caudate nucleus, putamen, and thalamus. In addition, a thin corpus callosum and frontotemporal and parietal white matter changes have been described.

Hypointensities are more widespread in **neuroferritinopathy.** Here, iron deposition extends from the globus pallidus to the nigra, cortex, and other nuclei of the basal ganglia. In addition, cavitations depicted as low T1 and high T2 signals, sometimes surrounded by a rim of T2 hypointensity, are found. Scans may also show generalized cortical and, in some cases, cerebellar atrophy. Furthermore, pencil lining, reflecting pathological iron deposition in the periphery of the cortex and other gray matter structures may be a clue toward the diagnosis of neuroferritinopathy. Finally, imaging changes may also be present in asymptomatic gene mutation carriers.

Iron also accumulates widely in **aceruloplasminemia**, affecting the caudate nucleus, putamen and pallidum, and thalamus, as well as the red nucleus and dentate. Cerebellar atrophy may also be seen.

In **Woodhouse–Sakati syndrome**, MRI reveals variable abnormalities in periventricular white matter. In addition, iron deposition in the globus pallidus may, rarely, be present.

In **SCP2-associated neurodegeneration**, MRI brain showed bilateral hyperintense signals in the thalamus, butterfly-like lesions in the pons, and lesions in the occipital region, without gadolinium enhancement, in one patient. There was no iron in this case. However, the second patient showed mineral deposition in the basal ganglia on SWI sequences [35, 36].

In ***GTPBP2*–associated neurodegeneration**, brain MRI shows atrophy of the cerebellar vermis. SWI demonstrates abnormal signal (hypointensity) in the globus pallidus and substantia nigra suggestive of abnormal iron deposition [37].

Differential Diagnosis

The clinical phenotype of NBIA syndromes is usually complex, involving numerous systems (extrapyramidal, pyramidal tract, cortical, cerebellum). Algorhithmic thinking may help when evaluating these patients

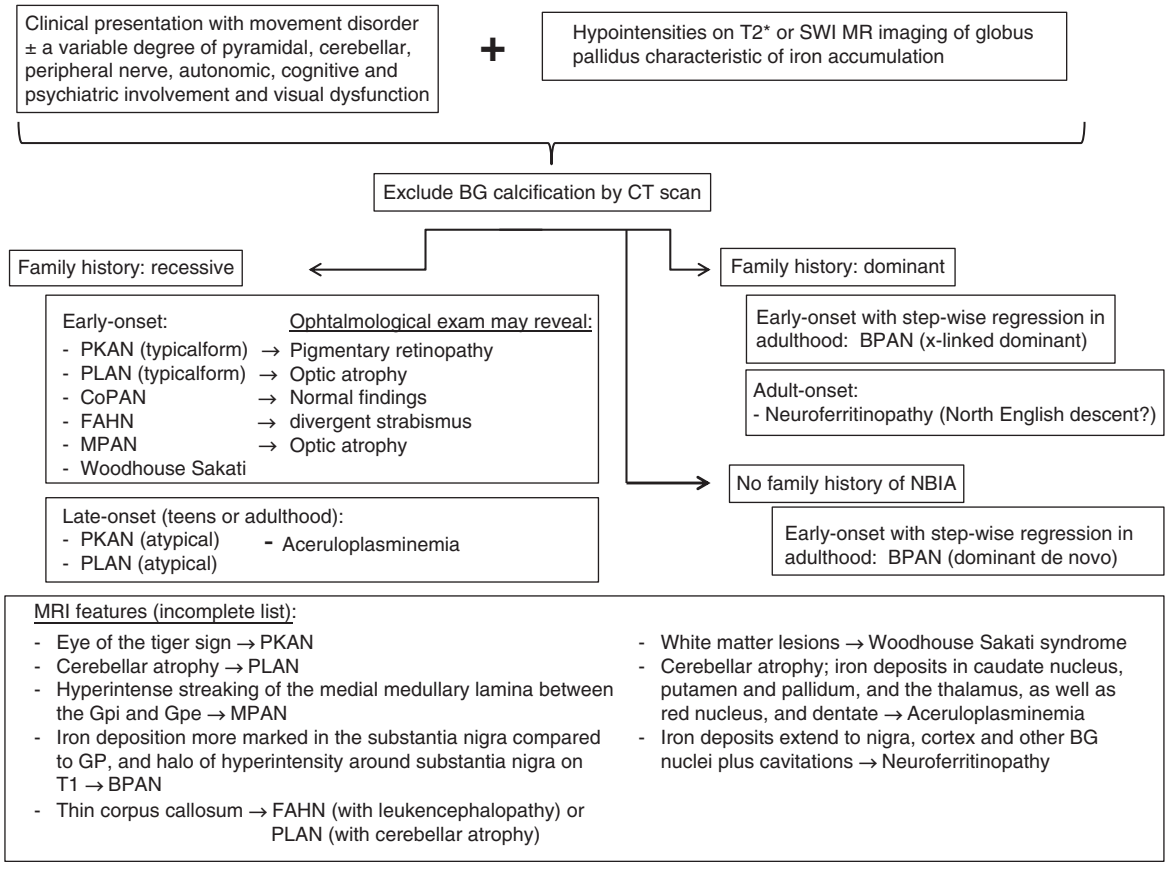

Figure 16.1 NBIA syndromes – an algorithm for diagnosis.Adapted from Schneider, 2016 [49].

(Figure 16.1). However, the differential diagnosis is broad, including various other inborn errors of metabolism, e.g. lysosomal storage diseases, hereditary spastic paraplegias, and other forms of dystonia–parkinsonism [50]. Radiologically, iron deposition may also be found in other non-NBIA disorders, including Parkinson disease (mainly affecting the substantia nigra) and atypical parkinsonian disorders, Friedreich ataxia, and multiple sclerosis [51]. This list continues to expand with improved high-resolution imaging (i.e. 7-Tesla MRI). On the other hand, the absence of iron in early disease phases may lead to false diagnoses (i.e. recessive ataxia in PLAN) or diagnostic delay. Sequential brain MRI may uncover NBIA syndromes and facilitate the diagnostic approach.

Genetics

Ten NBIA genes are accepted (*PANK2, PLA2G6*, *C19orf12*, *WDR45*, *FA2H*, *ATP13A2*, *FTL1*, *CP*, *DCAF17*, and *COASY*) and, more recently, two additional genes have been taken into account, *SCP2* and *GTBP2* [52, 53]. However, in a substantial number of patients, the disease-causing mutation remains elusive, suggesting that further NBIA genes remain to be characterized.

NBIA Genes

The most common condition is PKAN, which ranges from 35% to 50%, followed by PLAN, with approximately 20% of patients. PKAN is caused by mutations in the *PANK2* gene (OMIM 606157) transmitted in an autosomal-recessive fashion. Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP) syndrome is allelic with PKAN, although only a few cases are known. To date, 166 different mutations linked to PKAN have been reported, which reveals a high allelic heterogeneity.

However, in certain populations, some mutations are relatively prevalent due to founder effects: c.1142_1144delGAG in the Netherlands, c.680A>G (p.Tyr227Cys) in the Dominican Republic; and the c.1583C>T (p.Thr528Met) in the Gypsy population of the Iberian Peninsula. PLAN, also an autosomal-recessive entity, is due to mutations in *PLA2G6* (OMIM 603604). This form encompasses a continuum of three different and overlapping phenotypes: classic INAD, atypical neuroaxonal dystrophy (ANAD), and *PLA2G6*-related dystonia–parkinsonism. Recently, two siblings, compound heterozygotes for *PLA2G6* mutations, showed a complex hereditary spastic paraplegia with optic atrophy, expanding the *PLA2G6*-associated phenotypic spectrum. So far, 153 distinct clinical variants are known, with no recurrent mutation. It is striking that three PLAN patients have been published in whom the disease is caused by a *PLA2G6* change together with a partial uniparental disomy affecting chromosome 22.

These types are followed by MPAN that accounts for 6–10% and BPAN that occurs in and 1–2% of cases, although an increasing number affected with the latter have been identified in recent years. Mutations in the *C19orf12* gene (OMIM 614297) lead to MPAN, an autosomal-recessive disorder, and despite its low frequency, 34 clinical variants are known. A founder event has been associated with the p.Gly69ArgfsX10 change in a Polish cohort. The *C19orf12* gene has also been related to hereditary spastic paraplegia (HSP) type SPG43, although in a unique case. Regarding BPAN, patients carry mutations on the *WDR45* gene, often de novo, inherited in an X-linked dominant manner. To date, about 50 BPAN cases have been published with 64 different mutations.

The remaining NBIA forms are rare, with only a few patients described for each condition. Mutations in the *FA2H* gene (OMIM 611026) cause three distinct autosomal-recessive conditions: FAHN, leukodystrophy, and HSP type SPG35. Thus, 37 different mutations have been described, and most of them lead to SPG35. A similar scenario occurs for the *ATP13A2* gene (OMIM 610513), which is responsible for Kufor–Rakeb syndrome, Parkinson disease type 9, and neuronal ceroid lipofuscinosis.

Directly linked to iron metabolism, two NBIA genes, *CP* and *FTL1*, are known. Mutations in *CP*, inherited in an autosomal-recessive manner, cause aceruloplasminemia (OMIM 117700). To date, nearly 50 different mutations are described. Strikingly, patients carrying only one mutation can exhibit symptoms. Mutations, mainly small insertions, in the *FTL1* gene cause neuroferritinopathy (OMIM 134790), an autosomal-dominant NBIA form. Although more than 60 *FTL1* variants are known, the vast majority are associated with hyperferritinemia–cataract syndrome.

Other ultra-rare aceruloplasminemia NBIA forms are due to mutations in *DCAF17*, *COASY*, *SCP2*, and *GTPBP2*. About 12 pathological changes have been related to the autosomal-recessive multisystem syndrome known as Woodhouse–Sakati syndrome, which is caused by mutations in *DCAF17*, also named as *C2orf37* (OMIM 612515). Three distinct mutations in the *COASY* gene, which encodes for CoA synthase, are reported to cause CoPAN in three unrelated cases (OMIM 609855). Regarding *SCP2*, two NBIA cases have been reported (MIM 184755), and only one case with mutations in *GTPBP2* (OMIM 607434).

NBIA Mimics

NBIA disorders share the iron accumulation on brain MRI. Of course, these deposits can be the consequence of a primary molecular defect or a secondary effect. On the one hand, isolated patients are increasingly being recognized suffering from well-known neurological conditions with iron brain accumulation on MRI. Alternatively, new genetic conditions associated with NBIA are evolving. The rarity of most NBIA syndromes makes a diagnosis often difficult.

Subjects affected by Aicardi–Goutières syndrome caused by mutations in the *AGS2* gene [54], neurodegenerative encephalopathy due to changes in the *TBCE* gene [55], or by fucosidosis associated with mutations in the *FUCA1* gene [56] have been reported with evidence of excess iron accumulation in the globus pallidus. A similar pattern was found in an adult case affected by alpha-mannosidosis caused by mutations in the *MAN2B1* gene [57]. Patients suffering from HSP can also present with NBIA. Recently, in three siblings affected by a complex HSP, who harbored homozygous variants in *AP4M1*, deposits of iron on brain MRI were observed [58]. In line with this, another patient presenting with complex HSP with retinal dystrophy and NBIA has been reported, caused by a homozygous nonsense change in *DDHD1* [59]. Finally, a patient with a homozygous splice variant in *AP4S1*, which is

implicated in HSP type SPG52, is known; this affected girl had MRI findings compatible with NBIA [60].

A patient who suffered from a complex neurodegenerative disorder and carried two homozygous variants c.783+5G>T and p.D150RfsX48 in two disparate genes, *OSTM1* and *MANEAL*, respectively, was described [61]. *OSTM1* is involved in infantile malignant osteopetrosis and *MANEAL* was for the first time associated with human disease; consequently, the *MANEAL* gene could be considered in the context of NBIA syndromes. Similarly, a clinical series of individuals with a complex progressive early-onset dystonia due to mutations in *KMT2B* have been published and the majority of them (17 out of 22 subjects) showed symmetrical hypointensity of the globus pallidi on MRI imaging [62]. Recently, *REPS1* and *CRAT* were for the first time related to disease in NBIA patients [63]. *REPS1* encodes a protein involved in endocytosis and vesicular transport and *CRAT* encodes a carnitine acetyltransferase.

In summary, the growing list of NBIA and NBIA-mimics' genes highlight the fact that many genes remain to be discovered.

Pathophysiology

Despite being disorders with iron accumulation in the brain, only two known genes, *CP* and *FTL1*, are directly associated with iron metabolism. The remaining NBIA genes seem to play a role in several pathways related to CoA biosynthesis, lipid metabolism, and autophagy (see Figure 16.2) [52, 53].

PANK2 and COASY are implicated in biosynthesis of CoA. PANK2 catalyzes the ATP-dependent

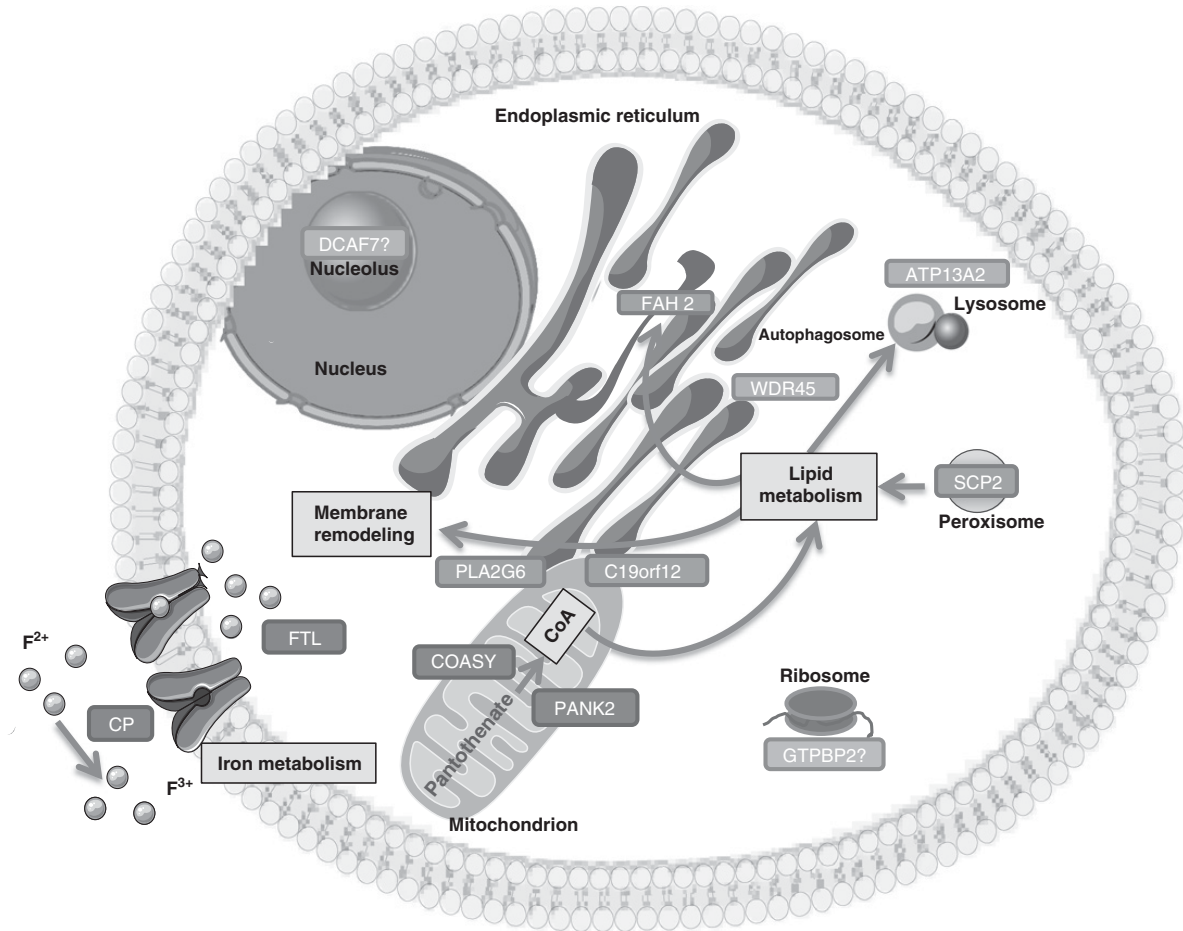

Figure 16.2 Biological processes associated with NBIA disorders. COASY and PANK2 are involved in CoA synthesis; FTL1 and CP are implicated in iron homeostasis-associated proteins; PLA2G6, C19orf12, FA2H, and SCP2, are proteins related to lipid metabolism and/or membrane remodeling; WDR45 and ATP13A2 are linked to autophagy; GTPBP2 and DCAF7 are poorly understood.

phosphorylation of pantothenate, the first step of CoA synthesis, whereas COASY regulates the last two steps in CoA synthesis. CoA is a key molecule for energy production and fatty acid metabolism. PANK2 and COASY are located in the mitochondria and hence the underlying pathophysiology could be related to dysfunction of cellular energy metabolism. Several transgenic flies are available for fumble (*fbl*), the orthologue of the human *PANK2* gene in *Drosophila melanogaster*, which shows decreased CoA levels, mitochondrial dysfunction, increased protein oxidation, and impairment of lipid homeostasis. The fly model presents with locomotor deficits, albeit without abnormal accumulation of iron, and treatment with pantethine is able to restore the phenotype. The *Pank2* knock-out mouse model shows a reduced life span and azoospermia, although neither movement disorder nor brain iron deposits have been observed in these mice. Neurological signs are observed in the null mouse model when fed with a ketogenic diet, and the phenotype is rescued with pantethine. A morpholino-mediated *Pank2* downregulation in zebrafish is also available [64]. The zebrafish orthologue of the human *PANK2* gene is expressed during all the development stages, and in adults, PANK2 is mainly present in central nervous system, dorsal aorta, and caudal vein. Thus, the zebrafish model for *Pank2* shows severe effects on the development of the nervous and vascular systems. In human samples (fibroblasts and plasma) of PKAN patients, lipid dyshomeostasis is detected; and in neuronal cells from the *Pank2* knock-out mouse model and from induced pluripotent stem cells of PKAN individuals, alteration of mitochondrial dynamics is observed, including impairment of mitochondrial respiration and electrophysiological properties [65]. PKAN seems to be the consequence of altered lipid metabolism that would affect mitochondrial homeostasis. Regarding COASY, the knock-out model in yeast results in lethality, and similarly, in zebrafish, the abrogation of its expression causes severe neuronal alterations of development with death after 72 hours, post fertilization.

WDR45 and ATP13A2 are mainly involved in autophagosome formation and degradation. WDR45 is a beta-propeller scaffold protein, crucial for autophagosome maturation. The orthologues of human *WDR45* in yeast and in *Caenorhabditis elegans* are required for autophagosome formation. Lymphoblast lines from BPAN patients present lower autophagic activity with accumulation of autophagic structures. The *Wdr45* knock-out mouse displays axonal swelling and behavioral abnormalities, in addition to altered autophagic flux and accumulation of ubiquitin-positive aggregates in the hippocampus and caudate nucleus [66]. *ATP13A2* encodes for a lysosomal 5-P-type ATPase; thus, fibroblasts from patients suffering from Kufor–Rakeb syndrome exhibit lysosomal deficiencies that cause decreased autophagosome clearance and, together with mitochondrial fragmentation, ATP depletion, oxidative stress, and disturbed mitochondrial DNA integrity. The *Atp13a2* knock-out mouse shows neuronal ceroid lipofuscinosis, limited alpha-synuclein accumulation, and sensorimotor alterations. In neuronal cell models, the expression of mutant *ATP13A2* leads to abnormalities of the autophagic-lysosomal system [67].

PLA2G6, C19orf12, FA2H, and SCP2 play a role in lipid metabolism. The protein encoded by *PLA2G6* hydrolyzes at the sn-2 position of glycerophospholipids to produce free fatty acids and lysophospholipids, and plays an essential function in lipid homeostasis and membrane remodeling. PLA2G6 is also linked to mitochondrial dynamics, since high levels of reactive oxygen species cause accumulation of PLA2G6 in mitochondria [68]. In fact, *Pla2g6* knock-out mice are characterized by progressive cerebellar atrophy, including Purkinje cell loss and inflammation, but no iron accumulation is observed. Moreover, this mouse model displays degeneration of mitochondria and axonal termini in the spinal cord due to an altered lipid profile, suggesting that loss of Pla2g6 may lead to abnormal membrane remodeling and impaired mitochondrial homeostasis. Similarly, C19orf12 has a function in lipid homeostasis and mitochondrial dynamics. C19orf12 locates to mitochondria, mitochondria associated membranes (MAMs), and endoplasmic reticulum. In MPAN patient fibroblasts, high mitochondrial Ca^{2+} levels and an inability to respond to oxidative stress have been observed. The location of C19orf12 in MAMs suggests a function probably related to the transport of phospholipids, and thus *C19orf12* is co-regulated with genes involved in fatty acid metabolism and branched-chain amino acid degradation. In *Drosophila melanogaster*, the knock-down of the two orthologue genes of *C19orf12* (*CG3740* and *CG11671*) cause a neurodegenerative phenotype, including morphological alterations in the brain, although there is no accumulation of iron. Finally, FA2H catalyzes the

hydroxylation of fatty acids, and the resulting 2-hydroxy-fatty acids are precursors for ceramide synthesis, an essential component of myelin. The *Fa2h* knock-out mouse exhibits profound axonal loss, abnormally enlarged axons, and significant demyelination. Furthermore, the absence of *FAH2* in oligodendrocytes causes deficits in spatial learning and memory, suggesting a role for *FA2H* in the development of neural connectivity in the hippocampus. Ultimately, *SCP2* codifies two proteins, SCPx and SCP2, as a result of two independent regulated promoters. Both are sterol carrier proteins with thiolase activity required for the breakdown of branched-chain fatty acids in peroxisomes. The loss of SCP2 causes the abnormal accumulation of branched-chain fatty acids.

The functions of *DCAF17* and *GTPBP2* remain poorly understood. *DCAF17* (*C2orf37*) encodes for a membrane nucleolar protein that belongs to the DCAF protein family. It is assumed that DCAF17 may exert a function related to protein ubiquitination involved in cell cycle control of DNA replication. *GTPBP2* encodes the GTP-binding protein 2, a ribosome rescue factor, which seems to be implicated in messenger RNA and/or ribosome turnover or stability.

As mentioned above, two NBIA genes that are directly linked to iron homeostasis are known: *CP* and *FTL1* [52, 53]. CP catalyzes the peroxidation of ferrous transferrin to ferric transferrin. Lack of CP leads to an impaired iron efflux and increased intracellular iron. In cell models, mutated CP proteins are retained in the endoplasmic reticulum, which triggers an endoplasmic reticulum stress response. *Cp* knock-out mice exhibit iron accumulation as well as lipid peroxidation in brain. FTL1 is one of the two subunits of ferritin, the main iron storage protein in the cell. Mutations in *Ftl* cause mitochondrial dysfunction and increased oxidative stress in cell and animals models. Several transgenic mouse models for *Ftl* show neurodegeneration caused by aggregates of proteins implicated in iron homeostasis, excess of iron, and oxidative stress. In cell models, the overexpression of a defective *FTL1* produces increased endogenous ferritin chains and decreased transferrin receptor 1 (TfR1) expression. Strikingly, Drecourt et al. [63], using patient-derived fibroblasts, demonstrated that the underlying pathomechanism for NBIA patients carrying mutations in *REPS1*, *CRAT*, *PANK2*, *PLA2G6*, *C19orf12*, or *FAH2* is related to defective TfR1 recycling and palmitoylation. It would be interesting to investigate the remaining established or putative NBIA genes in order to determine if they also share this altered process or a similar defective pathway, which could be useful for selection of appropriate treatment strategies.

Treatment

Treatment of PKAN

A guideline on current best practices and therapeutic approaches for the care of patients with PKAN has been published [69]. According to this guideline, trihexyphenidyl, clonazepam, and baclofen are the first-line drugs that are recommended for generalized dystonia in PKAN patients. Botulinum toxin is also useful in focal dystonia, i.e. blepharospasm, oromandibular dystonia, cervical dystonia, or writer's cramp. For patients with generalized drug-resistant dystonia, treatment with baclofen pumps and deep brain stimulation are options. With regard to deep brain stimulation (targeted at the internal globus pallidus), there are several case series and single case reports reporting benefits for patients in the first years; however, benefits are often not sustained as patients continue to deteriorate.

Over the last decade, research has focused on the role of iron in the pathophysiology of PKAN and a randomized, double-blinded, placebo-controlled trial of deferiprone in PKAN patients has been developed [70]. Deferiprone is an iron chelator that has the ability to cross the blood–brain barrier and remove labile iron from neuronal cells. Eighty-nine patients with PKAN were included in a double-blinded trial with deferiprone or placebo for 18 months. Brain iron measurements on MRI demonstrated that the deferiprone group had a significant reduction in brain iron compared to placebo. On the primary clinical outcome measure, the total Barry–Albright dystonia score, patients treated with deferiprone continued to deteriorate, with no significant differences in the rate of disease progression compared to placebo. However, within the subgroup of patients with atypical PKAN, patients who received deferiprone showed a significantly slower progression. In the trial, deferiprone was well tolerated and there were no life-threatening adverse events.

PKAN is caused by mutations in the *PANK2* gene which encodes pantothenate kinase (PanK). Phosphorylation of pantothenic acid (vitamin B5) by PanK is the rate-limiting step in CoA formation, a key factor in several cellular processes. The existence of residual enzyme activity of PanK in some individuals with PKAN has raised the possibility of treatment using high-dose pantethine, a derivative compound of pantothenate, which is the substrate of the defective enzyme PANK2. More recently, RE-024 (fosmetpantotenate) was tested as a potential disease-modifying phosphopantothenate replacement therapy. In preclinical models, fosmetpantotenate delivered intact phosphopantothenate intracellularly, which was incorporated into CoA in the liver and brain [71]. A phase 3 randomized, double-blinded, placebo-controlled trial testing efficacy and safety of fosmetpantotenate in adult and pediatric patients with PKAN (NCT03041116), however, was terminated early.

Treatment of PLAN

Several symptomatic treatments can be at least partially effective in improving the quality of life in patients with PLAN, with a special focus on spasticity, dystonia, seizures, dysphagia, constipation, and neuropsychiatric manifestations. Deep brain stimulation has been successfully utilized in one individual with atypical PLA2G6-associated neurodegeneration who had intractable dystonia [72].

In patients with *PLA2G6*-related dystonia–parkinsonism, the use of dopaminergic agents can be beneficial for parkinsonism and dystonia. Patients usually experience a positive effect followed by a reduction of the response and development of early dyskinesia, which complicates medical management.

Several experimental models of PLAN have demonstrated that loss of PLA2G6 leads to lipid peroxidation, mitochondrial dysfunction, and subsequent mitochondrial membrane abnormalities. In some experiments, supplementation with polyunsaturated fatty acids, which inhibit lipid peroxidation, was able to partially rescue the phenotype and restore mitochondrial function [73]. According to these experimental studies, dietary supplementation with docosahexaenoic acid is recommended in PLAN patients [74]. Moreover, a phase 2/3 single-arm open-label clinical trial is planned to evaluate the efficacy and safety of deuterated polyunsaturated fatty acids in children with INAD.

Treatment in Other NBIAs

Iron chelation therapy, particularly deferiprone that crosses the blood–brain barrier, has been investigated in many genetic conditions causing NBIA disorders [75]. In aceruloplasminemia and neuroferritinopathy, the two genetic conditions primarily linked to iron dyshomeostasis, iron chelation is indicated before the onset of neurological disturbances, as brain iron overload is already present before neurological dysfunction. In aceruloplasminemia, iron chelation leads to ferritin normalization, decrease of hepatic and cardiac iron content, and clinical improvement of anemia and diabetes mellitus. It is also thought to prevent brain iron accumulation and improve neurological outcome in the long term.

Overall, iron chelators decrease brain iron accumulation as documented by MRI studies. Yet, clinical observations do not support a consistent clinical benefit for any neurological disorder.

Severe generalized and disabling dystonia is common in most NBIA disorders, and thus several patients have been treated with deep brain stimulation, many of them reporting positive outcomes. A multicenter retrospective study on 23 NBIA patients treated with bilateral pallidal deep brain stimulation demonstrated an improvement of 20% or more in severity of dystonia in the majority of patients, together with an improvement in global quality of life ratings [76]. However, the clinical benefit is not as good and sustained as in the primary dystonias. Future controlled, multicenter prospective studies are necessary to assess the efficacy of deep brain stimulation and predict therapeutic outcomes.

Key Points and Clinical Pearls

- Hypokinetic and hyperkinetic movement disorders are common in neurodegeneration with brain iron accumulation (NBIA) syndromes.
- The most common among the NBIA disorders, pantothenate kinase-associated neurodegeneration (PKAN), manifests with dystonia.
- The importance of movement disorders is reflected in disease-specific rating scales such as the PKAN-DRS.
- Iron chelation therapy, particularly deferiprone that crosses the blood–brain barrier, has been investigated in several NBIA disorders.

Directions for Future Research

- The impact of novel disease-modifying therapies in movement disorders in NBIA remains to be investigated.
- Further evaluation of DBS for the treatment of dystonia in PKAN and other NBIA.

References

1. Schneider SA, Bhatia KP. Syndromes of neurodegeneration with brain iron accumulation. Semin Pediatr Neurol. 2012;**19**(2):57–66.
2. Hayflick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden–Spatz syndrome. N Engl J Med. 2003;**348**(1):33–40.
3. Hayflick SJ. Neurodegeneration with brain iron accumulation: From genes to pathogenesis. Semin Pediatr Neurol. 2006;**13**(3):182–5.
4. Egan RA, Weleber RG, Hogarth P, et al. Neuro-ophthalmologic and electroretinographic findings in pantothenate kinase-associated neurodegeneration (formerly Hallervorden–Spatz syndrome). Am J Ophthalmol. 2005;**140**(2):267–74.
5. Yoon WT, Lee WY, Shin HY, Lee ST, Ki CS. Novel *PANK2* gene mutations in Korean patient with pantothenate kinase-associated neurodegeneration presenting unilateral dystonic tremor. Mov Disord. 2010;**25**(2):245–7.
6. Aggarwal A, Schneider SA, Houlden H, et al. Indian-subcontinent NBIA: Unusual phenotypes, novel *PANK2* mutations, and undetermined genetic forms. Mov Disord. 2010;**25**(10):1424–31.
7. Chung SJ, Lee JH, Lee MC, Yoo HW, Kim GH. Focal hand dystonia in a patient with *PANK2* mutation. Mov Disord. 2008;**23**(3):466–8.
8. Vasconcelos OM, Harter DH, Duffy C, et al. Adult Hallervorden–Spatz syndrome simulating amyotrophic lateral sclerosis. Muscle Nerve. 2003;**28**(1):118–22.
9. Antonini A, Goldwurm S, Benti R, et al. Genetic, clinical, and imaging characterization of one patient with late-onset, slowly progressive, pantothenate kinase-associated neurodegeneration. Mov Disord. 2006;**21**(3):417–8.
10. Seo JH, Song SK, Lee PH. A novel *PANK2* mutation in a patient with atypical pantothenate-kinase-associated neurodegeneration presenting with adult-onset parkinsonism. J Clin Neurol. 2009;**5**(4):192–4.
11. Diaz N. Late onset atypical pantothenate-kinase-associated neurodegeneration. Case Rep Neurol Med. 2013;**2013**:860201.
12. Kurian MA, Morgan NV, MacPherson L, et al. Phenotypic spectrum of neurodegeneration associated with mutations in the *PLA2G6* gene (PLAN). Neurology. 2008;**70**(18):1623–9.
13. Morgan NV, Westaway SK, Morton JE, et al. *PLA2G6*, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. Nat Genet. 2006;**38**(7):752–4.
14. Paisan-Ruiz C, Li A, Schneider SA, et al. Widespread Lewy body and tau accumulation in childhood and adult onset dystonia–parkinsonism cases with *PLA2G6* mutations. Neurobiol Aging. 2012;**33**(4):814–23.
15. Gregory A, Westaway SK, Holm IE, et al. Neurodegeneration associated with genetic defects in phospholipase A(2). Neurology. 2008;**71**(18):1402–9.
16. Riku Y, Ikeuchi T, Yoshino H, Mimuro M, Mano K, Goto Y, et al. Extensive aggregation of alpha-synuclein and tau in juvenile-onset neuroaxonal dystrophy: An autopsied individual with a novel mutation in the *PLA2G6* gene-splicing site. Acta Neuropathol Commun. 2013;**1**:12.
17. Hayflick SJ, Kruer MC, Gregory A, et al. Beta-propeller protein-associated neurodegeneration: A new X-linked dominant disorder with brain iron accumulation. Brain. 2013;**136**(Pt 6):1708–17.
18. Saitsu H, Nishimura T, Muramatsu K, et al. De novo mutations in the autophagy gene *WDR45* cause static encephalopathy of childhood with neurodegeneration in adulthood. Nat Genet. 2013;**45**(4):445–9, 9e1.
19. Verhoeven WM, Egger JI, Koolen DA, et al. Beta-propeller protein-associated neurodegeneration (BPAN), a rare form of NBIA: Novel mutations and neuropsychiatric phenotype in three adult patients. Parkinsonism Relat Disord. 2013;**20**(3):332–6.
20. Skowronska M, Kmiec T, Jurkiewicz E, et al. Evolution and novel radiological changes of neurodegeneration associated with mutations in *C19orf12*. Parkinsonism Relat Disord. 2017;**39**:71–6.
21. Dezfouli MA, Alavi A, Rohani M, Rezvani M, Nekuie T, Klotzle B, et al. *PANK2* and *C19orf12* mutations are common causes of neurodegeneration with brain iron accumulation. Mov Disord. 2013;**28**(2):228–32.
22. Goldman JG, Eichenseer SR, Berry-Kravis E, et al. Clinical features of neurodegeneration with brain iron accumulation due to a *C19orf12* gene mutation. Mov Disord. 2013;**28**(10):1462–3.
23. Hogarth P, Gregory A, Kruer MC, et al. New NBIA subtype: Genetic, clinical, pathologic, and radiographic features of MPAN. Neurology. 2013;**80**(3):268–75.
24. Schulte EC, Claussen MC, Jochim A, et al. Mitochondrial membrane protein associated neurodegenration: A novel variant of

neurodegeneration with brain iron accumulation. Mov Disord. 2013;**28**(2):224–7.

25. Panteghini C, Zorzi G, Venco P, et al. *C19orf12* and *FA2H* mutations are rare in Italian patients with neurodegeneration with brain iron accumulation. Semin Pediatr Neurol. 2012;**19**(2):75–81.
26. Schottmann G, Stenzel W, Lutzkendorf S, Schuelke M, Knierim E. A novel frameshift mutation of *C19ORF12* causes NBIA4 with cerebellar atrophy and manifests with severe peripheral motor axonal neuropathy. Clin Genet. 2013;**85**(3):290–2.
27. Kruer MC, Salih MA, Mooney C, et al. *C19orf12* mutation leads to a pallido-pyramidal syndrome. Gene. 2014;**537**(2):352–6.
28. Kruer MC, Paisan-Ruiz C, Boddaert N, et al. Defective *FA2H* leads to a novel form of neurodegeneration with brain iron accumulation (NBIA). Ann Neurol. 2010;**68**(5):611–8.
29. Schneider SA, Paisan-Ruiz C, Quinn NP, et al. *ATP13A2* mutations (PARK9) cause neurodegeneration with brain iron accumulation. Mov Disord. 2010;**25**(8):979–84.
30. Bruggemann N, Hagenah J, Reetz K, et al. Recessively inherited parkinsonism: Effect of *ATP13A2* mutations on the clinical and neuroimaging phenotype. Arch Neurol. 2010;**67**(11):1357–63.
31. Behrens MI, Bruggemann N, Chana P, et al. Clinical spectrum of Kufor–Rakeb syndrome in the Chilean kindred with *ATP13A*2 mutations. Mov Disord. 2010;**25**(12):1929–37.
32. Dusi S, Valletta L, Haack TBet al. Exome sequence reveals mutations in CoA synthase as a cause of neurodegeneration with brain iron accumulation. Am J Hum Genet. 2014;**94**(1):11–22.
33. Vroegindeweij LH, van der Beek EH, Boon AJ, et al. Aceruloplasminemia presents as type 1 diabetes in non-obese adults: A detailed case series. Diabet Med. 2015;**32**(8):993–1000.
34. Bohlega SA, Alkuraya FS. Woodhouse–Sakati Syndrome. 1993.
35. Horvath R, Lewis-Smith D, Douroudis K, et al. *SCP2* mutations and neurodegeneration with brain iron accumulation. Neurology. 2015;**85**(21):1909–11.
36. Ferdinandusse S, Kostopoulos P, Denis S, et al. Mutations in the gene encoding peroxisomal sterol carrier protein x (*SCPx*) cause leukencephalopathy with dystonia and motor neuropathy. Am J Hum Genet. 2006;**78**(6):1046–52.
37. Jaberi E, Rohani M, Shahidi GA, et al. Identification of mutation in *GTPBP2* in patients of a family with neurodegeneration accompanied by iron deposition in the brain. Neurobiol Aging. 2016;**38**:216 e11-8.
38. Darling A, Tello C, Marti MJ, et al. Clinical rating scale for pantothenate kinase-associated neurodegeneration: A pilot study. Mov Disord. 2017;**32**(11):1620–30.
39. Greblikas F, Escolar M, Klopstock T, et al. The FOsmetpantotenate Replacement Therapy (FORT) Pivotal Trial: Utilization of a novel primary efficacy outcome in patients with pantothenate kinase-associated neurodegeneration (abstract 25). Mov Disord. 2018;**33**(Suppl 2):S11-2.
40. Amaral LL, Gaddikeri S, Chapman PR, et al. Neurodegeneration with brain iron accumulation: Clinicoradiological approach to diagnosis. J Neuroimaging. 2015;**25**(4):539–51.
41. Delgado RF, Sanchez PR, Speckter H, et al. Missense *PANK2* mutation without "eye of the tiger" sign: MR findings in a large group of patients with pantothenate kinase-associated neurodegeneration (PKAN). J Magn Reson Imaging. 2012;**35**(4):788–94.
42. Schenck JF, Zimmerman EA. High-field magnetic resonance imaging of brain iron: Birth of a biomarker? NMR Biomed. 2004;**17**(7):433–45.
43. Stankiewicz J, Panter SS, Neema M, et al. Iron in chronic brain disorders: Imaging and neurotherapeutic implications. Neurotherapeutics. 2007;**4**(3):371–86.
44. Fermin-Delgado R, Roa-Sanchez P, Speckter H, et al. Involvement of globus pallidus and midbrain nuclei in pantothenate kinase-associated neurodegeneration: Measurement of T2 and T2* time. Clin Neuroradiol. 2013;**23**(1):11–5.
45. Chiapparini L, Savoiardo M, D'Arrigo Set al. The "eye-of-the-tiger" sign may be absent in the early stages of classic pantothenate kinase associated neurodegeneration. Neuropediatrics. 2011;**42**(4):159–62.
46. Grandas F, Fernandez-Carballal C, Guzman-de-Villoria J, Ampuero I. Treatment of a dystonic storm with pallidal stimulation in a patient with *PANK2* mutation. Mov Disord. 2011;**26**(5):921–2.
47. Awasthi R, Gupta RK, Trivedi R, et al. Diffusion tensor MR imaging in children with pantothenate kinase-associated neurodegeneration with brain iron accumulation and their siblings. AJNR Am J Neuroradiol. 2010;**31**(3):442–7.
48. Haack TB, Hogarth P, Gregory A, Prokisch H, Hayflick SJ. BPAN: The only X-linked dominant NBIA disorder. Int Rev Neurobiol. 2013;**110**:85–90.
49. Schneider SA, Neurodegenerations with brain iron accumulation. Parkinsonism Relat Disord. 2016;**22**: S21–5.
50. Schneider SA, Bhatia KP, Hardy J. Complicated recessive dystonia parkinsonism syndromes. Mov Disord. 2009;**24**(4):490–9.

51. Kell DB. Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples. Arch Toxicol. 2010;**84**(11):825–89.
52. Di Meo I, Tiranti V. Classification and molecular pathogenesis of NBIA syndromes. Eur J Paediatr Neurol. 2018;**22**(2):272–84.
53. Tello C, Darling A, Lupo V, Perez-Duenas B, Espinos C. On the complexity of clinical and molecular bases of neurodegeneration with brain iron accumulation. Clin Genet. 2018;**93**(4):731–40.
54. Svingen L, Goheen M, Godfrey R, et al. Late diagnosis and atypical brain imaging of Aicardi–Goutières syndrome: Are we failing to diagnose Aicardi–Goutières syndrome-2? Dev Med Child Neurol. 2017;**59**(12):1307–11.
55. Sferra A, Baillat G, Rizza T, et al. *TBCE* Mutations cause early-onset progressive encephalopathy with distal spinal muscular atrophy. Am J Hum Genet. 2016;**99**(4):974–83.
56. Gautschi M, Merlini L, Calza AM, et al. Late diagnosis of fucosidosis in a child with progressive fixed dystonia, bilateral pallidal lesions and red spots on the skin. Eur J Paediatr Neurol. 2014;**18**(4):516–9.
57. Zoons E, de Koning TJ, Abeling NG, Tijssen MA. Neurodegeneration with brain iron accumulation on MRI: An adult case of alpha-mannosidosis. JIMD Rep. 2012;**4**:99–102.
58. Roubertie A, Hieu N, Roux CJ, et al. AP4 deficiency: A novel form of neurodegeneration with brain iron accumulation? Neurol Genet. 2018;**4**(1):e217.
59. Dard R, Meyniel C, Touitou V, et al. Mutations in *DDHD1*, encoding a phospholipase A1, is a novel cause of retinopathy and neurodegeneration with brain iron accumulation. Eur J Med Genet. 2017;**60**(12):639–42.
60. Vill K, Muller-Felber W, Alhaddad B, et al. A homozygous splice variant in *AP4S1* mimicking neurodegeneration with brain iron accumulation. Mov Disord. 2017;**32**(5):797–9.
61. Herebian D, Alhaddad B, Seibt A, et al. Coexisting variants in *OSTM1* and *MANEAL* cause a complex neurodegenerative disorder with NBIA-like brain abnormalities. Eur J Hum Genet. 2017;**25**(9):1092–5.
62. Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene *KMT2B* cause complex early-onset dystonia. Nat Genet. 2017;**49**(2):223–37.
63. Drecourt A, Babdor J, Dussiot M, et al. Impaired transferrin receptor palmitoylation and recycling in neurodegeneration with brain iron accumulation. Am J Hum Genet. 2018;**102**(2):266–77.
64. Brunetti D, Dusi S, Giordano C, et al. Pantethine treatment is effective in recovering the disease phenotype induced by ketogenic diet in a pantothenate kinase-associated neurodegeneration mouse model. Brain. 2014;**137**(Pt 1):57–68.
65. Orellana DI, Santambrogio P, Rubio A, et al. Coenzyme A corrects pathological defects in human neurons of *PANK2*-associated neurodegeneration. EMBO Mol Med. 2016;**8**(10):1197–211.
66. Zhao YG, Sun L, Miao G, et al. The autophagy gene *Wdr45/Wipi4* regulates learning and memory function and axonal homeostasis. Autophagy. 2015;**11**(6):881–90.
67. Schultheis PJ, Fleming SM, Clippinger AK, et al. Atp13a2-deficient mice exhibit neuronal ceroid lipofuscinosis, limited alpha-synuclein accumulation and age-dependent sensorimotor deficits. Hum Mol Genet. 2013;**22**(10):2067–82.
68. Zhao Z, Zhang X, Zhao C, et al. Protection of pancreatic beta-cells by group VIA phospholipase A(2)-mediated repair of mitochondrial membrane peroxidation. Endocrinology. 2010;**151**(7):3038–48.
69. Hogarth P, Kurian MA, Gregory A, et al. Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). Mol Genet Metab. 2017;**120**(3):278–87.
70. Klopstock T, Tricta F, Neumayr L, et al. A randomized trial of deferiprone for pantothenate kinase-associated neurodegeneration (abstr 471). Mov Disord. 2018;**33**(Suppl 2):S219.
71. Elbaum D, Beconi MG, Monteagudo E, et al. Fosmetpantotenate (RE-024), a phosphopantothenate replacement therapy for pantothenate kinase-associated neurodegeneration: Mechanism of action and efficacy in nonclinical models. PLoS One. 2018;**13**(3):e0192028.
72. Cif L, Kurian MA, Gonzalez V, et al. Atypical *PLA2G6*-associated neurodegeneration: social communication impairment, dystonia and response to deep brain stimulation. Mov Disord Clin Pract. 2014;**1**(2):128–31.
73. Kinghorn KJ, Castillo-Quan JI, Bartolome F, et al. Loss of PLA2G6 leads to elevated mitochondrial lipid peroxidation and mitochondrial dysfunction. Brain. 2015;**138**(Pt 7):1801–16.
74. Gregory A, Kurian MA, Maher ER, Hogarth P, Hayflick S. *PLA2G6*-associated neurodegeneration. GeneReviews®. 2008;Jun 19 (updated Mar 23, 2017).
75. Dusek P, Schneider SA, Aaseth J. Iron chelation in the treatment of neurodegenerative diseases. J Trace Elem Med Biol. 2016;**38**:81–92.
76. Timmermann L, Pauls KA, Wieland K, et al. Dystonia in neurodegeneration with brain iron accumulation: Outcome of bilateral pallidal stimulation. Brain. 2010;**133**(Pt 3):701–12.

Chapter 17

Metal Storage Disorders: Inherited Disorders of Copper and Manganese Metabolism and Movement Disorders

Karin Tuschl and Peter T. Clayton

Copper Metabolism and Transport, Deficiency, and Toxicity

Copper is one of the six transition metals that have important biochemical roles in humans, particularly in catalysis and electron transport [1, 2]. Because it can exist in two redox states (Cu^{2+}/Cu^{+}), it can participate in redox reactions involving transfer of an electron, but if it builds up it can also generate potentially toxic reactive oxygen species by Fenton chemistry. Examples of copper in redox enzymes include: complex IV of the mitochondrial respiratory chain, copper–zinc superoxide dismutase, ceruloplasmin (ferroxidase), lysyl oxidase, dopamine beta-hydroxylase, and tyrosinase.

Copper is present in many foods and in drinking water. The content is particularly high in organ meats (e.g. liver), shellfish, chocolate, nuts, and mushrooms. The content in food may be increased by cooking in copper-containing vessels. Copper absorption is reduced by gastric bypass surgery and this can lead to a myelopathy [3].

Copper is transported into the enterocyte via the CTR1 transporter. Export from the enterocyte is regulated by the copper-transporting ATPase, ATP7A. This protein is synthesized in the endoplasmic reticulum and resides in the trans-Golgi network, but, as intracellular copper levels rise, it translocates to the basolateral membrane where it allows copper export into the plasma. Mutations in *ATP7A* give rise to generalized copper deficiency, deficient activity of copper enzymes, and the symptoms of Menkes syndrome and variants [4].

On arriving at the liver, copper is taken up through CTR1 at the basolateral membrane and rising copper levels lead to translocation of ATP7B from the trans-Golgi network to the apical membrane where the copper is excreted into the bile canaliculus [4]. ATP7B is also required for the secretion of copper bound to ceruloplasmin from the liver into plasma. Mutations in *ATP7B* (Wilson disease) cause an accumulation of copper in the liver with reduced plasma concentrations of ceruloplasmin and ceruloplasmin-bound copper (normally the major fraction of plasma copper). As the disease progresses, levels of free copper in the plasma increase; urinary copper excretion is higher than normal. Copper deposition in the basal ganglia of the brain is responsible for the movement disorder, copper deposition in Descemet's membrane at the corneoscleral junction in the eye give rise to Kayser–Fleischer rings, copper deposition in the kidneys can cause a tubulopathy, and high free plasma copper can cause hemolysis.

Within the cell, chaperones are important in conveying copper to copper-dependent enzymes such as copper–zinc superoxide dismutase (chaperone: CCS) and complex IV of the respiratory chain (chaperones: SCO1 and SCO2). *SCO1* mutations in the mouse lead to severe cellular copper deficiency because, in addition to its role in complex IV assembly, SCO1 is required for expression of CTR1 and hence copper uptake [5].

Copper Toxicity Disorders

Wilson Disease (*ATP7B* Mutations)

Wilson disease is an autosomal-recessive disorder caused by bi-allelic mutations in the *ATP7B* gene on chromosome 13q14.3. The incidence is approximately 1 in 30,000 live births. As discussed, there is a failure of excretion of copper from the liver into the bile and of ceruloplasmin-bound copper into the plasma. The build-up of copper in the liver causes inflammation and fibrosis. Copper is deposited in the brain (particularly the basal ganglia), the eye (Kayser–Fleischer rings), and the kidney (tubulopathy).

In a series of 400 adult patients with Wilson disease, 50% presented with neurological and psychiatric

symptoms, 20% with neurological and hepatic symptoms, and 20% with purely hepatic symptoms [6].

In patients with neurological presentations, movement disorders are prominent. Dysarthria (speech difficulty) and dysgraphia are particularly characteristic. Major movement disorders include dystonia, rigidity, tremor, and choreiform movements.

Dystonia is common, present in about two-thirds of patients, and can be focal, multifocal, or generalized as the disease progresses. Focal forms of dystonia include blepharospasm, cervical dystonia, or *risus sardonicus*. With orofacial dystonia or oropharyngeal dyskinesia, patients may develop dysphonia, dysarthria, or dysphagia. Parkinsonism and ataxia are also found in Wilson disease although they are rarely an isolated clinical feature and are typically accompanied by other neurological deficits. Chorea is more common in children and adolescents with Wilson disease.

In patients with psychiatric presentations, common features include changes in personality (irritability, anger, poor self-control), depression, and anxiety. Frank psychosis can occur.

Ninety-five percent of patients with neurological signs have Kayser–Fleischer rings. Slit lamp examination may be required to visualize the golden/greenish-brown pigmentation in the early stages. It starts as a superior crescent and progresses inferiorly to become circumferential.

T2-weighted and fluid-attenuated inversion recovery MRI images typically show changes in the striatum but abnormalities can be present in other brain regions (Figure 17.1). In one recent series the incidence of

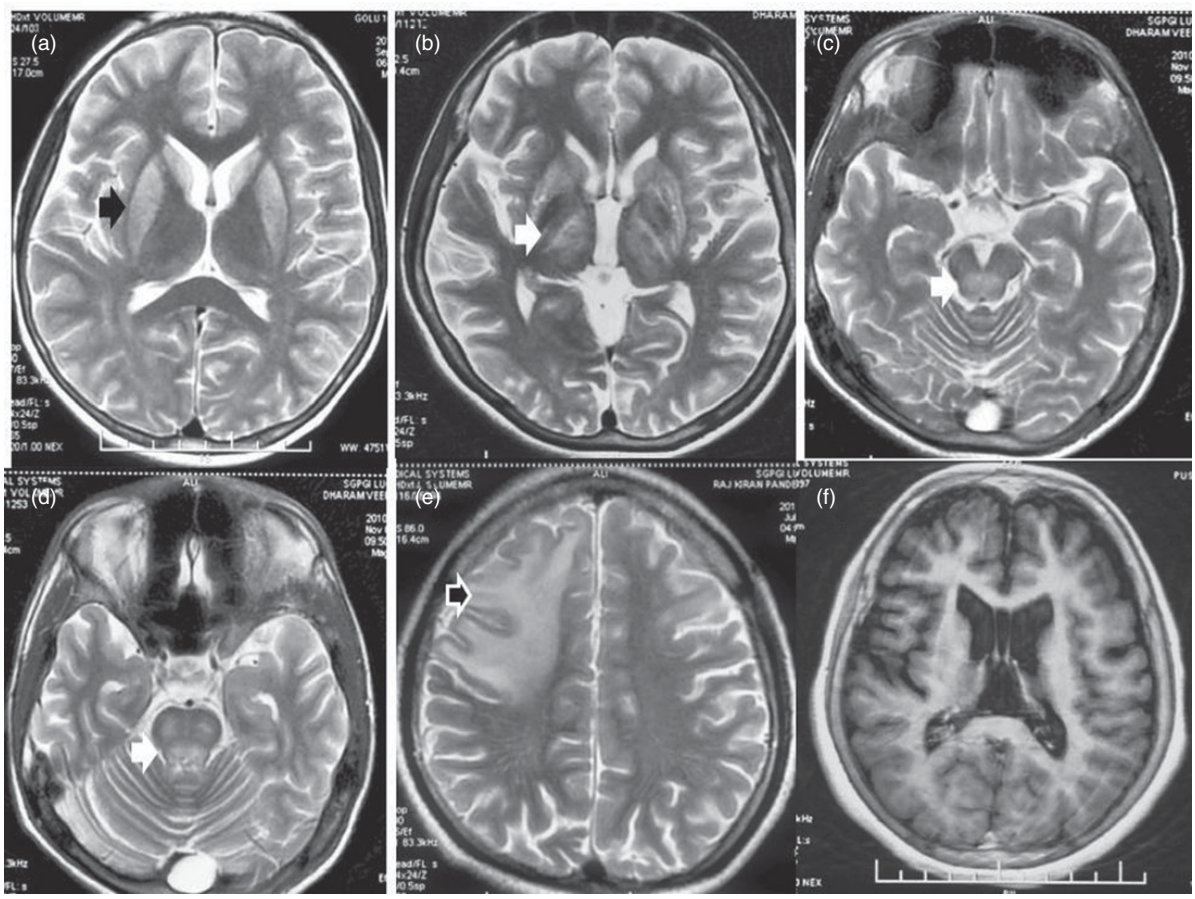

Figure 17.1 Representative cranial MRI findings in patients with Wilson disease having neurological manifestation in axial section. (a) Basal ganglia T2 hyperintensity (putamen, 85.3%; caudate, 67.6%; globus pallidus, 61.8% of patients). (b) Thalamus (58.8% of patients) and corpus striatum T2 hyperintensity. (c) Midbrain T2 hyperintensity (61.8% of patients). (d) Pontine T2 hyperintensity (61.8% of patients). (e) Frontoparietal subcortical white matter (23.5% of patients) and cortical (26.5% of patients) T2 hyperintensity. (f) Cortical atrophy in T1 sequence (20.5% of patients). From: Ranjan A, Kalita J, Kumar S et al. A study of MRI changes in Wilson disease and its correlation with clinical features and outcome. Clin Neurol Neurosurg 2015;138:31–6. Reproduced with permission.

Table 17.1 Diagnostic biochemical measurements in Wilson disease

	Wilson disease	Normal
Serum ceruloplasmin (mg/L)	0–200	200–400
Serum copper (μmol/L)	<11	11–24
Urinary copper (μmol/24 h)	>1.6	<0.6
Liver copper (μg/g dry weight)	>250	<50

abnormalities (percentage of patients) was: putamen, 85.3%; caudate, 67.6%; brainstem and globus pallidus, 61.8% each; thalamus, 58.8%; cerebral cortex, 26.5%; subcortical white matter, 23.5%; and cerebellum, 5.9% [7]. Both hyperintense and hypointense signals can be seen. Choreoathetosis correlated with thalamic, pallidal, and putaminal lesions; mini mental state examination, with subcortical white matter changes. MRI load correlated with age, tremor, psychiatric disorder, choreoathetosis, and severity of Wilson disease [7].

Laboratory investigations usually show abnormalities of liver function tests (even with a pure neurological presentation) although the levels of transaminases tend to be lower than other causes of chronic hepatitis (e.g. autoimmune). Clotting times may be prolonged. Plasma copper and ceruloplasmin are low; urinary excretion of copper is elevated (Table 17.1).

A liver biopsy shows chronic inflammation with fibrosis, with increased staining for copper-associated protein. The liver copper content is increased (Table 17.1).

Many different mutations in the *ATP7B* gene have been described (>500). Most patients are compound heterozygotes. R778L is a common mutation in Asian patients whereas H1069Q is a common mutation in Europeans. R778L causes complete loss of function of the copper ATPase; homozygotes present early with hepatic disease. H1069Q mutations are associated with some residual activity and homozygotes present with neurological disease at around 21 years of age [4].

The treatment options for Wilson disease include drugs that chelate copper and increase its excretion, and zinc. Zinc induces metallothionein synthesis in the intestinal epithelium and the metallothionein binds copper in the villus cells (preferentially over zinc). This reduces copper absorption and increases losses into the feces as the villus cells are shed into the intestinal lumen.

Treatment of neurological Wilson disease presents a major challenge. It may save the patient's life but make their movement disorder significantly worse and in 34% of cases where neurological deterioration occurs, it is irreversible. A recent study confirmed that worsening of neurological symptoms can occur in 35% of patients treated with D-penicillamine (n = 35) and 19% of patients treated with zinc sulphate (n = 21), a difference that was not statistically significant [8, 9]. On the other hand, a study in 2006 by Brewer et al. showed that neurological deterioration on treatment occurred in 27% of patients treated with trientine (n = 23) but in only 4% of patients treated with ammonium tetrathiomolybdate (n = 25), a difference that was significant at the $p < 0.05$ level [10]. Bis-choline tetrathiomolybdate is currently in a Stage III clinical trial (ClinicalTrials.gov).

Hepatic Wilson disease may require treatment of acute liver failure or end-stage chronic liver disease by liver transplantation. Liver transplantation for neurological Wilson disease remains controversial; there is a wide spectrum of outcomes post liver transplant – some with neurological recovery and others with continued disability and an overall increased mortality [11].

MEDNIK Syndrome

MEDNIK syndrome is an autosomal-recessive disorder caused by bi-allelic mutations in *AP1S1*, which encodes a protein that is needed for translocation of ATP7A and ATP7B from the trans-Golgi network to the cell membrane and other organelles. Plasma copper and ceruloplasmin concentrations are reduced but liver copper is elevated. The clinical features are those constituted in the acronym MEDNIK: "Mental retardation, Enteropathy, Deafness, peripheral Neuropathy, Ichthyosis, and Keratoderma" plus brain atrophy and cholestatic hepatopathy. Although brain atrophy is the most common finding on MRI, three patients have been described with symmetrical T2 hyperintensity of the basal ganglia, mainly affecting the caudate and putamen. However, a specific movement disorder has not been described. The disorder responds to treatment with zinc acetate [12, 13].

Copper Deficiency Disordes

Menkes Disease, Occipital Horn Syndrome, X-Linked Distal Hereditary Motor Neuropathy (*ATP7A* Mutations)

The *ATP7A* gene is on the X-chromosome, so mutations give rise to X-linked disorders. Menkes disease is

the most severe form; the milder forms are the occipital horn syndrome and X-linked distal hereditary motor neuropathy [4].

Many of the manifestations of Menkes syndrome can be understood in terms of the effect of copper deficiency on copper-dependent enzymes (see below). The reduced activity of complex IV of the respiratory chain, copper–zinc dismutase, and ceruloplasmin probably contribute to neurological disease; the reduced cross-linking of elastin and of collagen by lysyl oxidase contribute to cutis laxa, tortuosity of the arteries, and bladder and bowel diverticulae; the reduced activity of dopamine beta-hydroxylase impairs synthesis of adrenaline and noradrenaline and contributes to hypothermia and orthostatic hypotension; and the reduced activity of tyrosinase contributes to pallor of skin and hair.

Menkes disease occurs with an incidence of approximately 1 in 250,000 live births and is a progressive neurodegenerative disorder. Major neurological signs are hypotonia progressing to hypertonia and epilepsy.

Infants with Menkes syndrome may be born prematurely and some exhibit a large cephalhematoma and/or skin laxity. The hair breaks easily. Hypothermia can be a problem in the neonatal period. By 1–2 months, hypotonia is apparent as is the characteristic appearance with sagging cheeks and loose skin over the neck. Examination of the hair under the microscope reveals the characteristic pili torti. Feeding difficulties, chronic diarrhea, and failure to thrive are common problems although linear growth is usually preserved. Seizures tend to start at about 2 months. Many seizure types have been described, including infantile spasms with hypsarrhythmia on EEG. During the first year of life hypotonia is replaced by hypertonia, and a delay in achieving motor milestones becomes increasingly apparent. In one series from China, all patients were reported to have dystonia [14]. Urinary-tract infections are common and may be difficult to treat because of bladder diverticulae; chest infections are also common. Umbilical and inguinal hernias occur frequently as does pectus excavatum. In the past, most patients died before the age of 3 years of infections or vascular complications, although with good care, especially attention to feeding, better survival could be achieved.

Skeletal X-rays often show osteopenia and Wormian bones in the skull. MRI shows cerebral atrophy, ventriculomegaly, and cerebellar atrophy at first imaging in the majority of patients, and focal lesions in the basal ganglia also occur early in the course of the disease, between 2 months and 16 months of age [15]. These lesions are typically asymmetrical and involve the caudate and anterior putamen; they are hyperintense on T2-weighted images. Subdural collections are seen in under one-fifth of scans.

Serum copper is <11 μg/dL and ceruloplasmin <200 mg/L but low values like this can be seen in the first few months of life in normal (and especially premature) infants. The abnormalities of catecholamines and their metabolites provide better diagnostic markers in young infants. Examples of useful diagnostic parameters are the ratios in plasma of dopamine to noradrenaline or of dihydroxyphenylacetic acid to dihydroxyphenylglycol or the ratio of homovanillic acid (HVA) to vanillylmandelic acid (VMA) in the urine [16]. The latter has been proposed as a test that could be used for neonatal screening; early diagnosis is important for treatment to be successful.

Treatment with parenteral copper, usually in the form of copper histidine, can improve neurological outcomes. However, some patients show no significant improvement despite early treatment initiation [17].

The occipital horn syndrome is a milder form of Menkes syndrome seen in about 10% of cases. The connective-tissue abnormalities are similar to those seen in Menkes but development is much less affected. Exostoses are palpable at the sites of some muscle insertions; the occipital horn is at the site of insertion of the paraspinal muscles. Skin and joint laxity are common problems as are the bladder diverticulae. Chronic diarrhea and orthostatic hypotension are probably both consequences of dysautonomia, particularly impaired synthesis of adrenaline and noradrenaline.

The mildest phenotype caused by *ATP7A* mutations is X-linked distal hereditary motor neuropathy. Affected individuals present in late childhood/adult life with weakness associated with distal muscular atrophy.

All three phenotypes of ATP7A deficiency show an X-linked mode of inheritance but approximately one-third of patients have a new mutation. The mutations producing Menkes disease vary considerably from chromosomal abnormalities (principally X-autosome translocations) through intragenic deletions involving more than one exon to single base-pair changes. These mutations are predicted to lead to a non-functional

protein. In contrast, the occipital horn syndrome is usually caused by splice site mutations that permit small amounts of ATP7A protein to be produced and X-linked distal hereditary motor neuropathy is caused by a small number of missense mutations with even higher residual ATP7A activity [4].

Disorders of Specific Copper-Dependent Enzymes or Chaperones

Aceruloplasminemia

Aceruloplasminemia is an autosomal-recessive disorder caused by bi-allelic mutations in the *CP* gene encoding the copper-dependent enzyme ceruloplasmin [18]. Ceruloplasmin is undetectable in plasma. Patients have an accumulation of iron in the liver, islets of Langerhans, and brain. They present in adulthood with neurological symptoms (chorea, ataxia, dystonia, parkinsonism, and psychiatric disorders), retinal degeneration, and diabetes mellitus. Ceruloplasmin is a ferroxidase enzyme that converts ferrous iron (Fe^{2+}) into ferric iron (Fe^{3+}). It is believed to also be important in the conversion of Mn^{2+} to Mn^{3+} (see below). Patients have low serum iron (mostly transferrin-bound Fe^{3+}), high serum ferritin (produced from excess cellular Fe^{2+}), and low serum copper. Hepatic iron is increased.

Aceruloplasminemia is normally classified as one of the neurodegeneration with brain iron accumulation (NBIA) group and is discussed in Chapter 16.

Treatment with iron chelation and fresh frozen plasma may be useful to reduce the iron load in the central nervous system and to improve the neurological symptoms [19].

Deficiency of the Copper Chaperone for Superoxide Dismutase

The copper chaperone for superoxide dismutase (CCS) acts as a copper chaperone, delivering the metal to the copper–zinc superoxide dismutase (SOD1) enzyme. One patient with Huppke–Brendel syndrome and a homozygous truncating mutation in the *SLC33A1* gene, who was reported as having congenital cataracts, hearing loss, and neurodegeneration (see the next section), also had a variant of unknown significance in *CCS* [20]. The patient with the *CCS* variant had additional symptoms not present in the other patients with *SLC33A1* mutations, including neonatal hypotonia, hypoglycemia, and a pericardial effusion. At age 18 months, he had rapid developmental regression and epilepsy with persistent bilateral thalamic lesions on brain MRI. The activity of SOD1 was reduced in the fibroblasts.

Deficiency of Copper–Zinc Superoxide Dismutase

Mutations in *SOD1* encoding the copper–zinc superoxide dismutase enzyme cause amyotrophic lateral sclerosis (motor neuron disease) [21]. This suggests that a reduced activity of this enzyme caused by copper deficiency may contribute to the motor neuropathy of X-linked distal motor neuropathy.

Deficiency of the Cytochrome C Oxidase Assembly Protein SCO1

SCO1 is a copper chaperone involved in the assembly of complex IV of the mitochondrial respiratory chain and also plays a role in copper homeostasis. Bi-allelic mutations cause neonatal-onset hepatic failure and encephalopathy (with or without hypertrophic cardiomyopathy), with profound lactic acidosis and reduced activity of complex IV in the liver and muscle [22]. Affected infants are profoundly hypotonic. A patient who survived to 4 months initially had very poor truncal tone with increased peripheral tone but progressed to dystonic posturing [23].

Deficiency of the Cytochrome C Oxidase Assembly Protein SCO2

SCO2 is a paralogue of SCO1 and it also participates in the assembly of complex IV of the mitochondrial respiratory chain and in copper homeostasis. Bi-allelic mutations in *SCO2* cause neonatal encephalocardiomyopathy [24, 25]. Profound hypotonia and dystonia may be apparent. Recently, it has been shown that bi-allelic mutations in *SCO2* can also cause an axonal polyneuropathy with predominantly motor involvement [26]. Affected individuals have evidence of cellular copper deficiency.

Dopamine Beta-Hydroxylase

Bi-allelic mutations in *DBH* cause the isolated failure of autonomic noradrenergic neurotransmission because a defect in the beta-hydroxylation of dopamine in peripheral nerves leads to a failure of synthesis of

adrenaline and noradrenaline [27]. The main symptom is orthostatic hypotension. Hypothermia and hypoglycemia can occur in infancy. In two patients with lifelong orthostatic hypotension due to DBH deficiency, the oral administration of DL-dihydroxyphenylserine led to remarkable improvement [28].

Lysyl Oxidase

Heterozygous mutations in the *LOL* gene encoding lysyl oxidase cause autosomal-dominant familial thoracic aortic aneurysms [29].

Tyrosinase

Bi-allelic mutations in the *TYR* gene encoding tyrosinase cause autosomal-recessive oculocutaneous albinism [30]. Tyrosinase catalyzes the first two steps, and at least one subsequent step, in the conversion of tyrosine to melanin.

Disorders with Secondary Effects on Copper Levels

SLC33A1 Mutations/AT1 Deficiency/ Huppke–Brendel Syndrome, and Autosomal-Dominant Hereditary Spastic Paraplegia 42

Mutations in *SLC33A1* lead to a deficiency of the acetyl-coenzyme A (CoA) transporter AT1 that is required for entry of acetyl-CoA into the lumen of the Golgi apparatus where it participates in many acetylation reactions involving proteins and their glycans. The impaired synthesis and/or secretion of ceruloplasmin leads to low serum copper and ceruloplasmin. There is no evidence of copper deficiency or copper toxicity.

Homozygous mutations in *SLC33A1* have been reported in children with autosomal-recessive congenital cataracts, hearing loss, and neurodegeneration (Huppke–Brendel syndrome) [31]. Heterozygous mutations in *SLC33A1* have been described in autosomal-dominant hereditary spastic paraplegia type 42 [32].

Manganese Metabolism and Transport, Toxicity and Deficiency

Manganese is another of the six transition metals essential for human metabolism. It participates in group transfer reactions such as phosphorylation and glycosylation. Deficiency can lead to defective glycosylation of serum proteins such as transferrin. It can exist in a number of oxidation states; Mn^{2+} and Mn^{3+} are important in the body and their interconversion can facilitate redox reactions including manganese superoxide dismutase, the important mitochondrial scavenger of reactive oxygen species. Other enzymes for which manganese is a cofactor are involved in amino acid metabolism (e.g. arginase), lipid and carbohydrate metabolism, immune function, bone and connective-tissue growth, and blood clotting [33, 34].

Manganese is present in water supplies and in many foods. Foods particularly rich in manganese include cloves, saffron, nuts, mussels, dark chocolate, sesame, and sunflower seeds [35].

Uptake of manganese (Mn^{2+}) into cells can be facilitated by a number of transporters including SLC39A8 and SLC39A14, divalent metal transporter 1 (DMT1; SLC11A2), dopamine transporter (DAT), and citrate transporters [2, 36]. Iron competes with manganese for uptake by DMT1 and also at several other stages of manganese metabolism (e.g. binding to transferrin). This explains why increasing oral iron uptake can be used in the treatment of hypermanganesemia [37, 38]. Uptake by SLC39A8 probably also contributes to the uptake of manganese from the gut and the uptake of manganese into the cells that need it; hence, SLC39A8 deficiency leads to low plasma manganese levels and signs of cellular manganese deficiency, e.g. impaired glycosylation of transferrin [39–41]. On the other hand, the uptake of manganese into the liver, facilitated by SLC39A14, appears to be important in facilitating the biliary excretion of manganese; SLC39A14 deficiency is a cause of hypermanganesemia and deposition of manganese in the brain [42].

After uptake of Mn^{2+} from the gut, it is oxidized in the blood by ceruloplasmin to Mn^{3+}, which is then bound to transferrin, the major manganese-binding protein. Uptake of transferrin-bound Mn^{3+} occurs when it binds to the transferrin receptor and is internalized in an endocytotic vesicle (receptor-mediated endocytosis). In the endosome, Mn^{3+} is reduced to Mn^{2+} and uptake into the cytoplasm probably occurs mainly via DMT1 [36]. Stable tissue concentrations of manganese are maintained by tight homeostatic control of intestinal absorption and biliary excretion. When blood levels of manganese are elevated manganese may be deposited in the

brain, particularly in the basal ganglia. Affected areas of the brain can be visualized as they produce a hyperintense signal on T1-weighted MRI [42]. Brain manganese accumulation leads to a condition known as manganism, an extrapyramidal movement disorder characterized by dystonia, bradykinesia, and rigidity, accompanied by psychiatric and cognitive defects [42].

Manganese neurotoxicity has been attributed to impaired dopaminergic, glutamatergic, and GABAergic neurotransmission, mitochondrial dysfunction, oxidative stress, and neuroinflammation. While excessive levels of copper and iron can lead to the generation of reactive oxygen species by Fenton chemistry, manganese might increase reactive oxygen species production indirectly. Feeding rats a high manganese diet leads to an increase in markers of oxidative stress as well as a shift in the ratio Fe^{2+}/Fe^{3+} in the brain [43]. This suggests that the change in Fe^{2+}/Fe^{3+} might favor iron-induced production of reactive oxygen species.

Disorders Leading to Manganese Accumulation in the Brain

Manganese Poisoning

High levels of manganese in the blood can occur due to a high manganese intake, which is particularly likely if the mechanisms restricting entry through the gut are by-passed. Examples include parenteral nutrition, intravenous abuse of drugs contaminated with manganese, working in mines and battery factories, and welding [42].

Acquired Hepatocerebral Syndrome/ Acquired Hepatocerebral Degeneration

In patients with chronic liver disease (particularly cirrhosis), manganese excretion is impaired and blood manganese rises with the deposition of manganese in the basal ganglia and subsequent motor impairment. Clinical characteristics include movement disorders, mainly parkinsonism and ataxia-plus syndrome, as well as cognitive impairment with psychiatric features. Neuroimaging studies of acquired hepatocerebral degeneration (AHD) with parkinsonism show hyperintensity in the bilateral globus pallidus on T1-weighted magnetic resonance images, consistent with manganese accumulation. Ataxia-plus syndrome in AHD may demonstrate high-signal lesions in the middle cerebellar peduncles on T2-weighted images [44]. Iron deficiency is common in patients showing brain MRI abnormalities compatible with manganese deposits in thr basal ganglia. This observation suggests that iron deficiency could be an important risk factor for manganese-induced neurotoxicity and should, therefore, be carefully considered and treated [45].

Dystonia–Parkinsonism, Hypermanganesemia, Polycythemia, and Chronic Liver Disease (SLC30A10 Deficiency)

In 2012, it was shown that an autosomal-recessive syndrome of dystonia–parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease was caused by bi-allelic mutations in *SLC30A10* [37, 38, 46]. By 2017, 22 affected families had been described and it is now clear that the disease can present with liver disease, a movement disorder, or a combination of the two [47, 48].

The movement disorder can present as early as the second year or as late as the sixth decade of life. Difficulty with walking is a common early symptom. Extrapyramidal signs are variable, from severe dysdiadochokinesis but sparing of face and tongue (Video 17.1) and pure four-limb dystonia with a cock-walk, i.e. high-stepping, gait (Video 17.2), to typical parkinsonism with bradykinesia, cogwheel rigidity, hypomimia, and dysarthria [49]. One patient has spastic paraparesis without dystonia and two siblings have hypotonia with sensorimotor axonal neuropathy [38, 46]. The rate of progression of the movement disorder can be slow in adults but quite rapid in patients presenting in the second year of life.

MRI of the brain shows areas of hyperintensity on T1-weighted images consistent with increased levels of manganese. These are particularly seen in the globus pallidus, putamen, and subthalamic region (but sparing the thalamus), in the brainstem (but sparing the lower pons), and in the dentate nucleus and cerebellar white matter. In some, but not all, patients there is also hyperintensity of the cortical white matter and anterior pituitary (Figure 17.2).

MRI of the liver also shows hyperintenstiy on T1-weighted images consistent with raised manganese levels; this is not seen in SLC39A14 deficiency [42].

Clinical evidence of liver disease may be apparent, ranging from mild hepatomegaly to hepatic failure in early adulthood. Liver function tests show raised transaminases in most cases.

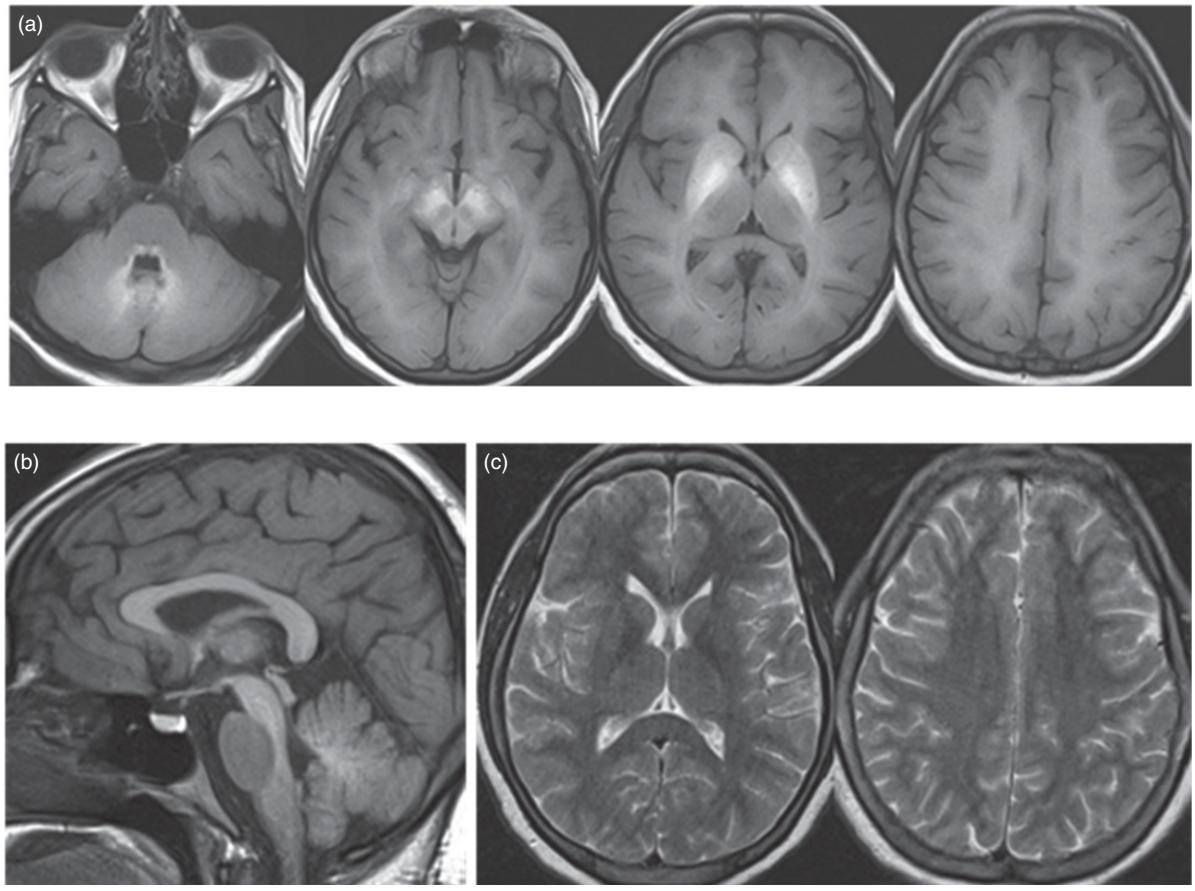

Figure 17.2 MRI brain appearances in SLC30A10 deficiency: T1-weighted MRI shows abnormally high signal on (a) transaxial images from the white matter, putamen, and globus pallidus bilaterally; and (b) on sagittal images from the anterior pituitary and white matter, particularly the corpus callosum, midbrain, dorsal pons, and medulla. (c) Transaxial T2-weighted images show abnormally low signal from the globus pallidus in the same distribution as the regions of highest signal on the T1-weighted images. From: Tuschl K, Clayton PT, Gospe SM Jr et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in *SLC30A10*, a manganese transporter in man. Am J Hum Genet. 2012; 90:457–66.

Other laboratory investigations usually show polycythemia, although in a patient with severe liver disease and gastrointestinal bleeding this may be masked. Whole blood manganese is usually >2000 nM (normal <320 nM).

The first successful treatment was achieved by the chelation of manganese with intravenous disodium calcium edetate together with an iron supplement to reduce manganese absorption. Chelation treatment led to the improvement of neurological symptoms, the halt of liver disease progression, the normalization of hemoglobin levels, and the reduction of manganese blood levels [37, 38, 46].

More recently, treatment using 2,3-dimercaptosuccinic acid as a manganese chelating agent showed satisfactory results with improvement of biochemical markers, hepatic manifestations, and relative amelioration of the neurological symptoms [47].

Infantile/Early-Childhood-Onset Dystonia with Hypermanganesemia (SLC39A14 Deficiency)

In 2016, patients with infantile/early-childhood-onset parkinsonism–dystonia with hypermanganesemia and MRI indicating increased manganese in the basal ganglia were shown to have bi-allelic mutations in *SLC39A14* [42]. To date, 29 cases from 11 families have been described [50, 51]. Individuals with SLC39A14 deficiency do not have liver disease or polycythemia.

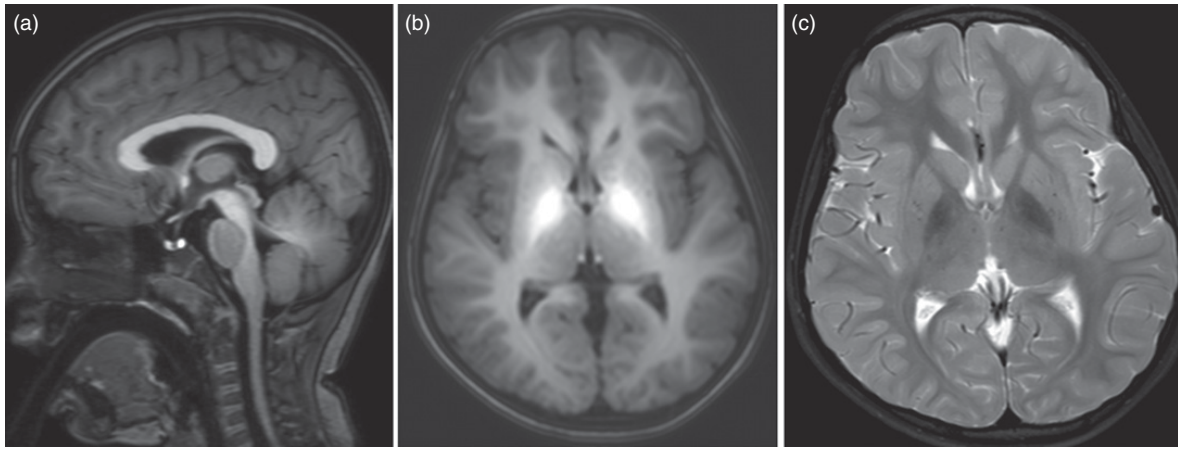

Figure 17.3 MRI brain appearances in SLC39A14 deficiency. Generalized T1 hyperintensity of (a) the white matter, including the dorsal pons and cerebellum, and the pituitary gland, on sagittal images; and (b) the cerebral white matter, globus pallidus, and striatum, on transaxial images, can be observed. (c) Hypointensity of the globus pallidus is also evident on T2-weighted imaging. From: Tuschl K, Meyer E, Valdivia LE et al Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism-dystonia. Nat Commun. 2016 May 27;7:11601

The median age of onset of the dystonia is younger than for SLC30A10 deficiency. Patients typically present between 5 months and 3 years with delayed walking or gait disturbance. Examination in the early course of the disease shows principally hypotonia. Later, examination reveals dystonia, spasticity, dysarthria, bulbar dysfunction, and parkinsonian features (bradykinesia, tremor, and hypomimia). It is a progressive disorder leading, by the age of 10 years, to generalized severe drug-resistant dystonia, limb deformities, scoliosis, and loss of independent walking. Patients may even die before the age of 10 years from complications (e.g. chest infection) [42].

MRI of the brain shows hyperintense areas on T1-weighted images, consistent with increased manganese levels. The areas principally affected are the globus pallidus and striatum with sparing of the thalamus; the T2-weighted images of these areas show hypointensity. In addition, the white matter T1 intensity is increased in the white matter. including the cerebellum, spinal cord, and dorsal pons (with sparing of the ventral pons) (Figure 17.3) [42].

Laboratory investigations show a markedly elevated whole blood manganese level (usually >1000 nM; reference range <320 nM).

Sequencing of *SLC39A14* in patients with infantile/early childhood-onset dystonia with hypermanganesemia has revealed missense mutations, nonsense mutations, and frameshift mutations, causing premature termination of translation.

Attempts to treat SLC39A14 deficiency with chelation therapy have met with some success [42]. A 5-year old girl was treated with intravenous disodium calcium edetate (20 mg/kg per dose) twice daily for 5 days a month (similar to the regimen that had been successful in SLC30A10 deficiency). After 6 months of treatment, the neurological signs had improved and the child had regained the ability to walk independently (Videos 17.3 and 17.4). In contrast, the attempted treatment of a 17-year-old girl with advanced disease was not successful. Prior to the start of treatment, she had severe generalized dystonia with prominent oromandibular involvement, contractures, and scoliosis. On treatment, her disease continued to progress with worsening tremor and stiffness. It is likely that, to be effective, chelation treatment for SLC39A14 deficiency will need to be started early in the course of the disease [42].

Other approaches to treatment include decreasing dietary manganese intake (using a manganese-depleted synthetic formula) and symptomatic treatment of dystonia such as oral trihexyphenidyl, botulinum toxin injections, and tendon-lengthening surgery [51].

Disorders Leading to Manganese Deficiency

SLC39A8 Deficiency

Two papers published simultaneously in 2015 described the effects of *SLC39A8* mutations [39, 40]. Six patients from the Hutterite community and an Egyptian sibling pair presented with developmental delay/intellectual disability, hypotonia, strabismus, and variable short stature. MRI scans showed cerebellar atrophy. Concentrations of manganese and zinc were variably reduced in plasma and increased in urine [39]. They all had a homozygous mutation (p. Gly38Arg) in *SLC39A8.* A further affected individual presented with cranial asymmetry, disproportionate (short-limbed) dwarfism, severe infantile spasms with hypsarrhythmia, hearing loss, and severe developmental delay. The blood manganese was below the limit of detection. The patient's plasma showed an abnormal transferrin glycosylation profile (type II pattern); this was consistent with the reduced activity of a manganese-dependent enzyme required for N-glycosylation – beta-1,4-galactosyltransferase [40]. The transferrin glycosylation profile improved with galactose treatment.

In 2017, two further patients with mutations in *SLC39A8* (homozygous p.Cys113Ser) were described [41]. They presented with features suggestive of Leigh syndrome: profound developmental delay, dystonia, seizures, and failure with to thrive, with basal ganglia T2 hyperintensities and elevated cerebrospinal fluid lactate (in one). This sibling was shown to have reduced activities of complexes II/III and IV in liver. However, the second sibling also had a type II abnormal transferrin pattern and blood and urine manganese levels were undetectably low. Interestingly, the brain imaging findings in both siblings were opposite to those seen in the disorders in which manganese accumulates (SLC30A10 and SLC39A14 deficiencies); the basal ganglia were hypointense on T1-weighted images and hyperintense on T2. The abnormal transferrin pattern was attributed to the reduced beta-1,4-galactosyltransferase activity, and the mitochondrial damage to a build-up of reactive oxygen species as a result of the reduced activity of manganese-dependent superoxide dismutase [41].

Treatment with high-dose manganese sulphate (15–20 mg/kg per day) led to a marked improvement in blood manganese, and transferrin glycosylation in two patients. In a child whose treatment was started at 8 months, previously intractable seizures came under control and there was an improvement in hearing, vision, and motor function (reduction in hyperextension, improved head control, and progress in motor milestones). Infantile spasms were fully controlled. In a 19-year-old woman with global psychomotor disability, seizures, strabismus, scoliosis, and cerebellar atrophy on MRI, motor function improved. Previously observed repetitive movements of the head were observed less frequently and she became able to perform the finger-to-nose test, indicating reduced ataxia. Muscle strength improved and she became able to sit without support [52]. Interestingly, a missense variant in *SLC39A8* was recently found to be associated with severe idiopathic scoliosis [53].

Disorders of Other Manganese Transporters

ATP13A2 Mutations (Kufor–Rakeb Syndrome)

ATP13A2 encodes a lysosomal transporter for divalent transition metals required to maintain intracellular manganese homeostasis [54]. Bi-allelic mutations cause two phenotypes. The first type is the autosomal-recessive Kufor–Rakeb syndrome, which presents in childhood with atypical parkinsonism, supranuclear gaze palsy, spasticity, and dementia [55]. MRI indicates the features of iron accumulation in the basal ganglia in some (so it is classified as one of the NBIA disorders, see Chapter 16). The second phenotype is spastic paraplegia type 78, a paraplegia plus disorder. Onset of spastic quadriplegia with bilateral pes cavus in the second decade is associated with other neurological abnormalities such as cognitive decline, ataxia, nystagmus, ophthalmoplegia, and axonal sensory and motor neuropathy. One patient has shown progressive parkinsonism but others have had no signs of basal ganglia dysfunction. MRI shows cerebral atrophy and changes in the basal ganglia, and dopamine transport scintigraphy may show marked depletion of dopamine transporter density in the putamen, even in the absence of extrapyramidal symptoms [56].

ATP13A1 Mutations

ATP13A1 encodes a transporter in the membrane of the endoplasmic reticulum. The yeast homolog was

shown to regulate manganese transport into the endoplasmic reticulum [57]. In a study of a cohort of individuals with intellectual disability, mutations in this gene have been reported in children with, in addition to intellectual disability, dysmorphic features (downslanting palpebral fissures, prominent nose, hyperplasia of the maxilla, abnormal finger nails), attention hyperactivity disorder, and recurrent respiratory infections [58].

Disorders of Individual Manganese-Dependent Enzymes

Deficiency of Manganese Superoxide Dismutase (SOD2)

In mice, homozygous mutations of *Sod2* lead to premature death within the first 10 days of life with a dilated cardiomyopathy, accumulation of lipid in liver and skeletal muscle, and metabolic acidosis [59]. The role of SOD2 in clinical disease remains under intense study [60].

Arginase Deficiency

Arginase deficiency is a urea cycle defect, causing high plasma arginine and episodic hyperammonemia. Untreated individuals develop spastic diplegia or tetraplegia, plateauing of cognitive development, epilepsy, and the subsequent loss of developmental milestones. Plasma arginine was normal in a severely affected infant with SLC39A8 deficiency [40].

Glutamine Synthase Deficiency

Glutamine synthase deficiency leads to low plasma glutamine, chronic hyperammonemia, epileptic encephalopathy, diarrhea, an erythematous skin rash, and multi-organ failure. Plasma glutamine was normal in a severely affected infant with SLC39A8 deficiency [40].

Prolidase Deficiency

Homozygous mutations in *PEPD* cause skin lesions (including skin ulcers and telangiectasias), recurrent infections, dysmorphic facial features, variable intellectual disability, and hepatomegaly. Biochemically, it is characterized by massive urinary excretion of imidodipeptides; this has not been reported in SLC39A8 deficiency.

Pyruvate Carboxylase Deficiency

Pyruvate carboxylase (PC) deficiency is characterized by failure to thrive, developmental delay, recurrent seizures, and lactic acidosis. However, infants with type B PC deficiency ("French phenotype") also present with neonatal-onset hypothermia, hypotonia, lethargy, convulsions, vomiting, and hepatomegaly. Bizarre ocular eye movements and especially rigidity and hypokinesia (hypokinetic–rigid syndrome) are important hallmarks and may suggest PC deficiency when associated with severe lactic acidosis [61].

Glycosyl Transferases

Glycosyl transferases are known to be manganese-containing enzymes. Hence, it is not surprising that manganese deficiency leads to defects in glycosylation [47]. The galactosyl transferase whose compromised activity is thought to give rise to the abnormal transferrin pattern in SLC39A8 deficiency is encoded by *B4GALT1*. Mutations in this gene cause congenital disorder of glycosylation type IId – described in a boy, born of non-consanguineous parents, who presented with macrocephaly due to Dandy–Walker malformation, hypotonia, coagulopathy, myopathy with elevated creatine kinase, mild developmental delay, motor retardation, and an abnormal serum transferrin pattern by isoelectric focusing [62].

Key Points and Clinical Pearls

- Copper and manganese perform essential roles in the basal ganglia and elsewhere in the nervous system.
- Neurological disease (particularly movement disorders) can result from deficiency or excess of copper/manganese.
- Maintenance of optimal levels of copper and manganese in the nervous system requires whole-body as well as local homeostatic mechanisms. Liver uptake and excretion are particularly important in preventing high levels in the blood and, as a result, in the brain
- Wilson disease can present with neurological disease, or liver disease or both. Kayser–Fleischer rings are an important clinical sign indicating that a movement disorder is due to Wilson disease. Low plasma copper and ceruloplasmin and increased urinary copper excretion provide confirmation.

- Movement disorders caused by manganese toxicity produce characteristic MRI images with high intensity of the basal ganglia (and other brain areas) on T1-weighted images – raised blood manganese provides confirmation.
- Deficiency of copper/managnese can be treated with supplements of the metal and toxicity due to high levels can be treated with chelators.

Directions for Future Research

- Better understanding of the basic science of how levels of copper and manganese are controlled in different organs and subcellular organelles.
- Improved early detection; therapies are most effective if started early.
- Improvement in therapy for Wilson disease: avoidance of the risk of neurological deterioration.
- Improvement in therapy for the disorders causing high levels of manganese in the brain, e.g. orally active chelation agents.

References

1. Metzler DE. Transition metals in catalysis and electron transport. In Metzler DE, Metzler CM, editors. Biochemistry: The Chemical Reactions of Living Cells, 2nd edn. San Diego, CA: Harcourt/Academic Press; 2003, vol. 1, ch. 16.
2. Clayton PT. Inherited disorders of transition metal metabolism: An update. J Inherit Metab Dis. 2017;**40**(4):519–9.
3. King D, Siau K, Senthil L, Kane KF, Cooper SC. Copper deficiency myelopathy after upper gastrointestinal surgery. Nutr Clin Pract. 2018;**33**(4):515–9.
4. van Hasselt PM, Clayton PT, Houwen RHJ. Disorders of the transport of copper, iron, magnesium, manganese, selenium and zinc. In Saudubray J-M, Baumgartner MR, Walter J, editors. Inborn Metabolic Diseases. Berlin: Springer; 2016, pp. 531–50.
5. Hlynialuk CJ, Ling B, Baker ZN, et al. The mitochondrial metallochaperone SCO1 is required to sustain expression of the high-affinity copper transporter CTR1 and preserve copper homeostasis. Cell Rep. 2015;**10**(6):933–43.
6. Dening TR, Berrios GE. Wilson's disease: Clinical groups in 400 cases. Acta Neurol Scand. 1989;**80**(6):527–34.
7. Ranjan A, Kalita J, Kumar S, Bhoi SK, Misra UK. A study of MRI changes in Wilson disease and its correlation with clinical features and outcome. Clin Neurol Neurosurg. 2015;**138**:31–6.
8. Czlonkowska A, Litwin T, Karlinski M, et al. D-penicillamine versus zinc sulfate as first-line therapy for Wilson's disease. Eur J Neurol. 2014;**21**(4):599–606.
9. Litwin T, Dziezyc K, Karlinski M, Chabik G, Czepiel W, Czlonkowska A. Early neurological worsening in patients with Wilson's disease. J Neurol Sci. 2015; **355** (1-2): 162–7.
10. Brewer GJ, Askari F, Lorincz MT, et al. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. Arch Neurol. 2006;**63**(4):521–7.
11. Ahmad A, Torrazza-Perez E, Schilsky ML. Liver transplantation for Wilson disease. Handb Clin Neurol. 2017;**142**:193–204.
12. Martinelli D, Travaglini L, Drouin CA, et al. MEDNIK syndrome: A novel defect of copper metabolism treatable by zinc acetate therapy. Brain. 2013;**136**(Pt 3):872–81.
13. Martinelli D, Dionisi-Vici C. *AP1S1* defect causing MEDNIK syndrome: A new adaptinopathy associated with defective copper metabolism. Ann N Y Acad Sci. 2014;**1314**:55–63.
14. Cao B, Yang X, Chen Y, et al. Identification of novel *ATP7A* mutations and prenatal diagnosis in Chinese patients with Menkes disease. Metab Brain Dis. 2017;**32**(4):1123–31.
15. Manara R, Rocco MC, D'Agata L, et al. Neuroimaging changes in Menkes disease: Part 2. AJNR Am J Neuroradiol. 2017;**38**(10):1858–65.
16. Lee T, Yagi M, Kusunoki N, et al. Standard values for the urine HVA/VMA ratio in neonates as a screen for Menkes disease. Brain Dev. 2015;**37**(1):114–9.
17. Kaler SG. *ATP7A*-related copper transport disorders. GeneReviews®. 2003;May 9 (updated Aug 18, 2016).
18. Miyajima H, Hosoi Y. Aceruloplasminemia. GeneReviews®. 2003;Aug 12 (updated Sep 27, 2018).
19. Poli L, Alberici A, Buzzi P, et al. Is aceruloplasminemia treatable? Combining iron chelation and fresh-frozen plasma treatment. Neurol Sci. 2017;**38**(2):357–60.
20. Huppke P, Brendel C, Korenke GC, et al. Molecular and biochemical characterization of a unique mutation in *CCS*, the human copper chaperone to superoxide dismutase. Hum Mutat. 2012;**33**(8):1207–15.

21. Rosen DR, Siddique T, Patterson D, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature. 1993;**362**(6415):59–62. Published erratum: Nature. 1993;**362**(6435):362.

22. Valnot I, Osmond S, Gigarel N, et al. Mutations of the *SCO1* gene in mitochondrial cytochrome c oxidase deficiency with neonatal-onset hepatic failure and encephalopathy. Am J Hum Genet. 2000;**67**(5):1104–9.

23. Leary SC, Antonicka H, Sasarman F, et al. Novel mutations in *SCO1* as a cause of fatal infantile encephalopathy and lactic acidosis. Hum Mutat. 2013;**34**(10):1366–70.

24. Jaksch M, Ogilvie I, Yao J, et al. Mutations in *SCO2* are associated with a distinct form of hypertrophic cardiomyopathy and cytochrome c oxidase deficiency. Hum Mol Genet. 2000;**9**(5):795–801.

25. Papadopoulou LC, Sue CM, Davidson MM, et al. Fatal infantile cardioencephalomyopathy with COX deficiency and mutations in *SCO2*, a COX assembly gene. Nat Genet. 1999;**23**(3):333–7.

26. Rebelo AP, Saade D, Pereira CV, et al. *SCO2* mutations cause early-onset axonal Charcot–Marie–Tooth disease associated with cellular copper deficiency. Brain. 2018;**141**(3):662–72.

27. Robertson D, Haile V, Perry SE, et al. Dopamine beta-hydroxylase deficiency. A genetic disorder of cardiovascular regulation. Hypertension. 1991;**18**(1):1–8.

28. Biaggioni I, Robertson D. Endogenous restoration of noradrenaline by precursor therapy in dopamine-beta-hydroxylase deficiency. Lancet. 1987;**2**(8569):1170–2.

29. Guo DC, Regalado ES, Gong L, et al. *LOX* mutations predispose to thoracic aortic aneurysms and dissections. Circ Res. 2016;**118**(6):928–34.

30. Lewis RA. Oculocutaneous albinism type 1. GeneReviews®. 2000;Jan 19 (updated May 16, 2013).

31. Huppke P, Brendel C, Kalscheuer V, et al. Mutations in *SLC33A1* cause a lethal autosomal-recessive disorder with congenital cataracts, hearing loss, and low serum copper and ceruloplasmin. Am J Hum Genet. 2012;**90**(1):61–8. Published erratum: Am J Hum Genet. 2012;**90**(2):378.

32. Lin P, Li J, Liu Q, et al. A missense mutation in *SLC33A1*, which encodes the acetyl-CoA transporter, causes autosomal-dominant spastic paraplegia (SPG42). Am J Hum Genet. 2008;**83**(6):752–9.

33. Tuschl K, Mills PB, Clayton PT. Manganese and the brain. Int Rev Neurobiol. 2013;**110**:277–312.

34. Li L, Yang X. The essential element manganese, oxidative stress, and metabolic diseases: Links and interactions. Oxid Med Cell Longev. 2018;**2018**:7580707.

35. Peres TV, Schettinger MR, Chen P, et al. Manganese-induced neurotoxicity: A review of its behavioral consequences and neuroprotective strategies. BMC Pharmacol Toxicol. 2016;**17**(1):57.

36. Chen P, Chakraborty S, Mukhopadhyay S, et al. Manganese homeostasis in the nervous system. J Neurochem. 2015;**134**(4):601–10.

37. Tuschl K, Mills PB, Parsons H, et al. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia: A new metabolic disorder. J Inherit Metab Dis. 2008;**31**(2):151–63.

38. Tuschl K, Clayton PT, Gospe SM, Jr., et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in *SLC30A10*, a manganese transporter in man. Am J Hum Genet. 2012;**90**(3):457–66.

39. Boycott KM, Beaulieu CL, Kernohan KD, et al. Autosomal-recessive intellectual disability with cerebellar atrophy syndrome caused by mutation of the manganese and zinc transporter gene *SLC39A8*. Am J Hum Genet. 2015;**97**(6):886–93.

40. Park JH, Hogrebe M, Gruneberg M, et al. SLC39A8 deficiency: A disorder of manganese transport and glycosylation. Am J Hum Genet. 2015;**97**(6):894–903.

41. Riley LG, Cowley MJ, Gayevskiy V, et al. A *SLC39A8* variant causes manganese deficiency, and glycosylation and mitochondrial disorders. J Inherit Metab Dis. 2017;**40**(2):261–9.

42. Tuschl K, Meyer E, Valdivia LE, et al. Mutations in *SLC39A14* disrupt manganese homeostasis and cause childhood-onset parkinsonism–dystonia. Nat Commun. 2016;**7**:11601.

43. Fernsebner K, Zorn J, Kanawati B, Walker A, Michalke B. Manganese leads to an increase in markers of oxidative stress as well as to a shift in the ratio of Fe(II)/(III) in rat brain tissue. Metallomics. 2014;**6**(4):921–31.

44. Shin HW, Park HK. Recent updates on acquired hepatocerebral degeneration. Tremor and Other Hyperkinet Movements (NY). 2017;**7**:463.

45. Herrero Hernandez E, Valentini MC, Discalzi G. T1-weighted hyperintensity in basal ganglia at brain magnetic resonance imaging: Are different pathologies sharing a common mechanism? Neurotoxicology. 2002;**23**(6):669–74.

46. Quadri M, Federico A, Zhao T, et al. Mutations in *SLC30A10* cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet. 2012;**90**(3):467–77.

47. Zaki MS, Issa MY, Elbendary HM, et al. Hypermanganesemia with dystonia, polycythemia and

cirrhosis in 10 patients: Six novel *SLC30A10* mutations and further phenotype delineation. Clin Genet. 2018;**93**(4):905–12.

48. Gulab S, Kayyali HR, Al-Said Y. Atypical neurologic phenotype and novel *SLC30A10* mutation in two brothers with hereditary hypermanganesemia. Neuropediatrics. 2018;**49**(1):72–5.
49. Stamelou M, Tuschl K, Chong WK, et al. Dystonia with brain manganese accumulation resulting from *SLC30A10* mutations: A new treatable disorder. Mov Disord. 2012;**27**(10):1317–22.
50. Zeglam A, Abugrara A, Kabuka M. Autosomal-recessive iron deficiency anemia, dystonia and hypermanganesemia caused by new variant mutation of the manganese transporter gene *SLC39A14*. *Acta Neurol Belg*. 2019;**119**(3):379–84.
51. Rodan LH, Hauptman M, D'Gama AM, et al. Novel founder intronic variant in *SLC39A14* in two families causing manganism and potential treatment strategies. Mol Genet Metab. 2018;**124**(2):161–7.
52. Park JH, Hogrebe M, Fobker M, et al. SLC39A8 deficiency: Biochemical correction and major clinical improvement by manganese therapy. Genet Med. 2018;**20**(2):259–68.
53. Haller G, McCall K, Jenkitkasemwong S, et al. A missense variant in *SLC39A8* is associated with severe idiopathic scoliosis. Nat Commun. 2018;**9**(1):4171.
54. Tan J, Zhang T, Jiang L, et al. Regulation of intracellular manganese homeostasis by Kufor–Rakeb syndrome-associated ATP13A2 protein. J Biol Chem. 2011;**286**(34):29654–62.
55. Park JS, Blair NF, Sue CM. The role of ATP13A2 in Parkinson's disease: Clinical phenotypes and molecular mechanisms. Mov Disord. 2015;**30**(6):770–9.
56. Estrada-Cuzcano A, Martin S, Chamova T, et al. Loss-of-function mutations in the *ATP13A2/PARK9* gene cause complicated hereditary spastic paraplegia (SPG78). Brain. 2017;**140**(2):287–305.
57. Cohen Y, Megyeri M, Chen OC, et al. The yeast p5 type ATPase, spf1, regulates manganese transport into the endoplasmic reticulum. PLoS One. 2013;**8**(12):e85519.
58. Anazi S, Maddirevula S, Salpietro V, et al. Expanding the genetic heterogeneity of intellectual disability. Hum Genet. 2017; **136** (11-12): 1419–29.
59. Li Y, Huang TT, Carlson EJ, et al. Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase. Nat Genet. 1995;**11**(4):376–81.
60. Konzack A, Kietzmann T. Manganese superoxide dismutase in carcinogenesis: Friend or foe? Biochem Soc Trans. 2014;**42**:1012–6.
61. De Meirleir L. Disorders of pyruvate metabolism. Handb Clin Neurol. 2013;**113**:1667–73.
62. Hansske B, Thiel C, Lubke T, et al. Deficiency of UDP-galactose: N-acetylglucosaminebeta-1,4-galactosyltransferase I causes the congenital disorder of glycosylation type IId. J Clin Invest. 2002;**109**(6):725–33.

Chapter 18

Metal Storage Disorders: Primary Familial Brain Calcification and Movement Disorders

Ana Westenberger and Christine Klein

Introduction

Bilateral calcium deposits are frequently encountered on brain imaging (typically CT scans) or post-mortem examination and may be found in as many as 7% [1] to 20% [2] of investigated individuals. In the majority of cases, calcification is considered physiological, i.e. the result of a normal aging process (with its prevalence almost tripling over 65 years of age) [2], and not clinically relevant [3]. In some instances, the accumulation of calcium may be an associated secondary finding of more than 50 environmental, metabolic, mitochondrial, autoimmune, and sporadic or inherited genetic conditions summarized in recent reviews [4, 5]. Mostly symmetrical bilateral calcifications of the basal ganglia and/or other brain regions, such as the thalamus, brainstem, cerebellum, and cerebral cortex, are occasionally the presentation of a rare group of genetic neurodegenerative disorders, termed primary familial brain calcification (PFBC) disorders. The goal of this chapter is to review and discuss the nomenclature, genetic and molecular mechanisms, and phenotypes of PFBC.

PFBC Nomenclature

Since the first description of "bilateral cerebral calcifications most prominent in the striatum," reported by the French physician Delacour [6], more than 40 different terms referring to calcium deposits in the basal ganglia have appeared in the literature [7–9]. Curiously, an eponym derived from the name of the German pathologist Theodor Fahr became a common term for basal ganglia calcification, although Fahr located calcifications predominantly to the white matter [10, 11], and published his work 80 years after Delacour. This eponym, as well as the second most frequent misnomer, "idiopathic familial basal ganglia calcification (IBGC)," have been replaced by the term "primary familial brain calcification (PFBC)" in recent years [9]. Since the discovery of the underlying genetic etiologies it was recognized that calcification is not confined to the basal ganglia. Consequently, the "idiopathic" and "basal ganglia" have been replaced with "primary" and "brain," and the more accurate term, "primary familial brain calcification," has been coined [4].

Nevertheless, IBGC remained a symbol for PFBC genetic loci, numbered in chronological order of the regional identification (Table 18.1), with the corresponding genes discovered years later [12–16]. According to the recent recommendations by the International Parkinson and Movement Disorder Society (MDS) Task Force for Nomenclature of Genetic Movement Disorders, genetically determined PFBC syndromes are labeled by the prefix PFBC, followed by the relevant gene name (Table 18.1) [17].

Genetics of PFBC

The number of large families with basal ganglia calcification reported in the literature over the last 70 years clearly indicated that PFBC is a hereditary disorder. Furthermore, the distribution of affected members within multigenerational pedigrees suggested a monogenic etiology and autosomal-dominant inheritance. Thus, until recently, PFBC was perceived as an autosomal-dominant disorder, and, indeed, this was supported by the discovery of heterozygous pathogenic changes in four different genes: *SLC20A2* [13], *PDGFRB* [18], *PDGFB* [19], and *XPR1* [20]. However, in 2018, biallelic mutations in *MYORG* [21] uncovered the first autosomal-recessive form of PFBC. Pathogenic changes in each of the five genes have been identified not only in PFBC families but also in single, sporadic patients.

Autosomal-Dominant PFBC

PFBC-*SLC20A2*

The first PFBC gene, *SLC20A2*, was identified in 2012 by fine-mapping of the IBGC3 locus and subsequent candidate gene sequencing [13]. In the same study, six other *SLC20A2* mutations were found, leaving little doubt as

Table 18.1 List of PFBC forms

PFBC designation	PFBC-*SLC20A2*	PFBC-*PDGFRB*	PFBC-*PDGFB*	PFBC-*XPR1*	PFBC-*MYORG*
Gene name	*SLC20A2*	*PDGFRB*	*PDGFB*	*XPR1*	*MYORG*
Protein name	Solute carrier family 20 member 2	Platelet-derived growth factor receptor beta	Platelet-derived growth factor subunit B	Xenotropic and polytropic retrovirus receptor 1	Myogenesis regulating glycosidase
Protein function	Inorganic phosphate importer (PiT2)	Tyrosine kinase-type receptor (PDGF-Rβ)	Platelet-derived growth factor subunit (PDGF-B)	Inorganic phosphate exporter (XPR1)	Protein glycosidase (MYORG)
Locus symbol	IBGC1, IBGC2, IBGC3	IBGC4	IBGC5	IBGC6	IBGC7
OMIM number	213600	615007	615483	616413	618317
Inheritance pattern	Autosomal-dominant	Autosomal-dominant	Autosomal-dominant	Autosomal-dominant	Autosomal-recessive
Type of mutations	Missense, nonsense, frameshift, large (exonic) deletions	Missense, nonsense	Missense, nonsense, frameshift, large (exonic) deletions	Missense	Missense, nonsense, frameshift

to whether or not *SLC20A2* was the right candidate. In more than 60 publications that followed, nearly 200 *SLC20A2* mutation carriers, mostly of Asian and Caucasian origin, were reported. These carry more than 50 different *SLC20A2* sequence changes, mostly missense, nonsense, and frameshift mutations [16, 22]. The majority of the changes are novel, i.e. not reported in public databases such as ExAC [23], gnomAD [23], or dbSNP [24], and are predicted to be highly deleterious (reflected in an average combined annotation dependent depletion (CADD) [25] score of >30, range: 14–48) [22]. Importantly, five large deletions, involving single exons (2 and 4) [26], multiple exons (4–5 and 6–10) [15, 26], and even the entire *SLC20A2* gene [27] were also discovered, stressing the importance of gene dosage analysis in *SLC20A2*. The coding region of *SLC20A2* encompasses 1,959 base pairs, spanning 11 exons. There seem to be no mutational hotspots and the reported variants can be found in each of the exons, with only a few changes detected in more than one index patient. Interestingly, among the *SLC20A2*-tested individuals, there were also members of the two large families initially linked to the IBGC1 and IBGC2 loci. They were found to carry deletions (single-nucleotide; c.508delT, and multiexonic; c.(613+1_614−1)_(1794+1_1795−1)del, respectively) [14, 15] in *SLC20A2*, collapsing loci IBGC1-3 into a single locus, IBGC1.

PFBC-*PDGFRB*

PRGFRB became implicated in PFBC by means of exome sequencing, carried out in a large three-generational French family [18]. This analysis revealed a missense *PDGFRB* change, completely segregating with the brain calcification phenotype [18]. However, only a few of the subsequent *PDGFRB* screening studies reported mutation carriers, indicating that changes in this gene are a cause of PFBC but not a very frequent one. Currently, only six different *PDGFRB* mutations (five missense and one variant of unknown effect, affecting the first codon) in three PFBC families and three sporadic patients have been identified [16, 22]. Three of the six variants are novel and three can be found at a very low frequency in ExAC (with CADD scores around 29, ranging from 23 to 34) [22]. The *PDGFRB* coding region has 3,321 base pairs, comprises 22 exons, and to date, mutations were found in the coding exons 1, 13–15, 21, and 22.

PFBC-*PDGFB*

Shortly after variants in *PDGFRB* had been linked to PFBC in 2013, mutations in a functionally related gene, *PDGFB*, have been discovered through next-generation sequencing in two families with basal ganglia calcification [19]. Since then, more than 50 predominantly Caucasian and Asian individuals, carrying ~15 different (mostly missense and nonsense) *PDGFB* mutations have been identified [16, 22]. One large structural change, a deletion of exons 3–5, has been reported [28]. Interestingly, none of the changes found in these PFBC patients is listed in ExAC. The mean CADD score of known *PDGFB* mutations is 29, with a range of 11–41 [22]. In comparison to *SLC20A2* and *PDGFRB*, *PDGFB* is relatively small and its coding region consists of 726 base pairs encompassing six exons. One-third of the mutations are situated in exon 4, and three changes were reported in two independent studies each [22].

PFBC-*XPR1*

XPR1 is the most recently identified gene for autosomal-dominant PFBC. The initial study, which uncovered the very first *XPR1* mutations, utilized exome sequencing in a large family of Swedish ancestry, also reported two more families and two sporadic patients with different *XPR1* changes [20]. To date, only one additional publication detected an *XPR1* mutation in a single patient [29], thus increasing the number of PFBC families/sporadic patients to six (all of the European origin), which collectively carry five different *XPR1* variants. All of those five mutations are missense variants, absent from the public databases, predicted to be pathogenic (CADD scores of 27–29) [22], and situated in the first third of the 2,091 base-pair-long coding region, in exons 4 and 6 of 15 exons.

Autosomal-Recessive PFBC

PFBC-*MYORG*

In 2018, after excluding the previously known PFBC causes in their collection of 51 families with bilateral brain calcifications, Yao and colleagues decided to focus on the subset of pedigrees with a seemingly autosomal-recessive mode of inheritance [21]. As a starting point, they performed exome sequencing in a family with documented consanguinity and detected homozygous mutations in *MYORG* and four other genes. Exome sequencing in another autosomal-recessive family revealed compound-heterozygous variants in *MYORG*, thus determining this as a nominee for further mutational screening efforts. Indeed, the authors discovered one more family with homozygous and three with compound-heterozygous *MYORG* variants. Of the nine different *MYORG* mutations found in the six autosomal-recessive families, three were nonsense, four were missense, and two were in-frame insertions [21]. The mutations were evenly distributed across the 2,145 base-pair-long coding region located within the single exon, and four were novel (i.e. absent from the publicly available databases). The CADD scores ranged between 22 and 39.

Molecular Mechanisms of PFBC

Once the four genes related to *autosomal-dominant* PFBC were identified and the functional roles of their protein investigated, possible pathogenic pathways leading to calcification readily emerged. These pathways currently evolve around two likely scenarios: the impairment of phosphate metabolism (caused by mutations in *SLC20A2* and *XPR1*) and dysfunction of the blood–brain barrier (BBB) (due to changes in *PDGFRB* and *PDGFB*). Whether the two mechanisms are independent of one another or whether they intersect or converge is still not clear. As to the process of development of *autosomal-recessive* PFBC, although the cellular distribution of the *MYORG*-encoded protein indicates a role in the integrity of the neurovascular unit (NVU; composed of BBB, astrocytes, neurons, etc.), this hypothesis requires further investigation.

Phosphate Metabolism Impairment

The *SLC20A2* and *XPR1* genes both encode inorganic phosphate (Pi) transporters that play an important role in Pi homeostasis.

PiT2

The solute carrier family 20, member 2 gene (*SLC20A2*) encodes a 652-amino acid-long and ubiquitously expressed type III sodium-dependent Pi transporter 2 (PiT2), responsible for uptake of Pi into the cell (Figure 18.1a). PiT2 is integrated into the plasma membrane through 12 transmembrane regions but also contains one large intracellular domain [30]. PFBC-causing changes severely decrease the ability of the mutant PiT2 to import Pi, thus, likely leading to an extracellular accumulation of this anion, and ensuing build-up of calcium phosphate [13]. *Slc20a2* homozygous knockout mice are viable and, at 19 weeks of age, show calcifications in the thalamus, basal ganglia, and cortex [31], which are absent in slightly older wild-type mice. Eight-week-old knockout mice already display histologically detectable and weakly calcified nodules in the brain, which become larger, more abundant, and more calcified as these mice age [32]. Almost all of the aggregates were associated with blood vessels, and electron microscopy indicated that calcifications are located intracellularly, mainly in pericytes and astrocytes [32]. In agreement with the autosomal-dominant inheritance pattern seen the PFBC patients, two reports described the presence of calcium aggregates in heterozygous knockout mice, first appearing at the age of 6 months [32, 33]. However, while one study found weak calcification in one out of seven investigated mice [32], other studies labeled the detected bilateral calcifications as "prominent" [33]. The discrepancy was hypothetically attributed to environmental differences [32].

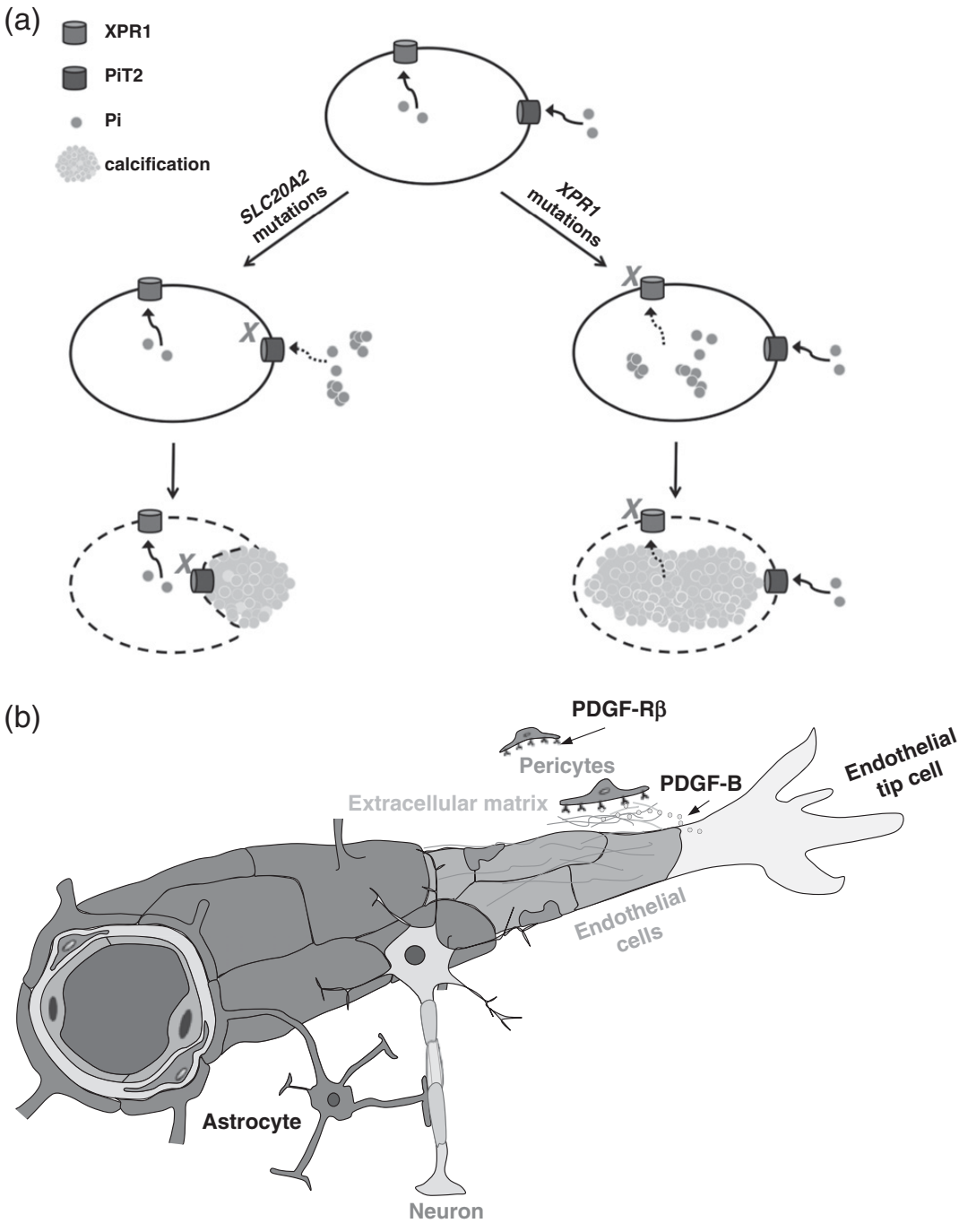

Figure 18.1 Schematic representation of the putative pathogenic mechanism of PFBC. (a) Pi in the brain parenchyma is taken up by PiT2 into the cells (possibly astrocytes and/or pericytes). From astrocytes/pericytes, Pi is exported through XPR1. If mutated, PiT2 is unable to import Pi, leading to an accumulation of Pi and subsequently of calcium phosphate in the extracellular matrix, and cell death. Mutated *XPR1* impairs Pi transport outside of the cell, leading to intracellular accumulation of calcium phosphate and cell death. (b) Structure of the NVU and recruitment of pericytes by endothelial cells. The NVU is an interactive network of vascular cells (pericytes and endothelial cells), glia (astrocytes), and neurons. During angiogenesis, PDGF-B is synthesized and secreted by angiogenic endothelial tip cells and retained in close vicinity to the growing blood vessel by the extracellular matrix. Incoming pericytes express PDGF-Rβ and are, hence, attracted to the PDGF-B-decorated endothelial cells, and depend on PDGF-B for proliferation and correct migration along the forming blood vessel.

Interestingly, in the mouse brain, Slc20a2 is expressed in tissues that produce and/or regulate cerebrospinal fluid (CSF) [33], such as the choroid plexus and arteriolar smooth muscle cells, and Pi levels in the CSF of the knockout mice are ~2.5-fold higher than in their wildtype littermates [34]. Hence, PiT2 might be important in sustaining the low levels of Pi in the CSF by exporting Pi from the CSF to the blood [34].

As previously explained, both nonsense and missense mutations in *SLC20A2* cause PFBC. While haploinsufficiency represents an obvious genetic mechanism behind the heterozygous null alleles, the same was initially suggested for the missense mutations (e.g. co-expression of the missense allele did not interfere with the activity of the wild-type protein *Xenopus laevis* oocytes, i.e. no dominant-negative effect was observed) [13]. Nonetheless, it is conceivable that at least some of the missense mutations may confer a dominant-negative effect. This was supported by a significantly (more than twice, as would be expected from a simple lack of one functional allele) lowered expression of PiT2 in the brain (and in particular in the astrocyte processes) of an autopsied p.Ser637Arg mutation carrier, in comparison to age-matched neurologically healthy controls [35]. In addition, three different mutants, each co-expressed with the wild-type PiT2 in fibroblasts of the homozygous knockout *Slc20a2* mice exhibited a dominant-negative effect evident from a significant decrease in Pi-uptake ability in comparison to cells only transfected with wild-type *Slc20a2* [36]. The possible dominant-negative effect may be explained by the fact that the functional PiT2 acts in a form of a homodimer. Thus, if a wild-type and mutated PiT2 oligomerize, they may be identified by the cell's quality-control system, and degraded.

XPR1

The xenotropic and polytropic retrovirus receptor 1 (*XPR1*) gene codes for a 696-amino acid multipass transmembrane Pi exporter. The *XPR1* mutations linked to PFBC have been shown to impair Pi efflux from the cell, thus likely increasing intracellular Pi levels (Figure 18.1a), leading to calcium phosphate precipitation [20]. Although the XPR1 protein is ubiquitously expressed, particularly high amounts of *XPR1* messenger RNA were detected in mouse brain and were peaking in the frequently calcified regions such as the cerebellum and striatum [37]. Functional studies indicate that PFBC-causing *XPR1* mutations might act through haploinsufficiency rather than via a dominant-negative effect [37]. Interestingly, analysis of the relation of XPR1 to the other PFBC-related proteins showed no interaction with PiT2 or PDGF-B. However, XPR1 co-localizes with PDGF-Rβ and may form a complex with this receptor, and such ability may be impaired by PFBC-inducing mutations [37].

Dysfunction of the BBB

PDGFB and *PDGFRB* code for the platelet-derived growth factor B (PDGF-B) and its receptor (PDGF-Rβ) that belong to the same signaling pathway. They are particularly important for angiogenesis and proper formation of the BBB; PDGF-B is secreted from angiogenic endothelial cells (Figure 18.1b) where it serves as an attractant for incoming PDGF-Rβ-positive mural cells (vascular smooth muscle cells [vSMCs] and pericytes) [38]. *Pdgfrb* and *Pdgfb* homozygous knockout mice are not viable (surviving only until around the time of birth) and have indistinguishable phenotypes with increased blood vessel diameter, vascular leakage, and dysfunction caused by vSMC and pericyte deficiency [39]. Importantly, mice homozygous for hypomorphic mutations are viable; however, the maturation of their BBB is severely impaired [39].

PDGF-Rβ

PDGF-Rβ is a 1,074-amino acid-long protein cell-surface tyrosine kinase receptor. It consists of an extracellular domain (that binds homodimerized PDGF-B), a transmembrane region, and an intracellular kinase domain that spans amino acid residues 600 to 962. Upon binding of the ligand, PDGF-Rβ becomes autophosphorylated, thus triggering downstream signaling pathways (e.g. cellular proliferation, differentiation, and migration) [40]. The two PFBC-associated mutations situated within the kinase domain, p.Leu658Pro and p.Arg695Cys, interfere with autophosphorylation by completely or partially abolishing it and thus impairing the receptor signaling. Another investigated change p.Arg987Trp was found to decrease protein stability [41, 42]. *PDGFRB* is the only PFBC-relevant gene in which missense mutations can cause conditions that do not have a primarily neurological phenotype. Namely, several heterozygous missense variants in *PDGFRB*, none of which have been reported in PFBC patients, are responsible for (i) a common benign soft-tissue

tumor in childhood and infancy (infantile myofibromatosis; OMIM 228550), (ii) Penttinen syndrome of premature aging syndrome (PENTT; OMIM 601812), and (iii) Kosaki overgrowth syndrome (KOGS; OMIM 616592), the latter two being caused by de novo changes [43]. Importantly, mutations leading to the non-PFBC phenotypes are considered to be the gain-of-function hypermorphic changes, whereas the calcification-inducing loss-of-function variants are regarded as hypomorphic [43].

PDGF-B

PDGFB is initially translated into a 241-amino acid precursor, which is further proteolytically processed to give rise to a 109-amino acid PDGF-B mature peptide. In order to function as a ligand, PDGF-B builds homo- or heterodimers with the related platelet-derived growth factor subunit A (PDGF-A) through disulfide bridging [39].

Mice homozygous for hypomorphic partially inactivating *Pdgfb* mutations develop calcifications that follow the same time course and expand in size and number in an age-dependent manner, as those arising in *Slc20a2* homozygous knockout mice [19]. Namely, at 2 months of age, a few small, laminated, and uncalcified nodules can be detected in midbrain and thalamus hypomorphic *Pdgfb* knockouts. The 4-month-old mice display clusters of spherical laminated and calcified aggregates in the same areas that develop into abundant calcifications at multiple locations in the basal forebrain, thalamus, midbrain, and pons of 1-year-old animals. Importantly, endothelial, but not neuronal re-expression of PDGF-B can rescue the phenotype, indicating that brain calcification forms because of a deficiency in PDGF-B synthesis in endothelial cells [19]. Mice heterozygous for a partially inactivating *Pdgfb* mutation, or having just one copy of *Pdgfb* or *Pdgfrb* (heterozygous knockouts) do not develop calcification [19]. Functional analysis of PFBC-causing *PDGFB* mutations showed that they lead to a complete loss of PDGF-B function or production, suggesting that, in humans, PDGF-B haploinsufficiency could be a sufficient cause of PFBC [44].

Given the importance of the PDGF-Rβ signaling pathway for BBB development [38], and considering that calcifications are mainly concentrated around blood vessels [31, 35] and that the first calcium aggregates likely develop within pericytes [32], it was initially hypothesized that PFBC occurs due to the impairment and ensuing increased permeability of the BBB [19]. Surprisingly, in the homozygous hypomorphic *Pdgfb*-mutation carrying mice, the calcification-prone brain regions (thalamus, mesencephalon, and dorsal pons) seem to have higher pericyte coverage and a more intact BBB compared to brain regions not prone to calcification (motor cortex, hippocampus, and myelencephalon) [44], thus indicating that the occurrence of vascular calcifications does not necessarily correlate spatially with the degree of pericyte loss and BBB impairment.

MYORG

The *MYORG* (myogenesis-regulating glycosidase) gene codes for a 714-amino-acid-long member of the glycosyl hydrolase 31 family with a single N-terminal transmembrane domain (amino acids: 57–77) and a C-terminal predicted glycosyl hydrolase domain (amino acids: 311–714). MYORG is expressed in myoblasts and is important for the myogenic differentiation during myogenesis.

In mice, Myorg is ubiquitously expressed, and in the brain, *Myorg* messenger RNA is present in high amounts in the cerebellum [21]. On the cellular level, Myorg seems to be expressed in astrocytes and is primarily situated in the endoplasmic reticulum (ER), and partially in the Golgi apparatus [21]. Thus, MYORG likely regulates protein glycosylation in the ER of brain astrocytes. *Myorg* homozygous knockout mice develop brain calcification later than the other available PFBC mouse models. That is, bilateral irregular calcified spheres were first observed in the thalamus of the 9-month-old *Myorg* knockout mice, indicating that loss of Myorg in mice causes PFBC-like calcified deposits [21]. Although the mechanism of PFBC caused by *MYORG* mutations is still unclear, it has been hypothesized that it is related to the BBB and/or NVU dysfunction [21]. Namely, the NVU consists of astrocytes, BBB, neurons, and extracellular matrix components. Thus, it is conceivable that *MYORG* mutations may lead to astrocyte dysfunction and subsequent impairment of the astrocyte–pericyte association within the NVU, causing the initiation of calcification.

Clinical Features of PFBC

All adult individuals carrying pathogenic mutations in the PFBC genes exhibit brain calcification. However, a subset of cases also manifest associated clinical features, which range from severe movement disorders to occasional headaches [45]. In addition, the presence of phenocopies (family members

showing the same phenotype as other affected individuals in the pedigree, but due to a different, frequently unknown, and possibly environmental etiology) is both anticipated and documented [12, 14, 15] for both clinical and imaging manifestations.

Brain Calcification

The presence of brain calcification among PFBC-mutation carriers is routinely investigated by neuroimaging. Among the genetically confirmed PFBC patents with CT scans available, calcifications are most frequently present in the basal ganglia (98% of the patients), followed by the cerebellum (43%), and the subcortical white matter and thalamus (40% each). Furthermore, in one-third of the patients (36%), only the basal ganglia are involved, while twice fewer of the mutation carriers (18%) have calcifications in all four regions. Each of all other combinations is present in more than 10% of the patients.

An autopsy report of an *SLC20A2* missense mutation carrier revealed multiple foci of bilateral calcification in the caudate nucleus, putamen, globus pallidus, thalamus, and deep layers of the cerebellar cortex containing coarse and oval-shaped aggregations of various sizes within the brain parenchyma and blood vessel walls [35]. In particular, a small number of arteries were severely calcified, whereas veins were rarely affected. The calcifications were composed of calcium, iron, and glycogen [35]. In comparison, a structural analysis of the aggregates in the *Slc20a2* homozygous knockout mice revealed the presence of calcium, phosphate, iron, zinc, and aluminium [32], while mostly calcium and phosphate were detected in the calcified nodules of mice homozygous for a hypomorphic *Pdgfb* mutation [19] and in the *Myorg* knockout mice [21].

It is difficult to elucidate when the calcifications develop in the PFBC patients, given that asymptomatic children carrying PFBC-causing mutations should not be subjected to a CT scan. The youngest patient reported to date is a 4-year old girl with bilateral calcification in the basal ganglia [46]. However, most likely, calcification aggregates do not appear commonly in children that young, and the only mutation carrier reported to date with no calcification visible on CT was 14 years old at the time of investigation [15]. Importantly, within the range of 20–70 years of age and based on the number of brain regions affected by bilateral calcification (at least one site with bilateral calcification in individuals between 20 and 40 years of age and at least two sites with bilateral calcification in individuals between 41 and 70 years of age), it may be possible to predict whether a given patient indeed carries a PFBC-causing mutation or represents a phenocopy [15].

Movement Disorders and Other Clinical Presentations of PFBC

Traditionally, and prior to the elucidation of the genetic etiology, PFBC was regarded as a condition that clinically manifests in middle adulthood and affects men more frequently than women [47]. A review of genetically confirmed PFBC patients reveals, however, that although the average age at onset is indeed at 36 years, all ages of onset from 1 year to 84 years are equally represented ([22] and unpublished data). Furthermore, as expected from an autosomal disorder, equal numbers of female and male PFBC mutations carriers have been reported. Clinically, PFBC manifests as a heterogeneous and progressive neurological disorder that includes movement disorders and neuropsychiatric symptoms. Movement disorders initially present as clumsiness, fatigue, unsteady gait, slow or slurred speech, dysphagia, involuntary movements, or muscle cramping [4] and may progress to parkinsonism, dystonia, ataxia, or chorea. Neuropsychiatric symptoms range from mild impairment of concentration and memory to changes in personality or behavior, psychosis, and dementia. In addition, various seizure types may occur and some patients suffer from migraines or chronic headaches and vertigo.

Approximately two thirds of the reported mutation carriers are clinically affected ([40] and unpublished data). However, attempts to elucidate the quality, range, and frequency of signs and symptoms of PFBC are significantly hindered by a reporting bias present in the literature and the consequent risk that clinical features of cases with complete and incomplete information may differ. Namely, in the majority of the publications (particularly in earlier reports), detailed clinical information is largely missing. This is a frequent obstacle when performing a systematic literature review, as recently illustrated by the example of genetically determined early-onset Parkinson disease where the percentage of data missing information reached up to 80%, even for the cardinal motor signs and symptoms [48].

Among all of the clinically affected PFBC patients for whom the presence or absence of motor signs was reported (reporting frequencies ranged from ~20% to ~80% for different signs), 80% had at least one of the

motor signs, 51% had parkinsonism, 47% had dystonia, 31% had ataxia, 30% had seizures, and 25% had chorea (unpublished data). Frequencies differ across genes and the current status of genotype–phenotype relationships can be most comprehensively assessed via the MDSGene database [22].

Interestingly, a three-generational family with brain calcification and dystonia was reported to carry a large chromosomal deletion [27]. This deletion encompassed several genes including *SLC20A2* and *THAP1*, a known dystonia-related gene, thereby challenging the assessment of the contribution that brain calcification alone has on the resulting phenotype.

Psychiatric symptoms have been assessed for ~30% of affected patients and, when present, included anxiety, psychotic disorder, and depression in 26%, 45%, and 46% of the patients, respectively. In addition, a possible cognitive deficit was evaluated in over 55% of the symptomatic individuals and identified in more than 65% of these cases. When investigated, speech difficulties and migraine were noticed in about half of the patients, and headache in 65% of cases.

Conclusions

PFBC is a rare genetic neurodegenerative disorder manifesting with mostly symmetrical bilateral calcifications of the basal ganglia or other brain regions. The term PFBC is suggested to replace the two widespread but inaccurate previous disease names, i.e. Fahr's disease and idiopathic basal ganglia calcification. According to the new nomenclature, the various genetic subtypes of PFBC are designated by the prefix PFBC followed by the relevant gene name (Table 18.1) [17].

PFBC is commonly inherited in an autosomal-dominant manner, but families with an autosomal-recessive pattern of inheritance have been described. *SLC20A2* seems to be the most frequently mutated gene in autosomal-dominant PFBC, followed by *PDGFB*, *XPR1*, and *PDGFRB*. In addition, compound heterozygous and homozygous changes in *MYORG* have been associated with autosomal-recessive PFBC. In addition to the various small sequence variations found in all five genes, large deletions involving an entire exon or gene have been reported for *SLC20A2* and *PDGFB*. Mutations in each of the five genes have also been described in sporadic patients. The genetic heterogeneity of PFBC is, however, yet to be fully appreciated, given that mutations in all five genes together account for the disease in slightly over 60% of PFBC families [21].

The mechanisms of PFBC pathogenesis have been investigated in cellular (overexpression) and mice (knockout or hypomorphic-mutant) models. Interestingly, while in all three available mouse models, calcification was found in the thalamus, in PFBC patients, calcifications are almost inevitably (98%) and sometimes exclusively (36%) present in the basal ganglia, and also in the cerebellum, subcortical white matter, and thalamus, in about 40% of cases each. Clinical phenotypes that result from brain calcification are highly variable and include movement disorders such as parkinsonism, dystonia or ataxia, but also non-motor symptoms such as headache or migraine, cognitive impairment, and psychiatric disorders. Importantly, some patients with severe calcifications may remain free of any clinical signs.

Key Points and Clinical Pearls

- Primary familial brain calcification (PFBC) disorder is a rare genetic neurodegenerative disorder manifesting with mostly symmetrical bilateral calcifications of the basal ganglia or other brain regions.
- PFBC is commonly inherited in an autosomal-dominant manner, but families with an autosomal-recessive pattern of inheritance have been described.
- *SLC20A2* appears to be the most frequently mutated gene in autosomal-dominant PFBC, followed by *PDGFB*, *XPR*1, and *PDGFRB*.
- The mechanisms of PFBC pathogenesis have been investigated in cellular (overexpression) and mice (knockout or hypomorphic-mutant) models.
- Clinical phenotypes highly variable and include movement disorders such as parkinsonism, dystonia or ataxia, and also non-motor symptoms such as headache or migraine, cognitive impairment, and psychiatric disorders.

Directions for Future Research

- Discovering further genetic causes of the disease.
- Understanding the basis of NVU impairment in PFBC and how it induces calcifications.
- Standardizing clinical data collection and reporting.

References

1. Slager UT, Wagner JA. The incidence, composition, and pathological significance of intracerebral vascular deposits in the basal ganglia. J Neuropathol Exp Neurol. 1956;**15**(4):417–31.
2. Yamada M, Asano T, Okamoto K, et al. High frequency of calcification in basal ganglia on brain computed tomography images in Japanese older adults. Geriatr Gerontol Int. 2013;**13**(3):706–10.
3. Forstl H, Krumm B, Eden S, Kohlmeyer K. Neurological disorders in 166 patients with basal ganglia calcification: A statistical evaluation. J Neurol. 1992;**239**(1):36–8.
4. Ramos EM, Oliveira J, Sobrido MJ, Coppola G. Primary familial brain calcification. GeneReviews®. 2004:Apr 18 (updated Aug 24, 2017).
5. Baba Y, Broderick DF, Uitti RJ, Hutton ML, Wszolek ZK. Heredofamilial brain calcinosis syndrome. Mayo Clin Proc. 2005;**80**(5):641–51.
6. Delacour A. Ossification des capillaires du cerveau. Ann Med Psychol (Paris). 1850;**2**:458–61.
7. Manyam BV. What is and what is not 'Fahr's disease'. Parkinsonism Relat Disord. 2005;**11**(2):73–80.
8. Casanova MF, Araque JM. Mineralization of the basal ganglia: Implications for neuropsychiatry, pathology and neuroimaging. Psychiatry Res. 2003;**121**(1):59–87.
9. Ferreira LD, Mendes de Oliveira JR. The need for consensus on primary familial brain calcification nomenclature. J Neuropsychiatry Clin Neurosci. 2018;**30**(4):291–3.
10. Fahr T. Idiopathische Verkalkung der Hirngefässe. Zbl Allg Pathol Pathol Anat 1930;**50**:129–30.
11. Klein C, Vieregge P. Fahr's disease: Far from a disease. Mov Disord. 1998;**13**(3):620–1.
12. Geschwind DH, Loginov M, Stern JM. Identification of a locus on chromosome 14q for idiopathic basal ganglia calcification (Fahr disease). Am J Hum Genet. 1999;**65**(3):764–72.
13. Wang C, Li Y, Shi L, et al. Mutations in *SLC20A2* link familial idiopathic basal ganglia calcification with phosphate homeostasis. Nat Genet. 2012;**44**(3):254–6.
14. Hsu SC, Sears RL, Lemos RR, et al. Mutations in *SLC20A2* are a major cause of familial idiopathic basal ganglia calcification. Neurogenetics. 2013;**14**(1):11–22.
15. Grutz K, Volpato CB, Domingo A, et al. Primary familial brain calcification in the 'IBGC2' kindred: All linkage roads lead to *SLC20A2*. Mov Disord. 2016;**31**(12):1901–4.
16. Westenberger A, Klein C. The genetics of primary familial brain calcifications. Curr Neurol Neurosci Rep. 2014;**14**(10):490.
17. Marras C, Lang A, van de Warrenburg BP, et al. Nomenclature of genetic movement disorders: Recommendations of the International Parkinson and Movement Disorder Society Task Force. Mov Disord. 2017;**32**(5):724–5.
18. Nicolas G, Pottier C, Maltete D, et al. Mutation of the *PDGFRB* gene as a cause of idiopathic basal ganglia calcification. Neurology. 2013;**80**(2):181–7.
19. Keller A, Westenberger A, Sobrido MJ, et al. Mutations in the gene encoding PDGF-B cause brain calcifications in humans and mice. Nat Genet. 2013;**45**(9):1077–82.
20. Legati A, Giovannini D, Nicolas G, et al. Mutations in *XPR1* cause primary familial brain calcification associated with altered phosphate export. Nat Genet. 2015;**47**(6):579-81.
21. Yao XP, Cheng X, Wang C, et al. Biallelic mutations in *MYORG* cause autosomal recessive primary familial brain calcification. Neuron. 2018;**98**(6):1116–23 e5.
22. The Movement Disorder Society Genetic mutation database (MDSGene). Lubeck: University of Lubeck (updated 2019 March 20; accessed March 26, 2019). Available from: www.mdsgene.org.
23. Lek M, Karczewski KJ, Minikel EV et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;**536**(7616):285–91.
24. Database of Single Nucleotide Polymorphisms (dbSNP). Bethesda, MD: National Center for Biotechnology Information, National Library of Medicine. Available from: www.ncbi.nlm.nih.gov/SNP.
25. Kircher M, Witten DM, Jain P, et al. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet. 2014;**46**(3):310–5.
26. David S, Ferreira J, Quenez O, et al. Identification of partial *SLC20A2* deletions in primary brain calcification using whole-exome sequencing. Eur J Hum Genet. 2016;**24**(11):1630–4.
27. Baker M, Strongosky AJ, Sanchez-Contreras MY, et al. *SLC20A2* and *THAP1* deletion in familial basal ganglia calcification with dystonia. Neurogenetics. 2014;**15**(1):23–30.
28. Nicolas G, Rovelet-Lecrux A, Pottier C, et al. *PDGFB* partial deletion: A new, rare mechanism causing brain calcification with leukoencephalopathy. J Mol Neurosci. 2014;**53**(2):171–5.
29. Anheim M, Lopez-Sanchez U, Giovannini D, et al. *XPR1* mutations are a rare cause of primary familial brain calcification. J Neurol. 2016;**263**(8):1559-64.
30. Bottger P, Pedersen L. Mapping of the minimal inorganic phosphate transporting unit of human PiT2 suggests a structure universal to PiT-related proteins from all kingdoms of life. BMC Biochem. 2011;**12**:21.

31. Jensen N, Schroder HD, Hejbol EK, et al. Loss of function of *Slc20a2* associated with familial idiopathic basal ganglia calcification in humans causes brain calcifications in mice. J Mol Neurosci. 2013;**51** (3):994–9.
32. Jensen N, Schroder HD, Hejbol EK, et al. Mice knocked out for the primary brain calcification-associated gene *Slc20a2* show unimpaired prenatal survival but retarded growth and nodules in the brain that grow and calcify over time. Am J Pathol. 2018;**188** (8):1865–81.
33. Wallingford MC, Chia JJ, Leaf EM, et al. SLC20A2 deficiency in mice leads to elevated phosphate levels in cerbrospinal fluid and glymphatic pathway-associated arteriolar calcification, and recapitulates human idiopathic basal ganglia calcification. Brain Pathol. 2017;**27**(1):64–76.
34. Jensen N, Autzen JK, Pedersen L. Slc20a2 is critical for maintaining a physiologic inorganic phosphate level in cerebrospinal fluid. Neurogenetics. 2016;**17** (2):125–30.
35. Kimura T, Miura T, Aoki K, et al. Familial idiopathic basal ganglia calcification: Histopathologic features of an autopsied patient with an *SLC20A2* mutation. Neuropathology. 2016;**36**(4):365–71.
36. Larsen FT, Jensen N, Autzen JK, Kongsfelt IB, Pedersen L. Primary brain calcification causal PiT2 transport-knockout variants can exert dominant negative effects on wild-type PiT2 transport function in mammalian cells. J Mol Neurosci. 2017;**61** (2):215–20.
37. Yao XP, Zhao M, Wang C, et al. Analysis of gene expression and functional characterization of *XPR1*: A pathogenic gene for primary familial brain calcification. Cell Tissue Res. 2017;**370**(2):267–73.
38. Gaengel K, Genove G, Armulik A, Betsholtz C. Endothelial-mural cell signaling in vascular development and angiogenesis. Arterioscler Thromb Vasc Biol. 2009;**29**(5):630–8.
39. Betsholtz C, Keller A. PDGF, pericytes and the pathogenesis of idiopathic basal ganglia calcification (IBGC). Brain Pathol. 2014;**24**(4):387–95.
40. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008;**22**(10):1276–312.
41. Arts FA, Velghe AI, Stevens M, et al. Idiopathic basal ganglia calcification-associated *PDGFRB* mutations impair the receptor signalling. J Cell Mol Med. 2015;**19** (1):239–48.
42. Sanchez-Contreras M, Baker MC, Finch NA, et al. Genetic screening and functional characterization of *PDGFRB* mutations associated with basal ganglia calcification of unknown etiology. Hum Mutat. 2014;**35**(8):964–71.
43. Minatogawa M, Takenouchi T, Tsuyusaki Y, et al. Expansion of the phenotype of Kosaki overgrowth syndrome. Am J Med Genet A. 2017;**173**(9):2422–7.
44. Vanlandewijck M, Lebouvier T, Andaloussi Mae M, et al. Functional characterization of germline mutations in *PDGFB* and *PDGFRB* in primary familial brain calcification. PLoS One. 2015;**10**(11):e0143407.
45. Tadic V, Westenberger A, Domingo A, et al. Primary familial brain calcification with known gene mutations: A systematic review and challenges of phenotypic characterization. JAMA Neurol. 2015;**72** (4):460–7.
46. Zhang Y, Guo X, Wu A. Association between a novel mutation in *SLC20A2* and familial idiopathic basal ganglia calcification. PLoS One. 2013;**8**(2):e57060.
47. Manyam BV, Walters AS, Narla KR. Bilateral striopallidodentate calcinosis: Clinical characteristics of patients seen in a registry. Mov Disord. 2001;**16** (2):258–64.
48. Kasten M, Hartmann C, Hampf J, et al. Genotype–phenotype relations for the Parkinson's disease genes *Parkin*, *PINK1*, *DJ1*: MDSGene systematic review. Mov Disord. 2018;**33**(5):730–41.

Chapter 19

Disorders of Glycosylation and Movement Disorders

Eva Morava, Carlos R. Ferreira, and Marc Patterson

Introduction

Congenital disorders of glycosylation (CDGs) are a group of diseases characterized by an abnormal glycosylation of proteins or lipids. It is estimated that more than half of all proteins in our body are glycosylated [1]. Defined as all the sugar chains (glycans) that an organism makes, the glycome is estimated to be 10^2–10^4 times larger than the proteome [2]. Given this complexity, it is not surprising that about 2% of our genes encode for proteins that are currently known to participate in glycosylation reactions [3]. CDGs are classified according to the deficient glycosylated substrates, which can include proteins, lipids, or multiple substrates. The classification of disorders of hypoglycosylation is divided into: (1) defects in protein N-linked glycosylation (glycans attached to the amino [N-] group of asparagine residues), (2) defects in protein O-linked glycosylation (sugars are attached to the hydroxyl [O-] groups of serine or threonine), (3) defects in glycosphingolipid and in glycosylphosphatidylinositol-anchor glycosylation, and (4) defects in multiple glycosylation pathways. No human disorders have been discovered yet in association with abnormal C-linked glycosylation [4].

The initial steps of N-glycosylation take place on the cytosolic side of the endoplasmic reticulum (ER) membrane, whereupon initial activation sugars are attached in a stepwise manner to dolichol pyrophosphate (Dol-PP) to form a lipid-linked oligosaccharide (LLO). First, two N-acetylglucosamines (GlcNAc) are attached to Dol-PP, followed by the addition of five mannose (Man) residues to form a Man5GlcNAc2 intermediate which is then translocated or "flipped" to the luminal side of the ER membrane. Up to this step, the sugars were donated by an activated nucleotide-sugar (UDP-GlcNAc and GDP-Man), with the attached nucleotide providing the necessary energy for the transfer of the sugar to the LLO. Once on the luminal side of the ER, the sugar donors are dolichylphosphoglucose (Dol-P-Glc) and dolichylphosphomannose (Dol-P-Man); subsequent sugars are attached to the LLO to finally form Glc3Man9GlcNAc2. This oligosaccharide is removed from its dolichol stem and transferred to a nascent protein by the action of an oligosaccharyltransferase (OST), a complex composed of eight subunits. Once the oligosaccharide chain has been transferred to the protein, further processing takes place, first by trimming the distal glucose by the action of a glycosidase in the ER. Then, the oligosaccharide is transported to the Golgi apparatus, where further removal of glucose and mannose residues and addition of other sugars take place by the action of several enzymes, e.g. mannosidases, fucosyltransferases, and sialyltransferases. Different types of CDGs have been found in affected individuals who have defective enzymes in individual steps of this complex pathway including dolichol synthesis and utilization, enzymes that transfer single sugars to the growing chain, interconvert activated monosaccharides, transfer the oligosaccharide from dolichol to protein, transport activated sugars across membranes, transfer glycosyl transferases between different vesicular compartments, and other integral steps.

O-glycosylation differs from N-glycosylation in that it occurs exclusively post-translationally, and only in the Golgi apparatus. There are many different types of O-glycosylation according to which type of sugar is attached to serine or threonine. For example, defects of O-mannosylation lead to an underglycosylation of alpha-dystroglycan, a protein necessary for the attachment of the subsarcolemmal cytoskeleton of the skeletal muscle cell to the extracellular matrix. When this protein is not glycosylated adequately, its anchoring function is lost, leading to various types of congenital muscular dystrophies. Defects in O-xylosylation lead to defective anchoring of glycosaminoglycans (GAGs) to proteins. Since many proteoglycans are important components of the skeleton and connective tissue, disorders of GAG synthesis usually lead to skeletal dysplasias or connective-tissue disorders.

Incorrectly glycosylated lipids can also lead to significant clinical issues, including intellectual disability, seizures, and spastic paraplegias. The biosynthesis of glycosylphosphatidylinositol (GPI) anchors, required for the attachment of over 150 human proteins to the plasma membrane [5], requires the concerted activity of more than 20 enzymes, the deficiency of most of which have been associated with human disease.

Many of the genetic defects of glycosylation involve multiple pathways. Examples are combined N- and O-glycosylation defects, like abnormal dolichol-phosphate mannose (DPM) synthesis, affecting ER-related mannosylation, O-mannosylation, and GPI-anchor biosynthesis, and disorders associated with the function of the components of the conserved oligomeric Golgi (COG) protein complex. Finally, NGLY1 deficiency represents a unique congenital disorder of deglycosylation with phenotypic similarities to CDGs, given that intracellular free oligosaccharides are not efficiently recycled into the glycosylation pathway.

In this chapter, we summarize the current knowledge on CDGs, with particular emphasis on the movement disorder accompanying some of them.

History, Nomenclature, and Classification of CDGs

CDGs were originally described in 1980 [6] in twin sisters, who were subsequently found to have hyposialylation of serum and cerebrospinal fluid (CSF) transferrin [7]. Two more patients had been described by 1984 [8], and seven more in Sweden by 1989 [9]. The condition was briefly known as disialotransferrin developmental deficiency syndrome. Twenty-six patients were presented by Dr. Jaak Jaeken and Dr. Helena Stibler at the Fifth International Congress of Inborn Errors of Metabolism (ICIEM, Asilomar, June 1–5, 1990), where the condition came to be known as carbohydrate-deficient glycoprotein syndrome. New subtypes were subsequently identified based on clinical and sialotransferrin differences. A new variant was described in 1991 [10], and came to be known as carbohydrate-deficient glycoprotein syndrome type II [11], and soon afterwards further subtypes were identified, known as type III [12] and type IV [13].

The enzymes and genes responsible for the first known CDGs were identified in the 1990s. The enzyme deficiency associated with carbohydrate-deficient glycoprotein syndrome type II was identified in 1994 [14] and the gene, in 1996 [15], while the enzyme associated with the carbohydrate-deficient glycoprotein syndrome type I was identified in 1995 [16] and the gene, in 1997 [17], and the enzyme and gene deficiencies responsible for type IV were described in 1999 [18]. Once the enzyme deficiencies came to be known, a new classification system was proposed by the participants of the First International Workshop on Carbohydrate-Deficient Glycoprotein Syndromes in Leuven, Belgium, that took place in 1999. Carbohydrate-deficient glycoprotein syndromes then became known as congenital disorders of glycosylation [19, 20]. CDGs were named according to the type of transferrin isoelectric focusing (IEF) abnormality, followed by a letter of the alphabet in the order in which they were described. For example, a deficiency of phosphomannomutase was called CDG-Ia (corresponding to carbohydrate-deficient glycoprotein syndrome type I), while carbohydrate-deficient glycoprotein syndrome type II came to be known as CDG-IIa, and carbohydrate-deficient glycoprotein syndrome type IV was renamed CDG-Id.

This classification system, however, presented some problems. First, some subtypes of disorders of N-glycosylation were not associated with abnormalities in transferrin IEF, such as for example CDG-IIb. Second, transferrin IEF only assesses N-glycosylation, since transferrin lacks any O-glycosylation sites; thus, defects in O-glycosylation were not amenable to this classification. Third, several disorders came to be known that did not include abnormalities in protein glycosylation, but rather lipid glycosylation. Fourth, this classification provided no biological insight about the basic protein defect. Fifth, there are too few letters of the alphabet to name all newly discovered CDGs – this occurred when the disorder associated with mutations in *NUS1* was designated CDG-Iaa. Thus, a new nomenclature system was proposed in 2008 [21, 22], to include the official gene symbol (not in italics) followed by "-CDG". As an example, the new nomenclature for CDG-Ia would be PMM2-CDG.

Table 19.1 summarizes the gene name and locus, protein deficiency and function, and disease nomenclature and inheritance pattern of the 149 different CDGs known to date.

Table 19.1 Overview of the CDGs

Gene	Gene locus OMIM number	Function	Localization of defect	Disease	Inheritance	Initial molecular characterization (PMID)
N-linked glycosylation defects						
Interconversion of monosaccharides						
PMM2	601785	Phosphomannomutase (converts Man-6-P to Man-1-P)	Cytosol	PMM2-CDG (CDG-Ia)	AR	9140401
MPI	154550	Phosphomannose isomerase (converts Fru-6-P to Man-6-P)	Cytosol	MPI-CDG (CDG-Ib)	AR	9525984
N-glycan lipid-linked oligosaccharide assembly						
DPAGT1	191350	GlcNAc-1-P-transferase (transfers 1st GlcNAc)	ER (cytosolic side)	DPAGT1-CDG (CDG-Ij); CMS13	AR	12872255
ALG13	300776	UDP-GlcNAc-transferase (transfers 2nd GlcNAc)	ER (cytosolic side)	ALG13-CDG (CDG-Is) in males; EEIE36 in females	XL	22492991
ALG14	612866	UDP-GlcNAc transferase (transfers 2nd GlcNAc)	ER (cytosolic side)	CMS15	AR	23404334
ALG1	605907	β1–4 Man-transferase (transfers 1st mannose)	ER (cytosolic side)	ALG1-CDG (CDG-Ik)	AR	14709599, 14973778, 14973782
ALG2	607905	α1–3/6 Man-transferase (transfers 2nd and 3rd mannoses)	ER (cytosolic side)	ALG2-CDG (CDG-Ii); CMS14	AR	12684507
ALG11	613666	α1–2 Man-transferase (transfers 4th and 5th mannoses)	ER (cytosolic side)	ALG11-CDG (CDG-Ip)	AR	20080937
RFT1	611908	Man5GlcNAc2-PP-Dol flippase	ER	RFT1-CDG (CDG-In)	AR	18313027
ALG3	608750	α1–3 Man-transferase (transfers 6th mannose)	ER (luminal side)	ALG3-CDG (CDG-Id)	AR	10581255
ALG9	606941	α1–2 Man-transferase (transfers 7th and 9th mannoses)	ER (luminal side)	ALG9-CDG (CDG-IL); Gillessen–Kaesbach–Nishimura syndrome	AR	15148656
ALG12	607144	α1–6 Man-transferase (transfers 8th mannose)	ER (luminal side)	ALG12-CDG (CDG-Ig)	AR	11983712
ALG6	604566	α1–3 Glc-transferase (transfers 1st glucose)	ER (luminal side)	ALG6-CDG (CDG-Ic)	AR	10359825
ALG8	608103	α1–3 Glc-transferase (transfers 2nd glucose)	ER (luminal side)	ALG8-CDG (CDG-Ih); polycystic liver disease 3	AR, AD	12480927; 28375157
Glycan transfer to nascent protein						
TUSC3	601385	OST subunit	ER	TUSC3-CDG (MRT7/MRT22)	AR	18455129, 18452889
DDOST	614507	OST subunit	ER	DDOST-CDG (CDG-Ir)	AR	22305527
STT3A	601134	OST subunit	ER	STT3A-CDG (CDG-Iw)	AR	23842455
STT3B	608605	OST subunit	ER	STT3B-CDG (CDG-Ix)	AR	23842455
MAGT1		OST subunit	ER	MAGT1-CDG; XMEN	XL	21796205
SSR4	300090	Translocon-associated protein, delta subunit	ER	SSR4-CDG (CDG-Iy)	XL	24218363
SEC63	608648	Translocon-associated protein	ER	Polycystic liver disease 2	AD	15133510

N-glycan processing						
MOGS	601336	α1–2 glucosidase I (removes Glc from Glc3Man9GlcNAc2)	ER	MOGS-CDG (CDG-IIb)	AR	10788335
GANAB	104160	α1–3 glucosidase II subunit alpha (removes last two Glc from Glc2Man9GlcNAc2)	ER	Polycystic kidney disease 3	AD	27259053
PRKCSH	177060	α1–3 glucosidase II subunit beta (removes last two Glc from Glc2Man9GlcNAc2)	ER	Polycystic liver disease 1	AD	12529853, 12577059
MAN1B1	604346	α1–2 mannosidase I (removes Man from Man9GlcNAc2 ➔ Man8GlcNAc2 isomer B)	ER	MAN1B1-CDG (MRT15)	AR	21763484
MGAT2	602616	β1–2 GlcNAc-transferase II (transfers GlcNAc to GlcNAcMan3GlcNAc2)	Medial-Golgi	MGAT2-CDG (CDG-IIa)	AR	8808595
B4GALT1	137060	β1–4 Gal-transferase (transfers Gal to either arm of GlcNAc2Man3GlcNAc2)	Trans-Golgi	B4GALT1-CDG (CDG-IId)	AR	11901181
FUT8	602589	α1–6 Fuc-transferase (adds core fucose)	Golgi	FUT8-CDG	AR	29304374
O-linked glycosylation defects						
O-mannosylation						
POMT1	607423	Protein O-Man-transferase	ER	MDDGA1, MDDGB1, MDDGC1	AR	12369018
POMT2	607439	Protein O-Man-transferase	ER	MDDGA2, MDDGB2, MDDGC2	AR	15894594
POMGNT1	606822	β1–2 GlcNAc-transferase (transfers GlcNAc to Man in core M1)	Golgi	MDDGA3, MDDGB3, MDDGC3, RP76	AR	11709191
POMGNT2	614828	β1–4 GlcNAc-transferase (transfers GlcNAc to Man in core M3)	ER	MDDGA8	AR	22958903
B3GALNT2	610194	β1–3 GalNAc-transferase II (transfers GalNAc to GlcNAcMan in core M3)	ER	MDDGA11	AR	23453667
POMK	615247	Phosphorylates 6-position of Man after addition of GlcNAc and GalNAc	ER	MDDGA12, MDDGC12	AR	23519211
ISPD	614631	Synthesizes CDP-ribitol	Cytosol	MDDGA7, MDDGC7	AR	22522420, 22522421
FKTN	607440	Adds ribitol-5-P to GalNAcGlcNAcMan6P	Golgi	MDDGA4, MDDGB4, MDDGC4	AR	9690476
FKRP	606596	Adds ribitol-5-P to Rbo5PGalNAcGlcNAcMan6P	Golgi	MDDGA5, MDDGB5, MDDGC5	AR	11592034
RXYLT1	605862	β1-4 xylosyltransferase (transfers xylose to Rbo5P Rbo5PGalNAcGlcNAcMan6P)	Golgi	MDDGA10	AR	23217329
B4GAT1	605581	β-1,4 glucuronyltransferase I (transfers GlcA to XylRbo5P Rbo5PGalNAcGlcNAcMan6P)	Golgi	MDDGA13	AR	23359570
LARGE1	603590	β1–3 GlcA-transferase/α1–3 Xyl-transferase (transfers GlcAXyl to GlcAXylRbo5P Rbo5PGalNAcGlcNAcMan6P)	Golgi	MDDGA6, MDDGB6	AR	12966029

Table 19.1 (cont.)

Gene	Gene locus OMIM number	Function	Localization of defect	Disease	Inheritance	Initial molecular characterization (PMID)
O-xylosylation and glycosaminoglycan synthesis						
XYLT1	608124	Xyl-transferase 1	Golgi	Desbuquois dysplasia type 2	AR	23982343
XYLT2	608125	Xyl-transferase 2	Golgi	Spondyloocular syndrome	AR	26027496
B4GALT7	604327	β1–4 Gal-transferase I (transfers galactose to Xyl)	Golgi	Progeroid EDS 1 (Larsen of Reunion Island syndrome)	AR	10473568, 10506123
B3GALT6	615291	β1–3 Gal-transferase II (transfers Gal to GalXyl)	Golgi	SEMDJL Beighton type (progeroid EDS type 2)	AR	23664117
B3GAT3	606374	β1–3 GlcA-transferase I (transfers GlcA to GalGalXyl to create linker tetrasaccharide)	Golgi	Larsen-like syndrome	AR	21763480
EXT1	608177	β1–4 GlcA-transferase II / α1–4 GlcNAc-transferase II (HS polymerase)	Golgi	Multiple hereditary exostoses type 1	AD	7550340
EXT2	608210	β1–4 GlcA-transferase II / α1–4 GlcNAc-transferase II (HS polymerase)	Golgi	Multiple hereditary exostoses type 2; seizures, scoliosis and macrocephaly syndrome	AD; AR	8782816; 26246518
EXTL3	605744	α1–4 GlcNAc-transferase I (transfers first GlcNAc to linker for HS initiation) and II (HS elongation)	Golgi	Immunoskeletal dysplasia with neurodevelopmental abnormalities	AR	28132690, 28148688
CHSY1	608183	β1–3 GlcA-transferase/ β1–4 GalNAc-transferase (CS elongation)	Golgi	Temtamy preaxial brachydactyly syndrome	AR	21129728
CHST3	603799	GalNAc-6-O-sulfotransferase (CS modification)	Golgi	SED with congenital joint dislocations (AR Larsen syndrome, SED Omani type, humerospinal dysostosis)	AR	15215498
CHST11	610128	GalNAc-4-O-sulfotransferase (CS modification)	Golgi	Chondrodysplasia, brachydactyly, overriding digits, clino-symphalangism and synpolydactyly	AR	29514872
CHST14	608429	GalNAc-4-O-sulfotransferase (DS modification)	Golgi	EDS musculocontractural type 1	AR	20004762
DSE	605942	Converts D-glucuronic acid to L-iduronic acid (DS epimerase)	Golgi	EDS musculocontractural type 2	AR	23704329
CSGALNACT1	616615	β1–4 GalNAc-transferase I (transfers first GalNAc to linker for CS initiation)	Golgi	Desbuquois dysplasia	AR	27599773
CHST6	605294	GlcNAc-6-O-sulfotransferase (KS modification)	Golgi	Macular corneal dystrophy	AR	11017086
CANT1	613165	UDP-Gal nucleotidase	ER and Golgi	Desbuquois dysplasia 1	AR	19853239
SLC26A2	606718	Sulfate transporter	Plasma membrane	Achondrogenesis type 1; atelosteogenesis type 2; diastrophic dysplasia; multiple epiphyseal dysplasia type 4	AR	7923357

PAPSS2	603005	Phosphoadenosine 5′-phosphosulfate synthetase	Cytosol	Spondyloepimetaphyseal dysplasia, Pakistani type	AR	9771708
IMPAD1	614010	Golgi-resident phosphoadenosine phosphate phosphatase	Golgi	Chondrodysplasia with joint dislocations, gPAPP type	AR	21549340
SLC10A7	611459	Transporter (unidentified substrate)	Plasma membrane	Skeletal dysplasia with amelogenesis imperfecta	AR	29878199; 30082715
O-GalNAcylation						
GALNT3	601756	Polypeptide GalNAc-transferase	Golgi	Hyperphosphatemic familial tumoral calcinosis	AR	15133511
C1GALT1C1	300611	Chaperone for the core 1 β1–3 galactosyltransferase	ER	Tn polyagglutination syndrome	Somatic	16251947
O-GlcNAcylation						
OGT	300255	O-GlcNAc-transferase	Nucleus and cytosol	MRX106	XL	28302723, 28584052
EOGT	614789	EGF-domain O-GlcNAc-transferase	ER	Adams–Oliver syndrome 4	AR	23522784
ST3GAL3	606494	α2–3 Sia-transferase (transfers Sia to Lewis a trisaccharide)	Golgi	MRT12; EIEE15	AR	21907012; 23252400
O-glucosylation						
POGLUT1	615618	Protein O-glucosyltransferase	ER	Dowling–Degos disease 4; LGMD2Z	AD; AR	24387993; 27807076
O-fucosylation						
POFUT1	607491	Protein O-fucosyltransferase for EGF repeats	ER	Dowling–Degos disease 2	AD	23684010
LFNG	602576	β1–3 GlcNAc-transferase (transfers GlcNAc to O-fucose on EGF repeats)	Golgi	Spondylocostal dysostosis type 3	AR	16385447
B3GLCT	610308	β1–3 Glc-transferase (transfers Glc to O-fucose on TSR)	ER	Peters plus syndrome	AR	16909395
GPI biosynthesis defects						
PIGA	311770	GlcNAc-transferase complex, catalytic subunit (transfers GlcNAc to PI)	ER (cytosolic side)	MCAHS2 (GPIBD4, EEIE20)	XL	22305531
PIGC	601730	GlcNAc-transferase complex	ER (cytosolic side)	PIGC-CDG	AR	27694521
PIGQ	605754	GlcNAc-transferase complex	ER (cytosolic side)	PIGQ-CDG	AR	24463883
PIGP	605938	GlcNAc-transferase complex	ER (cytosolic side)	EIEE55 (GPIBD14)	AR	28334793
PIGY	610662	GlcNAc-transferase complex	ER (cytosolic side)	HPMRS6 (GPIBD12)	AR	26293662
PIGH	600154	GlcNAc-transferase complex	ER (cytosolic side)	PIGH-CDG	AR	29573052, 29603516
PIGL	605947	GlcNAc-PI de-N-acetylase (GlcNAc-PI to GlcN-PI)	ER (cytosolic side)	CHIME syndrome (GPIBD5)	AR	22444671
PIGW	610275	Inositol acyltransferase (transfers fatty acid to GlcN-PI)	ER (luminal side)	HPMRS5 (GPIBD11)	AR	24367057
PIGM	610273	Man-transferase 1 (transfers Man to GlcN-aPI)	ER (luminal side)	GPIBD1	AR	16767100
PIGV	610274	Man-transferase 2 (transfers Man to ManGlcN-aPI)	ER (luminal side)	HPMRS1 (GPIBD2)	AR	20802478

Table 19.1 (cont.)

Gene	Gene locus OMIM number	Function	Localization of defect	Disease	Inheritance	Initial molecular characterization (PMID)
PIGN	606097	EtNP-transferase 1 (transfers EtNP to ManManGlcN-aPI)	ER (luminal side)	MCAHS1 (GPIBD3)	AR	21493957
PIGO	614730	EtNP-transferase 3 (transfers EtNP to ManMan(EtNP)ManGlcN-aPI)	ER (luminal side)	HPMRS2 (GPIBD6)	AR	22683086
PIGG	616918	EtNP-transferase 2 (transfers EtNP to EtNPManMan(EtNP) ManGlcN-aPI)	ER (luminal side)	MRT53 (GPIBD13)	AR	26996948
PIGT	610272	GPI transamidase (transfers protein to GPI anchor)	ER (luminal side)	MCAHS3 (GPIBD7)	AR	23636107
PIGS	610271	GPI transamidase (transfers protein to GPI anchor)	ER (luminal side)		AR	30269814
GPAA1	603048	GPI transamidase (transfers protein to GPI anchor)	ER (luminal side)	GPIBD15	AR	29100095
PGAP1	611655	Inositol deacylase (removes fatty acid)	ER (luminal side)	MRT42 (GPIBD9)	AR	24784135
PGAP3	611801	Phospholipase A2 (removes unsaturated fatty acid at sn-2)	Golgi	HPMRS4 (GPIBD10)	AR	24439110
PGAP2	615187	Reacylates sn-2 with stearic acid	Golgi	HPMRS3 (GPIBD8)	AR	23561846, 23561847
			Glycolipid glycosylation			
ST3GAL5	604402	α2–3 Sia-transferase (GM3 synthase)	Golgi	Amish infantile epilepsy syndrome (salt and pepper syndrome)	AR	15502825
B4GALNT1	601873	β1–4 GalNAc-transferase (GM2/GD2 synthase)	Golgi	SPG26	AR	23746551
A4GALT	607922	α1–4 Gal-transferase (GB3 synthase)	Golgi	NOR polyagglutination syndrome	AD	22965229
			Disorders of multiple pathways			
Monosaccharide synthesis						
GFPT1	138292	Glutamine:F6P amidotransferase (coverts F6P to GlcN-6P for UDP-GlcNAc synthesis)	Cytosol	CMS12	AR	21310273
GNE	603824	UDP-GlcNAc 2-epimerase/ManNac kinase (converts UDP-GlcNAc to ManNac and then to ManNac-6P)	Cytosol	GNE myopathy; sialuria	AR; AD	11528398; 10330343
NANS	605202	Converts ManNac6P to Neu5Ac-9P	Cytosol	SEMD, Camera–Genevieve type	AR	27213289
Monosaccharide interconversion						
PGM1	612934	Phosphoglucomutase (reversible conversion of Glc-1P to Glc-6P)	Cytosol	PGM1-CDG (CDG-It)	AR	19625727
PGM3	172100	Reversible conversion of GlcNAc-6P to GlcNAc-1P	Cytosol	Immunodeficiency 23	AR	24589341, 24698316, 24931394
G6PC3	611045	Glucose-6-phosphatase (Glc-6-P to Glc)	ER	Severe congenital neutropenia 4	AR	19118303

Dolichol biosynthesis						
DHDDS	608172	Cis-isoprenyltransferase	ER (cytosolic side)	Retinitis pigmentosa 59	AR, AD	21295283
NUS1	610463	Stabilizes cis-isoprenyltransferase	ER	NUS1-CDG (CDG-Iaa)	AR, AD	25066056
SRD5A3	611715	Polyprenol reductase	ER	SRD5A3-CDG (CDG-Iq)	AR	20637498
DOLK	610746	Dolichol kinase	ER	DOLK-CDG (CDG-Im)	AR	17273964
Dolichol-P-sugar biosynthesis and utilization						
DPM1	603503	Dol-P-Man synthase	ER (cytosolic side)	DPM1-CDG (CDG-Ie)	AR	10642597, 10642602
DPM2	603564	Dol-P-Man synthase	ER	DPM2-CDG (CDG-Iu)	AR	23109149
DPM3	605951	Dol-P-Man synthase	ER	DPM3-CDG (CDG-Io)	AR	19576565
MPDU1	604041	Dol-P-sugar availability	ER	MPDU1-CDG (CDG-If)	AR	11733564
Nucleotide-sugar synthesis						
CAD	114010	First 3 enzymes in pyrimidine biosynthesis	Cytosol	CAD-CDG (CDG-Iz, EEIE50)	AR	25678555
GMPPA	615495	Regulatory role or GMPPB	Cytosol	Alacrima, achalasia, and intellectual deficiency syndrome	AR	24035193
GMPPB	615320	Synthesizes GDP-mannose from Man-1-P and GTP	Cytosol	MDDGA14, MDDGB14, MDDGC14	AR	23768512
Transporters						
SLC35A1	605634	CMP-Sia transport	Golgi	SLC35A1-CDG (CDG-IIf)	AR	15576474
SLC35A2	314375	UDP-Galactose transport	Golgi	SLC35A2-CDG (EIEE22)	XL	23561849
SLC35A3	605632	UDP-GlcNAc transport	Golgi	SLC35A3-CDG	AR	24031089
SLC35C1	605881	GDP-Fuc transport	Golgi	SLC35C1-CDG (CDG-IIc)	AR	11326279
SLC35D1	610804	UDP-GlcA/UDP-GalNAc transport	Golgi	Schneckenbecken dysplasia	AR	17952091
SLC39A8	608732	Cation transporter	Plasma membrane	SLC39A8-CDG (CDG-IIn)	AR	26637978, 26637979
Vesicular trafficking						
COG1	606973	Golgi-to-ER retrograde transport	Vesicular membrane/ cytosol	COG1-CDG (CDG-IIg)	AR	16537452
COG2	606974	Golgi-to-ER retrograde transport	Vesicular membrane/ cytosol	COG2-CDG (CDG-IIq)	AR	24784932
COG4	606976	Golgi-to-ER retrograde transport	Vesicular membrane/ cytosol	COG4-CDG (CDG-IIj, AR), Saul–Wilson disease (AD)	AR, AD	19494034
COG5	606821	Golgi-to-ER retrograde transport	Vesicular membrane/ cytosol	COG5-CDG (CDG-IIi)	AR	19690088
COG6	606977	Golgi-to-ER retrograde transport	Vesicular membrane/ cytosol	COG6-CDG (CDG-III – 2L), Shaheen syndrome	AR	20605848
COG7	606978	Golgi-to-ER retrograde transport	Vesicular membrane/ cytosol	COG7-CDG (CDG-IIe)	AR	15107842
COG8	606979	Golgi-to-ER retrograde transport	Vesicular membrane/ cytosol	COG8-CDG (CDG-IIh)	AR	17220172
COPA	601924	COP-I subunit alpha (Golgi-to-ER transport)	Vesicular membrane/ cytosol	Autoimmune interstitial lung, joint, and kidney disease	AD	25894502

Table 19.1 (cont.)

Gene	Gene locus OMIM number	Function	Localization of defect	Disease	Inheritance	Initial molecular characterization (PMID)
COPB2	606990	COP-I subunit beta-2 (Golgi-to-ER transport)	Vesicular membrane/ cytosol	Primary microcephaly	AR	29036432
ARCN1	600820	COP-I subunit delta (Golgi-to-ER transport)	Vesicular membrane/ cytosol	Rhizomelic short stature with microcephaly, micrognathia, and developmental delay	AD	27476655
SEC23A	610511	COP-II component (ER-to-Golgi transport)	Vesicular membrane/ cytosol	Craniolenticulosutural dysplasia (Boyadjiev–Jabs syndrome)	AR	16980979
SEC23B	610512	COP-II component (ER-to-Golgi transport)	Vesicular membrane/ cytosol	Congenital dyserythropoietic anemia type II; Cowden syndrome 7	AR; AD	19561605, 19621418, 26522472
SEC24D	607186	COP-II component (ER-to-Golgi transport)	Vesicular membrane/ cytosol	Cole-Carpenter syndrome 2	AR	25683121
SAR1B	607690	COP-II GTPase (ER-to-Golgi transport)	Vesicular membrane/ cytosol	Chylomicron retention disease	AR	12692552
JAGN1	616012	COP interactor	Vesicular membrane/ cytosol	Severe congenital neutropenia type 6	AR	25129144
TRIP11	604505	Anterograde and retrograde transport	cis-Golgi	Achondrogenesis IA; odontochondrodysplasia	AR	20089971
TRAPPC2	300202	Subunit of TRAPP tethering complex	Vesicular membrane/ cytosol	SED tarda	XL	10431248
TRAPPC6B	610397	Subunit of TRAPP tethering complex	Vesicular membrane/ cytosol	TRAPPC8B-CDG	AR	28626029
TRAPPC9	611966	Subunit of TRAPP tethering complex	Vesicular membrane/ cytosol	MRT13	AR	20004763, 20004764, 20004765
TRAPPC11	614138	Subunit of TRAPP tethering complex	Vesicular membrane/ cytosol	LGMD2S	AR	23830518
TRAPPC12	614139	Subunit of TRAPP tethering complex	Vesicular membrane/ cytosol	TRAPPC12-CDG	AR	28777934
VPS13B	607817	Subunit of VPS13 complex	Vesicular membrane/ cytosol	Cohen syndrome	AR	12730828
GOSR2	604027	SNARE protein	Vesicular membrane/ cytosol	Progressive myoclonic epilepsy type 6	AR	21549339
Golgi homeostasis						
ATP6V0A2	611716	pH (subunit of vacuolar ATPase)	Vacuolar membrane	Autosomal recessive cutis laxa type IIA (wrinkly skin syndrome)	AR	18157129
ATP6AP1	300197	pH (subunit of vacuolar ATPase)	Vacuolar membrane	Immunodeficiency 47	XL	27231034
ATP6AP2		pH (subunit of vacuolar ATPase)	Vacuolar membrane	X-linked intellectual deficiency, Hedera type	XL	15746149
ATP6V1A	607027	pH (subunit of vacuolar ATPase)	Vacuolar membrane	Autosomal recessive cutis laxa type IID	AR	28065471
ATP6V1E1	108746	pH (subunit of vacuolar ATPase)	Vacuolar membrane	Autosomal recessive cutis laxa type IIC	AR	28065471

TMEM199	616815	Assembly factor for vacuolar ATPase	Vacuolar membrane	TMEM199-CDG (CDG-IIp)	AR	26833330
CCDC115	613734	Assembly factor for vacuolar ATPase	Vacuolar membrane	CCDC115-CDG (CDG-Ip)	AR	26833332
VMA21	300913	Assembly factor for vacuolar ATPase	Vacuolar membrane	X-linked myopathy with excessive autophagy	XL	23315026
TMEM165	614726	pH, manganese and calcium homeostasis	Golgi	TMEM165-CDG (CDG-IIk)	AR	22683087
SLC9A7	300368	pH homeostasis	Golgi	SLC9A7-CDG	XLR	30335141
Deglycosylation						
NGLY1	610661	Cleaves glycan chain from asparagine	Cytosol	NGLY1-CDG	AR	22581936
Unknown						
TGDS	616146	TDP-Glc 4,6-dehydratase	Unknown	Catel-Manzke syndrome	AR	25480037

Abbreviations: AD, autosomal-dominant; AR, autosomal-recessive; CMS, congenital myasthenic syndrome; CS, chondroitin sulfate; DS, dermatan sulfate; EDS, Ehlers–Danlos syndrome; EGF, epidermal growth factor-like; EIEE, early-infantile epileptic encephalopathy; EtNP, Ethanolamine phosphate; F6P, fructose 6-phosphate; GPIBD, glycosylphosphatidylinositol biosynthesis defect; HPMRS, hyperphosphatasia with mental retardation syndrome; HS, heparin sulfate; KS, keratan sulfate; LGMD, limb-girdle muscular dystrophy; MCAHS, multiple congenital anomalies-hypotonia-seizures syndrome; MDDG, muscular dystrophy-dystroglycanopathy; MRT, "mental retardation"; Neu5Ac, N-aceteylneuraminic acid; PI, phosphatidylinositol; OST, oligosaccharyltransferase; RP, retinitis pigmentosa; SED, spondyloepiphyseal dysplasia; SEMDJL, spondyloepimetaphyseal dysplasia with joint laxity; SPG, spastic paraplegia; TSR, thrombospondin type 1 repeats; XL, X-linked.

Diagnosis

Serum transferrin has two N-linked glycans, each containing two sialic acids; thus, when using transferrin IEF, normal serum transferrin is mainly composed of tetrasialotransferrin. The absence of entire glycans is designated as a type 1 pattern (CDG-I) and would therefore be characterized by an increase of both disialo- and asialotransferrin, and a decrease of tetrasialotransferrin; this happens because the OST complex mainly transfers entire glycan chains (Gluc3Man9GlcNAc2, and not aborted forms of this LLO) into the nascent protein, so a type 1 pattern indicates a defect in the assembly of N-glycans. Loss of an odd number of sialic acid residues was designated as a CDG type 2 pattern (CDG-II); in this pattern there is also an increase of the tri- and/or monosialotransferrin bands, and this happens when there is a defect in the processing stage (in the Golgi) of N-glycans.

Serum transferrin IEF is the traditional screening method for N-glycosylation defects. Transferrin glycoforms missing terminal sialic acid residues show different cathodal shifts by IEF. Transferrin glycoforms are also detectable by mass spectrometry (MS), which is currently the most frequently used method for N-glycosylation analysis [23]. Certain other disorders can cause a false-positive transferrin isoform pattern, including galactosemia, hereditary fructose intolerance, and excessive alcohol use. The transferrin assay can be unreliable in the first 3 weeks of life, and after puberty [24–26]. Matrix-assisted laser desorption/ionization (MALDI)-time of flight (TOF) and Q-TOF-based methods give additional insight into truncated glycan abnormalities in Golgi-related N-glycan defects [27]. Phosphomannomutase and phosphomannose isomerase enzyme analyses are available in leukocytes and fibroblasts. Apoprotein CIII (Apo-CIII) is a secretory (mucine) type of O-glycan, which can be assayed in combined N-and O-glycosylation disorders (IEF or MS). Most O-glycosylation disorders however are traditionally diagnosed by genetic analysis, or histopathology; for example, congenital muscular dystrophies caused by defective O-mannosylation can be diagnosed with the use of monoclonal antibodies (IIH6 and VIA4-1) that recognize the glycan itself, as opposed to intact dystroglycan in the surface of muscle cells. Some patients with GPI-anchor defects have increased levels of alkaline phosphatase (ALP, a GPI-anchored protein), while others can be identified using flow cytometry of GPI-anchored proteins, such as CD16, CD24, CD55, CD59, and FLAER (fluorescein labeled proaerolysin) on leukocytes [28].

Movement Disorders in CDGs with Clinically Recognizable Phenotypes

PMM2-CDG

PMM2-CDG is the most common disorder of N-glycosylation. Recognizable clinical features include strabismus, dysmorphic facial features (deep-set eyes, long philtrum, large ears), inverted nipples, and abnormal fat pads. Many patients have long, slender fingers. The early clinical presentation includes hypotonia with feeding difficulties. Psychomotor delay and intellectual disability is present in most patients. The multisystem phenotype is life threatening, with malabsorption, cardiomyopathy, liver function abnormalities, abnormal endocrine regulation, and coagulopathy. Neurological involvement includes seizures, stroke-like episodes, proximal myopathy, spasticity, and peripheral neuropathy [29, 30].

Movement disorders are very common in PMM2-CDG. Nystagmus (associated with pontocerebellar and vermis hypoplasia) may be noticeable in the first few months of life. Ataxia is usually severe and is the most important reason hindering patients from standing and walking independently, leading to wheelchair dependency. Dystonia [31] with frequent involuntary movements, athetosis, or tremor can also occur. Many milder PMM2-CDG cases present with titubation, worsening with stress [30].

The movement disorder component of the disease might be difficult to recognize in patients with significant spasticity. Muscle relaxant therapy might worsen the clinical picture in some of these patients, owing to the reappearance of severe dyskinesia (personal observation).

GPI Biosynthetic Defects and Disorders of Glycolipid Glycosylation

The two main phenotypic groups of GPI biosynthetic defects include multiple congenital anomalies–hypotonia–seizures syndrome (MCAHS) and the hyperphosphatasia with mental retardation syndrome (HPMRS), of which Mabry syndrome (HPMRS1) was the first described. About half of all patients with PGAP3-CDG (HPMRS4) develop ataxia [32]. Ataxia was seen in seven and cerebellar atrophy in nine out of ten patients with GPAA1-CDG [33]; these patients also have intellectual disability, early-onset seizures, and osteopenia.

The subgroups of disorders of glycolipid glycosylation are also accompanied by movement disorders. ST3GAL5-CDG (GM3 synthase deficiency) is common in the Old Order Amish population due to a founder mutation, and these patients have nonpurposeful hand movements with a choreoathetoid component, as well as severe intellectual disability, seizures, visual loss, and cutaneous dyspigmentation [34–36]. Patients with B4GALNT1-CDG have a complex form of spastic paraplegia, that was complicated by ataxia in 11 of 14 patients [37]. One of those patients had an interesting phenotype of isolated fever-induced ataxia with myokymia [37].

NGLY1 Deficiency

N-glycanase 1 deficiency represents the first congenital disorder of deglycosylation. Patients feature a clinical tetrad of developmental delay/intellectual disability of variable severity, hypo- or alacrima, elevated liver transaminases, and a hyperkinetic movement disorder [38]. A total of 18 affected subjects from 14 different families have been reported so far [38].

In a cohort of 12 individuals who were prospectively phenotyped, all showed a hyperkinetic movement disorder (see Video 19.1) that was variously described as choreiform, athetoid, dystonic, myoclonic, action tremor, and dysmetric [39]. An exaggerated startle response was described in a few patients during infancy.

The movement disorder is most typically first noted during infancy, does not extinguish during sleep, affects the extremities more than the trunk, and the upper extremities more than the lower extremities. It worsens with movement or fatigue, and in some cases worsens while in others improves with time. No abnormalities are seen in transferrin analysis, but a specific oligosaccharide can be found by urine MS analysis.

Other Recognizable Congenital Disorders of Glycosylation

Some of the CDG types with movement disorders present as recognizable genetic syndromes.

SRD5A3-CDG is a disorder of dolichol metabolism with severe multisystem disease, including neurological (ataxia, cerebellar malformations), skin, and eye involvement. Ophthalmological involvement includes retinal abnormalities, e.g. retinitis pigmentosa, optic atrophy, and even congenital anomalies including retinal and iris coloboma, glaucoma, or congenital cataracts. There is a severe developmental delay and frequently autistic behavior. Stereotypical and dystonic movements were seen in 3 of 12 patients [40, 41]. Ichthyosis of varying severity has been detected in half of the affected children [42]. Patients show a type I glycosylation defect [43].

DPM1-CDG is another recognizable phenotype with profound developmental delay, amaurosis, microcephaly, seizures, contractures, muscle dystrophy, and elevated creatine kinase levels. Patients with a milder form of the disease present predominantly with cerebellar ataxia [44, 45]. The diagnosis can be confirmed by muscle biopsy as well, which shows an alpha-dystroglycanopathy [46]. Patients show a type I glycosylation defect.

MPDU1-CDG patients have a recognizable presentation with microcephaly, visual loss, seizures, and severe developmental delay with progressive spasticity. Feeding problems lead to failure to thrive [47]. Dry and frequently scalding skin (ichthyosiform dermatitis) and erythroderma have been detected in several patients [48]. Ataxia is common, sometimes camouflaged by the progressive spasticity, and mostly recognizable as axial problems with balance (patients are unable to sit) or nystagmus. Patients show a type I glycosylation defect.

RFT1-CDG is almost always associated with hearing loss. The classic presentation is a severe neurological disease with early or congenital visual loss, seizures, and psychomotor delay. Besides the hearing loss, common features include hepatosplenomegaly, feeding problems, short stature, and multiple laboratory anomalies (coagulation and endocrine abnormalities). Milder patients have more noticeable ataxia [49]. Patients show a type I glycosylation defect.

SLC39A8-CDG is a unique N-linked glycan disease with abnormal glycosylation in the Golgi (type II CDG). The underlying defect is in manganese transport, which leads to a severe neurological presentation including developmental delay, seizures, ataxia, and basal ganglia disease leading to dystonia [50]. Other features are short stature and skeletal abnormalities [51]. Patients show a type II glycosylation defect. Some patients present with mitochondrial dysfunction [50].

Patients with **GOSR2-CDG**, a disorder of vesicular trafficking, present with progressive ataxia between 1 year and 3 years of age, followed by action myoclonus between 6 years and 10 years of age [52]. The myoclonus is exacerbated by stress or stimuli [53]. These patients also have muscle involvement with creatine kinase elevation from hypoglycosylation of dystroglycan [54].

Diagnostic Considerations

Nystagmus in a baby, delayed development with signs of ataxia in a young child or infant, or abnormal gait, head tremor (titubation), and adiadochokinesia in children are symptoms which are highly suggestive for a congenital cerebellar (vermis) abnormality, and a potential neurometabolic disorder. Although the differential diagnosis is quite extensive, the combination of ataxia and vermis hypoplasia with abnormal fat distribution, fat pads, inverted nipples, and strabismus, especially in the presence of systemic disease (diarrhea, liver involvement, hypoglycemia, etc.) is highly suggestive for PMM2-CDG. SRD5A3-CDG is another "syndromal presentation" with ataxia, severe eye involvement (frequent blindness), and ichthyosis in many patients. ALG6-CDG is less characteristic, but relatively common, and is frequently accompanied by proximal muscle weakness, seizures, and ataxia [55]. SLC39A8-CDG is a neurodevelopmental syndrome with seizures, ataxia, and dystonia [50].

Several other N-glycosylation types are associated with ataxia as well, although with a less recognizable phenotype. Ataxia is part of other ER-related disorders leading to abnormal LLO synthesis, such as ALG1-CDG [56]. In disorders involving the Golgi apparatus, ataxia is frequent in the group of conserved oligomeric Golgi defects (COG4-CDG, COG5-CDG, COG8-CDG). These disorders are all easily "screenable" by transferrin isoform analysis in serum or plasma. Even in case of negative results, genetic panels could be useful for early recognition.

Non-purposeful hand movements in ST3GAL5-CDG patients can mimic Rett syndrome. The presence of ataxia and elevated alkaline phosphatase in the absence of cholestasis should raise suspicion for PGAP3-CDG. The tetrad of developmental delay, alacrima, elevated liver transaminases, and a hyperkinetic movement disorder is diagnostic of NGLY1-CDDG.

Tremor in CDGs could be due to cerebellar abnormalities but also due to dystonic tremor.

Athetosis, chorea, and ballismus are relatively rare in N-glycosylation defects, and mostly present in milder forms of PMM2-CDG, and more prominently in N-glycanase 1 deficiency.

Therapeutic Developments

Novel therapeutic approaches in CDGs mostly aim at the restoration of missing activated sugar metabolites, substrates of sugar activation or glycan synthesis, facilitating a sugar metabolite's transport to a specific compartment, or restoring the homeostasis of cofactors regulating glycosylation. Examples are oral galactose or manganese therapy in SLC39A8-CDG, fucose therapy in SLC35C1-CDG, or uridine supplementation in CAD-CDG [57, 58]. Although these disorders are almost always associated with central nervous system involvement (seizures, developmental delay, and/or ataxia), there is no scientific evidence on successful intervention of the movement disorder component of the neurological phenotype.

There are no Food and Drug Administration-approved agents for the management of ataxia in any condition, but many drugs may exacerbate ataxia, including antiseizure medications, which should be used cautiously, with this adverse effect in mind. Apparent progression of ataxia in PMM2-CDG may occur in some patients with demyelinating peripheral neuropathy. Physical therapy, with emphasis on gait training and strengthening of core muscles, is the mainstay of management in patients with ataxia. Gait aids and orthoses may also be useful. A significant number of PMM2-CDG patients will eventually be mobile only with wheelchair assistance.

Dystonia is challenging to manage whatever its etiology, but a trial of levodopa is a practical starting point, and may be effective in 10–20 % of patients with dystonia of many causes. Exposure of 1–2 weeks is adequate to determine the efficacy of this agent. Anticholinergic agents may also be of benefit; trihexyphenidyl is frequently used, and may be tolerated in higher dose in children than in adults. Benefit may be not be apparent for several weeks, and anticholinergic adverse effects (confusion, dry mouth, anhidrosis, tachycardia, and urinary retention) should be anticipated and carefully monitored. Tetrabenazine is a monoaminergic amine depletor and partial dopamine antagonist that may also be helpful in dystonia; it may also produce parkinsonism and severe depression and should therefore be used only as a second- or third-line agent.

Physical measures that may be useful include local injection of botulinum toxin, which may weaken overactive muscles for periods of up to 6 months. This treatment is expensive and requires expert administration.

Deep brain stimulation is an option to consider when less invasive approaches have been unsuccessful, and where the dystonia is disabling. Given the increased potential for infection and hemorrhage in many forms of CDGs, deep brain stimulation is likely to be used sparingly. There are, as yet, no published reports of its use in CDGs.

Myoclonus often responds to valproic acid, although this must be used cautiously in patients with liver disease; options include levetiracetam, brivaracetam, and clonazepam. Aggressive treatment of fever, which often exacerbates myoclonus and other movement disorders, as well as provoking seizures and stroke-like episodes in many patients, is essential.

Key Points and Clinical Pearls

- Congenital disorders of glycosylation (CDGs) are a rapidly growing group of more than 140 genetic disorders frequently associated with vermis hypoplasia, cerebellar atrophy, and cerebellar ataxia.
- The presence of characteristic findings such as inverted nipples or lipodystrophy/fat pads, strabismus, or endocrine and coagulation abnormalities, in the setting of ataxia, should raise concern for a CDG.
- Transferrin glycoform analysis is a reliable screening in most N-glycosylation defects, but not in all CDG types and not in all ages.
- The tetrad of developmental delay, alacrima, elevated liver transaminases, and a hyperkinetic movement disorder is diagnostic of NGLY1-CDDG.

Directions for Future Research

- There is still a poor understanding of the natural history of most subtypes of CDGs.
- Novel and better biomarkers are needed in many CDG types.
- Understanding the role of glycosylation in organ development; specifically the role of abnormal glycosylation in the pathogenesis of cerebellar vermis malformations.
- Designing and testing dietary treatments with a focus on the central nervous system symptoms in CDGs.

References

1. Apweiler R, Hermjakob H, Sharon N. On the frequency of protein glycosylation, as deduced from analysis of the SWISS–PROT database. Biochim Biophys Acta. 1999;**1473**(1):4–8.
2. Freeze HH. Genetic defects in the human glycome. Nat Rev Genet. 2006;(7):537–51.
3. Freeze HH. Understanding human glycosylation disorders: Biochemistry leads the charge. J Biol Chem. 2013;**288**(10):6936–45.
4. Péanne R, de Lonlay P, Foulquier F, et al. Congenital disorders of glycosylation (CDG): Quo vadis? Eur J Med Genet. 2018;**61**(11):643–63.
5. Kinoshita T, Fujita M. Biosynthesis of GPI-anchored proteins: Special emphasis on GPI lipid remodeling. J Lipid Res. 2016;**57**(1):6–24.
6. Jaeken J, Vanderschueren-Lodeweyckx M, Casaer P, et al. Familial psychomotor retardation with markedly fluctuating serum prolactin, FSH and GH levels, partial TBG-deficiency, increased serum arylsulphatase A and increased CSF protein: A new syndrome[quest]: 90. Pediatr Res. 1980;**14**(2):179–179.
7. Jaeken J, van Eijk HG, van der Heul C, et al. Sialic acid-deficient serum and cerebrospinal fluid transferrin in a newly recognized genetic syndrome. Clin Chim Acta. 1984;**144**(2–3):245–7.
8. Jaeken J, Eggermont E, Stibler H. An apparent homozygous X-linked disorder with carbohydrate-deficient serum glycoproteins. Lancet. 1987;**2**(8572):1398.
9. Kristiansson B, Andersson M, Tonnby B, Hagberg B. Disialotransferrin developmental deficiency syndrome. Arch Dis Child. 1989;**64**(1):71–6.
10. Ramaekers VT, Stibler H, Kint J, Jaeken J. A new variant of the carbohydrate deficient glycoproteins syndrome. J Inherit Metab Dis. 1991;**14**(3):385–8.
11. Jaeken J, De Cock P, Stibler H, et al. Carbohydrate-deficient glycoprotein syndrome type II. J Inherit Metab Dis. 1993;**16**(6):1041.
12. Stibler H, Westerberg B, Hanefeld F, Hagberg B. Carbohydrate-deficient glycoprotein (CDG) syndrome: A new variant, type III. Neuropediatrics. 1993;**24**(1):51–2.
13. Stibler H, Stephani U, Kutsch U. Carbohydrate-deficient glycoprotein syndrome: A fourth subtype. Neuropediatrics. 1995;**26**(5):235–7.
14. Jaeken J, Schachter H, Carchon H, et al. Carbohydrate deficient glycoprotein syndrome type II: A deficiency in Golgi localised N-acetyl-glucosaminyltransferase II. Arch Dis Child. 1994;**71**(2):123–7.

15. Tan J, Dunn J, Jaeken J, Schachter H. Mutations in the *MGAT2* gene controlling complex N-glycan synthesis cause carbohydrate-deficient glycoprotein syndrome type II, an autosomal recessive disease with defective brain development. Am J Hum Genet. 1996;**59**(4):810–7.

16. Van Schaftingen E, Jaeken J. Phosphomannomutase deficiency is a cause of carbohydrate-deficient glycoprotein syndrome type I. FEBS Lett. 1995;**377**(3):318–20.

17. Matthijs G, Schollen E, Pardon E, et al. Mutations in *PMM2*, a phosphomannomutase gene on chromosome 16p13, in carbohydrate-deficient glycoprotein type I syndrome (Jaeken syndrome). Nat Genet. 1997;**16**(1):88–92.

18. Körner C, Knauer R, Stephani U, Marquardt T, Lehle L, von Figura K. Carbohydrate deficient glycoprotein syndrome type IV: Deficiency of dolichyl-P-Man: Man(5)GlcNAc(2)-PP-dolichylmannosyltransferase. EMBO J. 1999;**18**(23):6816–22.

19. Aebi M, Helenius A, Schenk B, et al. Carbohydrate-deficient glycoprotein syndromes become congenital disorders of glycosylation: An updated nomenclature for CDG. First International Workshop on CDGS. Glycoconj J. 1999;**16**(11):669–71.

20. Matthijs G. Congenital disorders of glycosylation. Trends Biochem Sci. 2000;**25**(9):428.

21. Jaeken J, Hennet T, Freeze HH, Matthijs G. On the nomenclature of congenital disorders of glycosylation (CDG). J Inherit Metab Dis. 2008;**31**(6):669–72.

22. Jaeken J, Hennet T, Matthijs G, Freeze HH. CDG nomenclature: Time for a change! Biochim Biophys Acta. 2009;**1792**(9):825–6.

23. van Scherpenzeel M, Steenbergen G, Morava E, Wevers RA, Lefeber DJ. High-resolution mass spectrometry glycoprofiling of intact transferrin for diagnosis and subtype identification in the congenital disorders of glycosylation. Transl Res. 2015;**166**(6):639–649.e1.

24. Clayton P, Winchester B, Di Tomaso E, et al. Carbohydrate-deficient glycoprotein syndrome: Normal glycosylation in the fetus. Lancet. 1993;**341**(8850):956.

25. Stibler H, Skovby F. Failure to diagnose carbohydrate-deficient glycoprotein syndrome prenatally. Pediatr Neurol. 1994;**11**(1):71.

26. Vermeer S, Kremer HPH, Leijten QH, et al. Cerebellar ataxia and congenital disorder of glycosylation Ia (CDG-Ia) with normal routine CDG screening. J Neurol. 2007;**254**(10):1356–8.

27. Abu Bakar N, Voermans NC, Marquardt T, et al. Intact transferrin and total plasma glycoprofiling for diagnosis and therapy monitoring in phosphoglucomutase-I deficiency. Transl Res. 2018;**199**:62–76.

28. Ng BG, Freeze HH. Human genetic disorders involving glycosylphosphatidylinositol (GPI) anchors and glycosphingolipids (GSL). J Inherit Metab Dis. 2015;**38**(1):171–8.

29. Ferreira CR, Altassan R, Marques-Da-Silva D, et al. Recognizable phenotypes in CDG. J Inherit Metab Dis. 2018;**41**(3):541–53.

30. Witters P, Honzik T, Bauchart E, et al. Long-term follow-up in PMM2-CDG: Are we ready to start treatment trials? *Genet Med*. 2019;**21**(5):1181–8.

31. Rossi M, Medina Escobar A, Ameghino L, Merello M. Expanding the phenotype of phosphomannomutase-2 gene congenital disorder of glycosylation: Cervical dystonia. J Neurol Sci. 2017;**378**:52–4.

32. Knaus A, Pantel JT, Pendziwiat M, et al. Characterization of glycosylphosphatidylinositol biosynthesis defects by clinical features, flow cytometry, and automated image analysis. Genome Med. 2018;**10**(1):3.

33. Nguyen TTM, Murakami Y, Sheridan E, et al. Mutations in *GPAA1*, encoding a GPI transamidase complex protein, cause developmental delay, epilepsy, cerebellar atrophy, and osteopenia. Am J Hum Genet. 2017;**101**(5):856–65.

34. Lee JS, Yoo Y, Lim BCet al. GM3 synthase deficiency due to *ST3GAL5* variants in two Korean female siblings: Masquerading as Rett syndrome-like phenotype. Am J Med Genet A. 2016;170(**8**):2200–5.

35. Trinchera M, Parini R, Indellicato R, Domenighini R, dall'Olio F. Diseases of ganglioside biosynthesis: An expanding group of congenital disorders of glycosylation. Mol Genet Metab. 2018;**124**(4):230–7.

36. Gordon-Lipkin E, Cohen JS, Srivastava S, Soares BP, Levey E, Fatemi A. ST3GAL5-related disorders: A deficiency in ganglioside metabolism and a genetic cause of intellectual disability and choreoathetosis. J Child Neurol. 2018;**33**(13):825–31.

37. Dad R, Walker S, Scherer SW, et al. Febrile ataxia and myokymia broaden the *SPG26* hereditary spastic paraplegia phenotype. Neurol Genet, 2017;**3**(3):e156.

38. Lam C, Wolfe L, Need A, Shashi V, Enns G. *NGLY1*-related congenital disorder of deglycosylation. GeneReviews®. 2018; Feb 8.

39. Lam C, Ferreira C, Krasnewich D, et al. Prospective phenotyping of NGLY1-CDDG, the first congenital disorder of deglycosylation. Genet Med. 2017;**19**(2):160–8.

40. Prietsch V, Peters V, Hackler R, et al. A new case of CDG-x with stereotyped dystonic hand movements

and optic atrophy. J Inherit Metab Dis. 2002;**25**(2):126–30.

41. Morava E, Wevers RA, Cantagrel V, et al. A novel cerebello-ocular syndrome with abnormal glycosylation due to abnormalities in dolichol metabolism. Brain. 2010;**133**(**11**):3210–20.
42. Wheeler PG, Ng BG, Sanford L, et al. SRD5A3-CDG: Expanding the phenotype of a congenital disorder of glycosylation with emphasis on adult onset features. Am J Med Genet A. 2016;**170**(12):3165–71.
43. Cantagrel V, Lefeber DJ, Ng BG, et al. SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. Cell. 2010;**142**(2):203–17.
44. García-Silva MT, Matthijs G, Schollen E, et al. Congenital disorder of glycosylation (CDG) type Ie. A new patient. J Inherit Metab Dis. 2004;**27**(5):591–600.
45. Dancourt J, Vuillaumier-Barrot S, de Baulny HO, et al. A new intronic mutation in the *DPM1* gene is associated with a milder form of CDG Ie in two French siblings. Pediatr Res. 2006 Jun;**59**(6):835–9.
46. Yang AC, Ng BG, Moore SA, et al. Congenital disorder of glycosylation due to *DPM1* mutations presenting with dystroglycanopathy-type congenital muscular dystrophy. Mol Genet Metab. 2013 Nov;**110**(3):345–51.
47. Kranz C, Denecke J, Lehrman MA, et al. A mutation in the human *MPDU1* gene causes congenital disorder of glycosylation type If (CDG-If). J Clin Invest. 2001 Dec;**108**(11):1613–9.
48. Thiel C, Wortmann S, Riedhammer K, et al. Severe ichthyosis in MPDU1-CDG. J Inherit Metab Dis. 2018;**41**(6):1293–4.
49. Ondruskova N, Vesela K, Hansikova H, et al. RFT1-CDG in adult siblings with novel mutations. Mol Genet Metab. 2012;**107**(4):760–2.
50. Riley LG, Cowley MJ, Gayevskiy V, et al. A *SLC39A8* variant causes manganese deficiency, and glycosylation and mitochondrial disorders. J Inherit Metab Dis. 2017;**40**(2):261–9.
51. Park JH, Hogrebe M, Grüneberg M, et al. SLC39A8 deficiency: A disorder of manganese transport and glycosylation. Am J Hum Genet. 2015;**97**(6):894–903.
52. Corbett MA, Schwake M, Bahlo M, et al. A mutation in the Golgi Qb-SNARE gene *GOSR2* causes progressive myoclonus epilepsy with early ataxia. Am J Hum Genet. 2011;**88**(5):657–63.
53. van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay Hunt syndrome: Clinical characterization of progressive myoclonus ataxia caused by *GOSR2* mutation. Mov Disord. 2014 Jan;**29**(1):139–43.
54. Larson AA, Baker PR, Milev MP, et al. *TRAPPC11* and *GOSR2* mutations associate with hypoglycosylation of α-dystroglycan and muscular dystrophy. Skelet Muscle. 2018;**8**(1):17.
55. Morava E, Tiemes V, Thiel C, et al. ALG6-CDG: A recognizable phenotype with epilepsy, proximal muscle weakness, ataxia and behavioral and limb anomalies. J Inherit Metab Dis. 2016;**39**(5):713–23.
56. Morava E, Vodopiutz J, Lefeber DJ, et al. Defining the phenotype in congenital disorder of glycosylation due to *ALG1* mutations. Pediatrics. 2012;**130**(4):e1034-1039.
57. Witters P, Cassiman D, Morava E. Nutritional therapies in congenital disorders of glycosylation (CDG). Nutrients. 2017;**9**(11):E1222.
58. Brasil S, Pascoal C, Francisco R, et al. CDG therapies: From bench to bedside. Int J Mol Sci. 2018;**19**(5):E1304.

Chapter

20

Disorders of Post-Translational Modifications/Degradation: Autophagy and Movement Disorders

Afshin Saffari and Darius Ebrahimi-Fakhari

Introduction

Autophagy is a term derived from the Ancient Greek word *autóphagos*, meaning "self-eating" or "self-devouring." The term is used to describe a major cellular degradation process that ensures cellular quality control. By targeting dysfunctional cellular components and delivering them to the endosome–lysosome system for degradation, autophagy clears cells of cellular debris and recycles basic building blocks for de novo synthesis of cellular components. The term autophagy was coined in the 1960s by the Belgian biochemist Christian de Duve who observed that certain intracellular vesicles contained the properties to encircle and digest cytoplasmic material. He named these vesicles "lysosomes" and the process of cellular self-devouring "autophagy." In 1974 he was awarded the Nobel Prize in Physiology or Medicine for his "discoveries concerning the structural and functional organization of the cell." Around 20 years later, the Japanese cell biologist Yoshinori Ohsumi identified and isolated 15 autophagy genes in yeast, which he named *Atg1-15*. For his "discoveries of mechanisms for autophagy" he was awarded the Nobel Prize in Physiology or Medicine in 2016. In recent years, the broad availability of next-generation sequencing technologies allowed the identification of a number of pathogenic variants in core autophagy genes that give rise to a novel class of inborn disorders of neurometabolism [1–3]. These "congenital disorders of autophagy" share striking phenotypic similarities and often affect the cerebellum, the long white matter tracts, and the basal ganglia leading to complex movement disorders. Here, we provide an overview of the molecular mechanisms of autophagy and discuss congenital disorders of autophagy with prominent movement disorders by the examples of eight recently identified single gene disorders.

The Autophagy Pathway: Molecular Mechanisms

Autophagy has been classically divided into three subtypes: microautophagy, chaperone-mediated autophagy, and macroautophagy. Macroautophagy, hereafter referred to as "autophagy," is the most important and extensively studied subtype occurring in all eukaryotic cells (Figure 20.1). Autophagy is an evolutionary highly conserved degradation pathway characterized by de novo synthesis of double-membrane vesicles, termed autophagosomes, that selectively target cellular molecules and organelles and deliver them to the lysosomal degradation machinery [4, 5]. This precise stepwise degradation process of cellular components is tightly controlled by a core set of autophagy-related genes. To ensure cellular homeostasis, autophagy dynamically integrates external and internal environmental stimuli to meet the metabolic needs of the cell. Whenever the cell's energy stores are filled, anabolic pathways block autophagic degradation of cellular components and fuel protein and organelle biosynthesis. Conversely, in situations of cellular energy depletion, catabolic pathways activate autophagy to ensure the breakdown of macromolecules to maintain cellular metabolism. To efficiently regulate these complex cellular processes, key regulatory pathways of cellular metabolism, namely the mTORC1 and AMPK pathways, converge on autophagy initiation and tightly regulate this early step (Figure 20.1).

Once autophagy is initiated, an isolation membrane (the phagophore) forms and subsequently undergoes elongation and maturation (Figure 20.1). This is regulated by Atg family members involving two ubiquitination-like conjugation systems. During the process of elongation and maturation, specific autophagy receptors and anchoring molecules such as SQSTM1/p62 recruit cargo labelled for autophagic

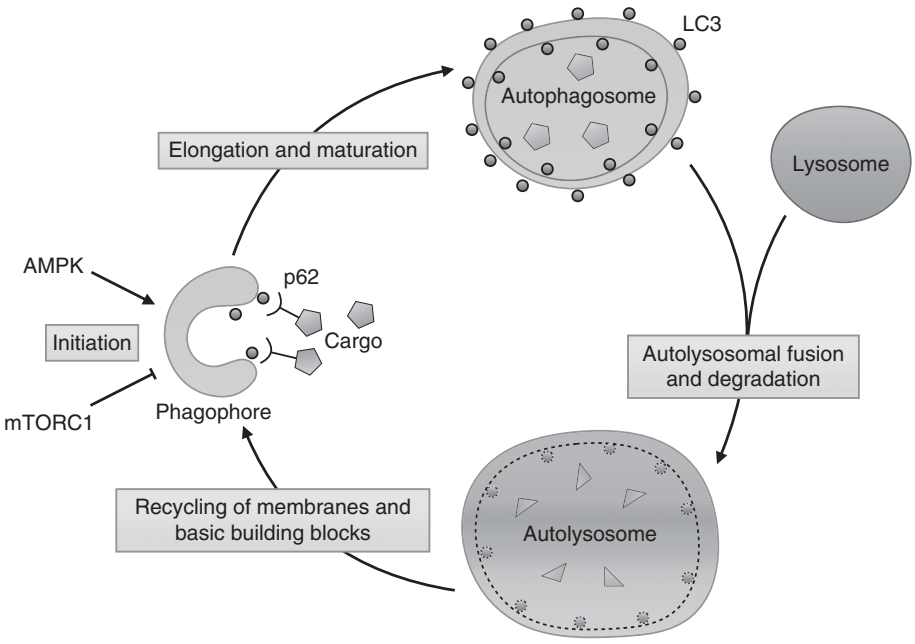

Figure 20.1 Overview of macroautophagy. Macroautophagy is a stepwise process resulting in the formation of double-membrane-bound autophagic vesicles that engulf their cargo before fusing with lysosomes. The principle stages of macroautophagy include: Initiation with nucleation of an isolation membrane (also called phagophore); elongation of evolving autophagic vesicles; engulfment of cargo and closure of the autophagosomal membrane; autophagosome maturation; fusion with late endosomes or lysosomes; and finally degradation of cargo through lysosomal hydrolases. The last step yields basic metabolites that are then recycled.

degradation to the growing phagophore. Eventually, the phagophore closes and forms a mature autophagosome, a double-membrane vesicle coated with the surface protein LC3, a widely used laboratory marker to monitor autophagy [6]. In the next step, the mature autophagosome fuses with late endosomes or lysosomes, forming what is called an autolysosome (Figure 20.1). Here, hydrolytic lysosomal enzymes are introduced, enabling degradation of the sequestered cargo under an acidic pH. Finally, the basic molecular building blocks are recycled to the cytosol for de novo synthesis of cellular components. Similarly, the lysosomal membranes are retrieved and re-join the perinuclear lysosomal pool, readily available for a new cycle of autophagy (Figure 20.1).

The Role of Autophagy in Health and Disease

Autophagy acts as a survival mechanism under conditions of stress and low energy levels by selectively clearing cells of macromolecules and dysfunctional organelles and regenerating metabolic precursors. Thus, autophagy can be regarded as a protective mechanism preventing cell death. Autophagic pathways are involved in multiple cellular processes, and important roles in adaptive immune response, pulmonary disease, vascular disease, metabolic disease, cancer, and aging have been reported [5]. Efficient autophagic flux is particularly important for post-mitotic cells, such as neurons, that lack the ability to dispose of dysfunctional organelles through cell division. In neurodevelopment, autophagy is a critical pathway that holds a key role in axon outgrowth, synaptic function, and neurotransmission. Not surprisingly, primary disorders of autophagy present with profound neurological manifestations. Interestingly, the cerebellum, the long white matter tracts, and the basal ganglia seem to be particularly vulnerable to disruptions in autophagy and lysosomal degradation pathways, clinically resulting in complex movement disorders such as ataxia, spasticity, dystonia, and parkinsonism. To illustrate the impact of perturbed autophagy on neurometabolism and the development of movement disorders, we summarize eight congenital disorders of autophagy.

Congenital Disorders of Autophagy

In recent years, a number of distinct childhood-onset neurological diseases caused by mutations in core autophagy genes have been identified. This group is rapidly expanding. The so-far identified genetic variants are mostly inherited in an autosomal-recessive manner (except X-linked BPAN, see below). All known variants map to genes in core autophagy genes and are believed to be loss-of-function mutations, perturbing autophagic flux.

Unifying Features

Congenital disorders of autophagy are single-gene disorders of the autophagy pathway. All congenital disorders of autophagy have an onset in early childhood, often as early as the neonatal period. Since autophagy is a ubiquitously expressed pathway, perturbations in the pathway often lead to multisystem disease. Due to the dependence of post-mitotic cells on efficient autophagic flux, neurons are severely affected, leading to neuronal dysfunction and neurodegeneration. Common brain imaging findings include cerebellar hypoplasia or atrophy, thinning of the corpus callosum, and storage disease phenotypes in some. Most disorders show a neurodevelopmental and neurodegenerative phenotype with developmental delay, intellectual disability, seizures, and movement disorders such as ataxia, gait disorders, spasticity, dystonia, and parkinsonism.

WDR45-Associated BPAN

Beta-propeller protein-associated neurodegeneration (BPAN) is a rare subtype of neurodegeneration with brain iron accumulation (NBIA). The NBIA spectrum encompasses a heterogeneous group of diseases sharing the key unifying features of an abnormal iron deposition in the basal ganglia, mainly the globus pallidus and substantia nigra. However, the cortex and cerebellum can also be affected. The clinical picture of NBIA spectrum diseases can range from severe early-onset neurodegeneration with rapid neurodevelopmental regression to a mild parkinsonian syndrome with minimal cognitive impairment in adulthood [7]. BPAN is the only X-linked subtype of the NBIA spectrum and affects mostly females, although some male patients have been reported. The underlying genetic causes are variants in *WDR45*, a gene that plays an important role in autophagosome formation and elongation [8]. Most mutations are sporadic and no mutational hotspots or genotype–phenotype correlations are known. Clinically, BPAN is characterized by a remarkable biphasic disease course with global developmental delay in childhood, followed by gradual neurodegeneration in adulthood, presenting with progressive dystonia, parkinsonism, and dementia [9]. Due to its distinct biphasic disease course BPAN was previously described as "static encephalopathy of childhood with neurodegeneration in adulthood" (SENDA) [8]. Affected children present with developmental delay, intellectual disability, and motor symptoms, such as spasticity or a broad-based, ataxic gait. Seizures are common and reported seizure types include focal seizures with impaired awareness, absence seizures, atonic seizures with head nodding, epileptic spasms, generalized tonic–clonic seizures, and myoclonic seizures. Individuals may present with multiple seizure types that may be refractory to medical therapy. Some patients show sleep disorders, ocular defects, and Rett-like hand stereotypies.

After a static disease phase, the second phase begins in adolescence or early adulthood when patients develop parkinsonism, dystonia, and progressive cognitive deficits. The parkinsonian features include bradykinesia, rigidity, freezing, and postural instability. Tremor is less common.

Therapeutic management can be challenging. For parkinsonism and dystonia, some short-lived response to levodopa has been observed; however, nearly all patients experienced early motor fluctuations, rapidly progressing to disabling dyskinesia [9, 10], requiring discontinuation of treatment. Cognitive decline may be insidious at first with the gradual loss of expressive language; however, eventually all patients advance to profound dementia.

Neuroimaging can establish the diagnosis. On T2-weighted sequences, iron accumulation can be detected as hypointensities in the globus pallidus, substantia nigra, and cerebral peduncles. On T1 sequences, the pathogenic changes in the substantia nigra produce a pathognomonic hyperintense "halo" sign, extending to the cerebral peduncles. These imaging findings are thought to represent iron-neuromelanin complexes, which are formed following neuromelanin release from degenerating neurons of the substantia nigra pars compacta. Further, non-specific findings on MRI include hypomyelination, thinning of the corpus callosum, cerebellar atrophy, and, as the diseases progresses, global cerebral atrophy.

Using exome sequencing, mutations in the X-chromosomal gene *WDR45*, the human ortholog of yeast *Atg18*, have been discovered as the genetic cause of BPAN [8, 11]. WDR45 is a member of the WD40 repeat family of proteins. WD40 repeat proteins assume a highly symmetrical, seven-bladed, beta-propeller scaffold that serves as a platform for specific protein interactions. WDR45 enables interactions with phospholipids, and importantly acts as a platform for protein interaction of the known autophagy proteins Atg2 and Atg9, which are involved in autophagosome formation and elongation [12].

SNX14-Associated Autosomal-Recessive Spinocerebellar Ataxia 20

Autosomal-recessive spinocerebellar ataxia 20 (SCAR20) has been described as a distinct recognizable ataxia syndrome, characterized by early-onset cerebellar atrophy and a storage-phenotype due to mutations in the sorting nexin 14 (*SNX14*) gene. Most patients with SCAR20 come to clinical attention in the first year of life due to global developmental delay and hypotonia. On examination, most patients show ataxia, nystagmus, impaired ambulation, and reduced deep tendon reflexes. Progressive coarsening of facial features with a prominent forehead, epicanthal folds, upturned nares, long philtrum, full lips, hypertrichosis, kyphoscoliosis, and hepatosplenomegaly have been reported and confirm an overlap with lysosomal storage disorders. Additional features include sensorineural hearing loss, camptodactyly, relative macrocephaly, and seizures [13].

On neuroimaging, cerebellar atrophy involving both cerebellar hemispheres and the vermis is evident. Separation of the folia, indicating atrophy rather than hypoplasia, with relative sparing of the pons represents distinctive features from the group of pontocerebellar hypoplasias [14]. The underlying molecular genetic defects of SCAR20 were recently identified as truncating bi-allelic mutations in the *SNX14* gene on chromosome 6q14.3, encoding a ubiquitously expressed modular PX-domain-containing sorting factor [13]. SNX14 is expressed in all brain regions with the highest expression levels in the cerebellum. SNX14 localizes to lysosomes and associates with phosphatidyl-inositol residues, a key component in late endosome/lysosome pathways. Induced-pluripotent-stem-cell-derived neuronal precursor cells from SNX14-patients show enlarged lysosomes and slower autophagy flux with the accumulation of autophagy markers such as LC3-II and p62, confirming disruption in the autophagy pathway [13, 14].

ATG5-Associated Autosomal-Recessive Ataxia Syndrome

In 2016, a homozygous missense variant in the *ATG5* gene was identified in siblings with cerebellar hypoplasia and early-onset non-progressive ataxia [15]. *ATG5* is one of the core autophagy proteins involved in the elongation of the phagophore. As part of the Atg5–Atg12–Atg16L1 conjugation system, *ATG5* is involved in the lipidation of LC3-I to LC3-II, therefore supporting elongation and closure of the autophagosome. Interestingly, the ataxia in these siblings was non-progressive and no signs of cerebellar degeneration on neuroimaging could be detected on close follow-up over two decades. In yeast, the homologous *Atg5* mutation led to a 30–50% reduction of induced autophagy and a *Drosophila melanogaster* model expressing pathogenic E122D human *ATG5* confirmed an ataxic phenotype. These findings illustrate that even slight perturbations in the autophagy pathway, although not leading to prominent cerebellar neurodegeneration, may still cause clinically significant disturbances in cerebellar pathways.

SQSTM1/p62-Associated Childhood-Onset Neurodegeneration

Bi-allelic loss-of-function mutations in the *SQSTM1/p62* gene were recently reported to cause an early-onset neurodegenerative syndrome characterized by cerebellar atrophy, brain iron accumulation, and a complex movement disorder [16]. All cases known to date show a prominent cerebellar syndrome with dysarthria and ataxia leading to wheelchair dependence in some. Further features of the disease include dystonia, vertical gaze palsy, and mild cognitive decline. SQSTM1/p62 is a multidomain scaffolding protein with involvement in multiple cellular pathways. Heterozygous mutations in *SQSTM1/p62* have been associated with Paget disease of the bone and the classic neurodegenerative disorders amyotrophic lateral sclerosis and frontotemporal dementia. Besides other roles in multiple cellular pathways, SQSTM1/p62 acts as a selective adapter protein for autophagy substrates. SQSTM1/p62 possesses both an ubiquitin-binding sequence and a 22-residue sequence allowing direct binding to Atg8/LC3. Thus, SQSTM1/p62 can selectively bind polyubiquitinated macromolecules and proteins, act as a cellular label for autophagic degradation, and recruit its cargo to the growing autophagosome. This process seems to be particularly important for the selective degradation of dysfunctional mitochondria (mitophagy). SQSTM1/p62 appears to control perinuclear clustering of damaged mitochondria, enabling their degradation, therefore aiding in maintaining a healthy cellular pool of mitochondria [16].

Autophagy-Associated Hereditary Spastic Paraplegia

The hereditary spastic paraplegias (HSPs) are a group of heterogeneous disorders that share the

neuropathological feature of progressive retrograde axonal degeneration of the corticospinal tracts and posterior columns. The key clinical findings are walking difficulties due to progressive spasticity. On examination, affected individuals show lower limb spasticity, increased deep tendon reflexes, and a positive extensor plantar response. HSPs have traditionally been divided into pure and complicated forms, depending on the presence of other neurological features, such as ataxia, optic atrophy, pigmentary retinopathy, deafness, intellectual disability, dementia, amyotrophy, peripheral neuropathy, and epilepsy [17].

Particularly childhood-onset HSP is often misdiagnosed as infantile cerebral palsy. However, the progressive nature of the HSP and the above-mentioned associated clinical findings as well as recognizable neuroradiological clues can help distinguish these two entities. The main neuropathological finding in HSPs is the axonal degeneration of the terminal portions of the long descending and ascending pathways in the spinal cord. These remote axonal compartments are particularly vulnerable to disturbances in axonal trafficking, mitochondrial function, and autophagy [18]. Indeed, several types of HSP have been found to result from pathogenic mutations in core autophagy genes. HSP-*SPG11* (SPG11) and HSP-*ZFYVE26* (SPG15) are the most common types of autosomal-recessive HSP with thin corpus callosum, and they are often indistinguishable on clinical examination [19]. In the majority of cases, motor signs are preceded by cognitive impairment and most individuals become clinically apparent with learning difficulties or mild intellectual disability in childhood before developing walking difficulties and progressive lower limb spasticity in the second or third decade of life. Levodopa-responsive parkinsonism, including bradykinesia and upper limb rigidity have been reported in a few patients with SPG15 [20]. Further symptoms include maculopathy, cerebellar ataxia, and peripheral neuropathy. On brain MRI, recognizable features include: moderate to severe thinning of the corpus callosum; diffuse white matter hyperintensities, particularly surrounding the frontal horns; and enlargement of the lateral ventricles and the cerebral sulci. The "ears of the lynx" sign on MRI is highly specific [21]. The proteins mutated in these two types of HSP, namely spatacsin (SPG11) and spastizin (ZFYVE26) are required for autophagic lysosome formation, a recycling mechanism that generates new lysosomes and poses a prerequisite to enable autophagy. Upon depletion of spatacsin or spastizin, the lysosomal availability for fusion with autophagosomes declines, leading to the accumulation of autophagic vesicles in the soma, which triggers degeneration in susceptible post-mitotic neurons [22].

Besides these two relatively common forms of HSP, other more rare forms of HSP associated with autophagy exist. The HSP-*AP-4* spectrum consists of four clinically similar types of HSP (SPG47, SPG50, SPG51, and SPG52) that are caused by mutations in any of the subunits of the adaptor protein complex 4 (AP-4), leading to aberrant localization of AP-4 cargo proteins. As an example, HSP-*AP4B1* (SPG47) [23] presents with infantile hypotonia progressing to spastic paraplegia, early developmental delay, and intellectual disability. The disease becomes clinically apparent in the neonatal or early-infantile period, with truncal and appendicular hypotonia progressing to lower limb spasticity. Ambulation, if achieved, is generally impaired and the gait is described as a wide-based and unsteady spastic gait. Intellectual disability is in the moderate to severe range in older individuals. Speech is usually not acquired or is limited to a few words. Additional features include microcephaly (in the 2- to 3-standard deviation range), short statue, epilepsy (in about 60% of patients), and stereotypical episodes of unprovoked laughter.

On neuroimaging, characteristic brain findings include the triad of thinning of the corpus callosum (particularly of the posterior parts), delayed myelination or loss of supratentorial white matter, and subsequent ventriculomegaly. The underlying genetic causes are biallelic loss-of-function mutations in the *AP4B1* gene, a subunit of the AP-4 complex, a heterotetrameric protein complex that mediates vesicle trafficking from the trans-Golgi network to early and late endosomes. In neuronal models, AP-4 was found to mediate alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking with *Ap4b1*$^{-/-}$ mice showing autophagy-dependent aberrant localization of AMPA receptors to distal axons, where they were found within accumulating autophagosomes, driving neurodegeneration. Another rare form of HSP is HSP-*TECPR2* (SPG49). This subtype of HSP is characterized by distinct dysmorphic features, developmental delay, ataxia, and initial hypotonia progressing to spasticity [24]. Individuals usually suffer from central apnea episodes, often requiring mechanical ventilation and recurrent pulmonary infections due to gastresophageal-reflux disease. Ambulation, if achieved, is marked by a rigid

spastic and ataxic gait. Further cerebellar signs include dysmetria and dysarthric speech. Neuroradiological findings include a thin corpus callosum and progressive cerebral and cerebellar vermian atrophy.

The underlying genetic causes are bi-allelic mutations in the *TECPR2* gene on chromosome 14q32.31. TECPR2 interacts with the Atg8 protein family, including LC3, and is a probable positive regulator of autophagosome formation. TECPR2 regulates endoplasmic reticulum exit sites, which may serve as scaffolds for the formation of autophagosomes. In cultured cell lines and fibroblasts from HSP-*TECPR2* patients, loss of *TECPR2* leads to a reduction in the number of autophagosomes and impaired autophagy flux, indicating a derangement of the early autophagy stages.

Congenital Disorders of Autophagy and Movement Disorders

Autophagy plays a critical role in neurodevelopment, synaptic function, and neurotransmission, and it is of pivotal importance to maintaining neuronal integrity. As demonstrated above, perturbations in autophagy and lysosomal degradation pathways may lead to structural brain abnormalities and neurodegeneration. The cerebellum, the long white matter tracts, and the basal ganglia seem to be particularly vulnerable to disturbed autophagy (for movement disorder phenotypes see Table 20.1). Cerebellar pathology is present in nearly all congenital disorders of autophagy, with clinical overlap to the autosomal-recessive cerebellar ataxias. Cerebellar ataxia is characterized by incoordination of movement and unsteadiness. Patients clinically present with an abnormal gait (imbalance, staggering, and difficulties with tandem walking), truncal and appendicular ataxia, dysmetria of upper and lower limbs, dysdiadochokinesia, hypotonia, dysarthria, and impairment of saccadic eye movements. Cerebellar ataxia can present in early infancy or develop gradually over months and years with worsening of gait and balance or excessive clumsiness. Important accompanying signs on history and examination can be cognitive impairment, epilepsy, signs of peripheral neuropathy (decreased or absent deep tendon reflexes and decreased vibration sense in the ankles), extrapyramidal movement disorders such as chorea, dystonia, oculomotor abnormalities, and pyramidal-tract dysfunction (extensor plantar responses, hyperreflexia, and spasticity) [25].

Imaging studies usually reveal atrophy of the cerebellum as a sign of cerebellar neurodegeneration due to progressive Purkinje cell loss. However, *ATG5*-associated autosomal-recessive ataxia syndrome illustrates that even slight perturbations in autophagy might be sufficient to produce a cerebellar syndrome secondary to cerebellar hypoplasia and dysfunction.

The classic childhood-onset cerebellar ataxias include Friedreich ataxia and ataxia–telangiectasia. However, there is a highly heterogeneous group of disorders with early-onset ataxia as the predominant feature and an exact diagnosis is often challenging. Autosomal-recessive cerebellar ataxias show a clinical overlap with lysosomal storage diseases. Many lysosomal diseases such as Niemann–Pick type C, Tay–Sachs disease, and I-cell disease show cerebellar ataxia and evidence of Purkinje cell loss, in addition to the classic storage-phenotype consisting of coarsening of facial features and enlarged organs. Interestingly, SCAR20, in addition to prominent cerebellar atrophy shows a storage-

Table 20.1 Congenital disorders of autophagy and movement disorders

Disorder	Dystonia	Ataxia	Parkinsonism	Spasticity
BPAN	X	X	X	X
SNX14-associated SCAR20		X		
ATG5-associated autosomal-recessive ataxia syndrome		X		
SQSTM1/p62-associated childhood-onset neurodegeneration	X	X		
HSP-*SPG11* and HSP-*SPG15*		X	X	X
HSP-*AP4*				X
HSP-*TECPR2*		X		X

phenotype reminiscent of lysosomal storage diseases. These links between cerebellar pathology and lysosomal dysfunction further highlight the importance of lysosomal degradation pathways for cerebellar function and the vulnerability of the cerebellum to disruptions in autophagic flux [13].

Basal ganglia pathology is another common theme in congenital disorders of autophagy. Autophagy seems to be involved in clearing iron from vulnerable brain regions such as the basal ganglia, highlighted by the fact that disruptions in the autophagy pathway result in iron deposition as seen in BPAN and *SQSTM1/p62*-associated childhood-onset neurodegeneration. Basal ganglia pathology leads to complex extrapyramidal movement disorders including dystonia and parkinsonism, the latter characterized by bradykinesia, rigidity, freezing, and postural instability and, less commonly, a resting tremor. Interestingly, familial forms of Parkinson disease have been shown to be due to bi-allelic mutations in the genes involved in autophagic degradation of dysfunctional mitochondria, illustrating another pathomechanism for basal ganglia dysfunction due to disturbed autophagy [26].

Conclusions

Congenital disorders of autophagy are a novel group of inborn errors of neuro-metabolism caused by monogenic mutations in the autophagy pathway. Clinically, this heterogeneous group shares many clinical similarities such as an early disease onset and the prominent involvement of the central nervous system. Common neurological manifestations include cerebellar hypoplasia or atrophy, thinning of the corpus callosum, and basal ganglia dysfunction. Most of the congenital disorders of autophagy present with developmental delay and intellectual disability, seizures, and prominent movement disorders such as ataxia, gait disorders, spasticity, dystonia, and parkinsonism. The underlying genetic defects map to core genes of the autophagy pathway, highlighting the role of this essential cellular degradation pathway in neurodevelopment and neurodegeneration. With the increased availability of next-generation sequencing, the group of congenital disorders of autophagy is rapidly expanding and the identification of novel diseases will provide further insights into the role of autophagy in brain development and neuronal function.

Key Points and Clinical Pearls

- Autophagy is a fundamental pathway in health and disease.
- Congenital disorders of autophagy provide a "genetic window" into the role of autophagy in humans.
- Congenital disorders of autophagy are multisystem diseases with prominent neurological involvement.
- Most congenital disorders of autophagy present with movement disorders and movement disorders account for substantial morbidity.

Directions for Future Research

- Discovery of novel congenital disorders of autophagy through next-generation sequencing.
- Definition of the natural history and the spectrum of movement disorders in congenital disorders of autophagy.
- Understanding the regulation of autophagy will provide insights into novel "druggable" pathways and therapeutic targets.

References

1. Ebrahimi-Fakhari D, Saffari A, Wahlster L, et al. Congenital disorders of autophagy: An emerging novel class of inborn errors of neuro-metabolism. Brain. 2016;**139**(Pt 2):317–37.
2. Ebrahimi-Fakhari D. Congenital disorders of autophagy: What a pediatric neurologist should know. Neuropediatrics. 2018;**49**(1):18–25.
3. Teinert J, Behne R, Wimmer M, Ebrahimi-Fakhari D. Novel insights into the clinical and molecular spectrum of congenital disorders of autophagy. *J Inherit Metab Dis.* 2019;doi:10.1002/jimd.12084.
4. Mizushima N, Komatsu M. Autophagy: Renovation of cells and tissues. Cell. 2011;**147**(4):728–41.
5. Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. N Engl J Med. 2013;**368**(19):1845–6.
6. Klionsky DJ, Abdalla FC, Abeliovich H, et al. Guidelines for the use and interpretation of assays for monitoring autophagy. Autophagy. 2012;**8**(4):445–544.

7. Hogarth P. Neurodegeneration with brain iron accumulation: Diagnosis and management. J Mov Disord. 2015;**8**(1):1–13.
8. Saitsu H, Nishimura T, Muramatsu K, et al. De novo mutations in the autophagy gene *WDR45* cause static encephalopathy of childhood with neurodegeneration in adulthood. Nat Genet. 2013;**45**(4):445–9, 9e1.
9. Hayflick SJ, Kruer MC, Gregory A, et al. Beta-propeller protein-associated neurodegeneration: A new X-linked dominant disorder with brain iron accumulation. Brain. 2013;**136**(Pt 6):1708–17.
10. Gregory A, Kurian MA, Haack T, Hayflick SJ, Hogarth P. Beta-propeller protein-associated neurodegeneration. *GeneReviews®*. 2017;Feb 16.
11. Haack TB, Hogarth P, Kruer MC, et al. Exome sequencing reveals de novo *WDR45* mutations causing a phenotypically distinct, X-linked dominant form of NBIA. Am J Hum Genet. 2012;**91**(6):1144–9.
12. Behrends C, Sowa ME, Gygi SP, Harper JW. Network organization of the human autophagy system. Nature. 2010;**466**(7302):68–76.
13. Akizu N, Cantagrel V, Zaki MS, et al. Biallelic mutations in *SNX14* cause a syndromic form of cerebellar atrophy and lysosome–autophagosome dysfunction. Nat Genet. 2015;**47**(5):528–34.
14. Thomas AC, Williams H, Seto-Salvia N, et al. Mutations in *SNX14* cause a distinctive autosomal-recessive cerebellar ataxia and intellectual disability syndrome. Am J Hum Genet. 2014;**95**(5):611–21.
15. Kim M, Sandford E, Gatica D, et al. Mutation in *ATG5* reduces autophagy and leads to ataxia with developmental delay. *Elife.* 2016;5.
16. Haack TB, Ignatius E, Calvo-Garrido J, et al. Absence of the autophagy adaptor SQSTM1/p62 causes childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy. Am J Hum Genet. 2016;**99**(3):735–43.
17. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: Clinical features and pathogenetic mechanisms. Lancet Neurol. 2008;**7**(12):1127–38.
18. Ashrafi G, Schwarz TL. The pathways of mitophagy for quality control and clearance of mitochondria. Cell Death Differ. 2013;**20**(1):31–42.
19. Pensato V, Castellotti B, Gellera C, et al. Overlapping phenotypes in complex spastic paraplegias SPG11, SPG15, SPG35 and SPG48. Brain. 2014;**137**(Pt 7):1907–20.
20. Mallaret M, Lagha-Boukbiza O, Biskup S, et al. SPG15: A cause of juvenile atypical levodopa responsive parkinsonism. J Neurol. 2014;**261**(2):435–7.
21. Pascual B, de Bot ST, Daniels MR, et al. "Ears of the lynx" MRI sign is associated with SPG11 and SPG15 hereditary spastic paraplegia. AJNR Am J Neuroradiol. 2019;**40**(1):199–203.
22. Chang J, Lee S, Blackstone C. Spastic paraplegia proteins spastizin and spatacsin mediate autophagic lysosome reformation. J Clin Invest. 2014;**124**(12):5249–62.
23. Ebrahimi-Fakhari D, Cheng C, Dies K, et al. Clinical and genetic characterization of *AP4B1*-associated SPG47. Am J Med Genet A. 2018;**176**(2):311–8.
24. Oz-Levi D, Ben-Zeev B, Ruzzo EK, et al. Mutation in *TECPR2* reveals a role for autophagy in hereditary spastic paraparesis. Am J Hum Genet. 2012;**91**(6):1065–72.
25. Anheim M, Tranchant C, Koenig M. The autosomal recessive cerebellar ataxias. N Engl J Med. 2012;**366**(7):636–46.
26. Pickrell AM, Youle RJ. The roles of PINK1, Parkin, and mitochondrial fidelity in Parkinson's disease. Neuron. 2015;**85**(2):257–73.

Chapter

21

Neurotransmitter Disorders: Disorders of Dopamine Metabolism and Movement Disorders

Thomas Opladen and Heiko Brennenstuhl

Introduction

Muscular tone and movements are highly dependent on the communication of neurons and muscle cells. This complex process is achieved by neurotransmitters, chemical substances synthesized and stored in presynaptic neurons, which are released into the synaptic cleft upon specific stimuli. Neurotransmitters can traverse the synaptic cleft and bind to highly specific receptors on the postsynaptic membrane. This process causes an electric response in the form of depolarization and triggers further complex intracellular signaling. The termination of the synaptic signaling is achieved by reuptake or degradation of the neurotransmitter (Figure 21.1).

The term "neurotransmitter" refers to several subgroups including amino acid neurotransmitters such as glycine and gamma-aminobutyric acid (GABA). It also refers to the catecholamines: dopamine, norepinephrine epinephrine, and serotonin. Inherited deficiencies of monoamine neurotransmitters are rare genetic defects of enzymes involved in the synthesis, transport, or degradation of dopamine and serotonin, and deficiencies of cofactors, mainly involving pterin metabolism, necessary for monoamine synthesis. These diseases result in a wide variety of clinical presentations with a continuum of early-onset encephalopathy to late-onset movement disorders with a milder clinical picture [1].

Enzymatic defects of tyrosine hydroxylase (TH), tryptophan hydroxylase (TPH), and phenylalanine hydroxylase (PAH) have an impact on phenylalanine levels and can therefore be diagnosed in newborn screening. However, other deficiencies present with clinical symptoms similar to neurological syndromes such as childhood epileptic encephalopathies or cerebral palsy, which can lead to a delayed diagnosis [2]. Especially given that neuroimaging typically appears normal, thorough clinical characterization combined with blood tests, urine sampling, and investigation of neurotransmitter metabolites in the cerebrospinal fluid (CSF) are necessary to establish a diagnosis. This chapter elucidates pathophysiological concepts, diagnostic approaches, and treatment strategies in inherited neurotransmitter disorders with a special focus on their individual impact on motor function.

Neurotransmitter deficiencies can be clustered into five distinct groups (Table 21.1): (1) Disorders of tetrahydrobiopterin (BH_4) synthesis with or without hyperphenylalaninemia (HPA); (2) primary enzymatic defects of monoamine neurotransmitter synthesis; (3) monoamine catabolism disorders; (4) monoamine transporter defects; and (5) chaperone-associated disorders, which are the subject of Chapter 22. Figure 21.1 shows an overview of the enzymatic reactions involved in the synthesis of BH_4 and/or neurotransmitters dopamine and serotonin, as well as their transport and degradation.

The clinical phenotype of the majority of the disorders in this chapter is predominantly based on the inherited deficiency of dopamine. Symptoms highly vary with the degree of dopamine deficiency. Thus, a mild form of TH deficiency might cause a clinical picture similar to autosomal-dominant GTP cyclohydrolase 1 (GTPCH1) deficiency, usually referred to as a "Segawa-like phenotype" with diurnal fluctuation of symptoms and the reconstitution of motor functions after sleep. Especially in young children, the clinical phenotype of pterin synthesis defects is hardly distinguishable from severe autosomal-recessive GTPCH1 deficiency. Only very few features, however, are pathognomonic for a distinct disease type, e.g. intracranial calcifications are found specifically in dihydropterine reductase (DHPR) deficiency.

Dopamine deficiency causes truncal hypotonia in early life that slowly progresses towards a more parkinsonian phenotype with progressive dystonia. Oculogyric crises can be seen in many neurotransmitter disorders and are often misinterpreted as epileptic activity. Serotonin deficiency presumably directly contributes

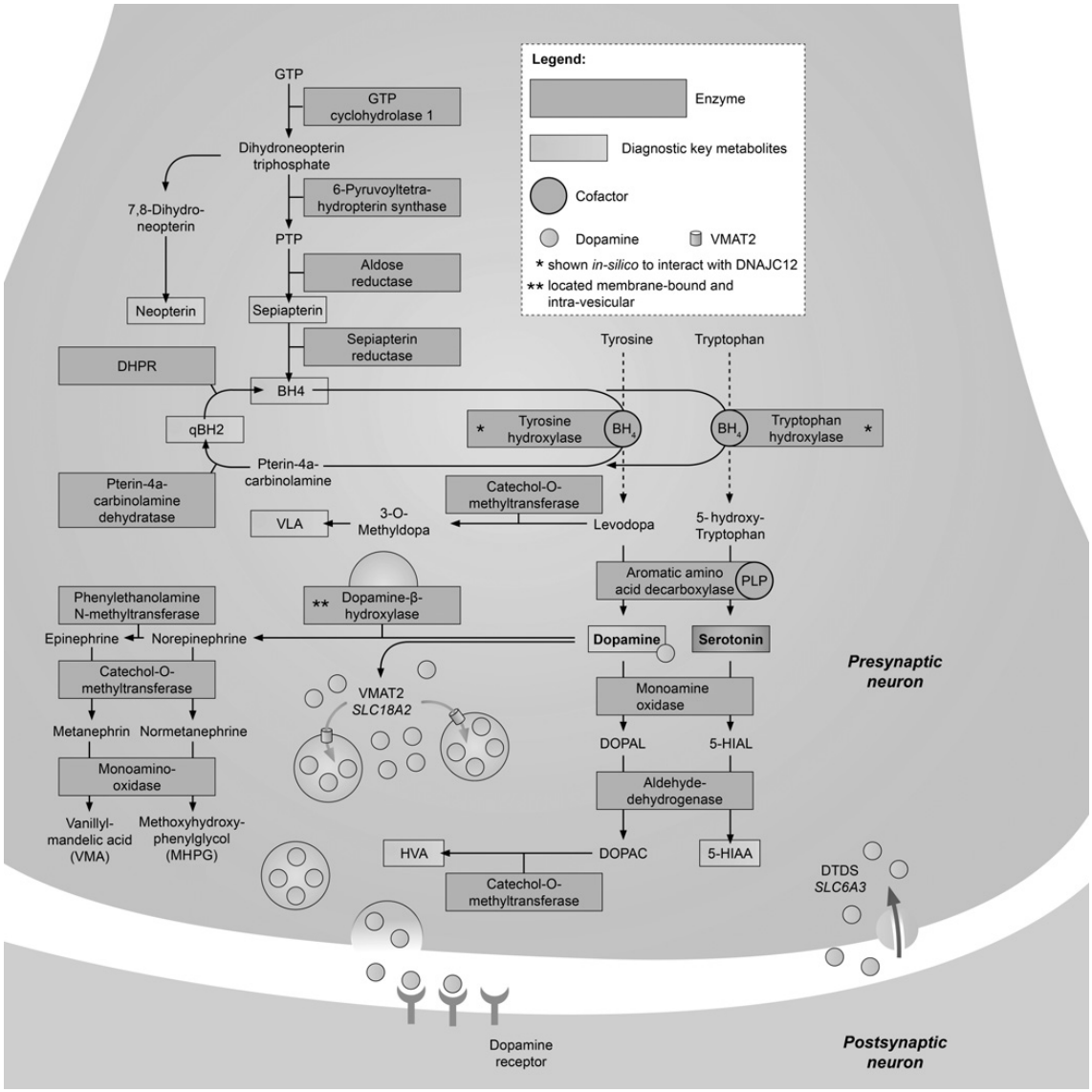

Figure 21.1 Pathways of neurotransmitter and biopterin synthesis, degradation, and recycling. Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HIAL, 5-hydroxyindoleacetaldehyde; qBH2, quinonoid dihydrobiopterin; BH_4, tetrahydrobiopterin; DHPR, dihydropterine reductase; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPAL, 3,4-dihydroxyphenylacetaldehyde; DTDS, dopamine transport deficiency syndrome; GTP, guanosine-5′-triphosphate; HVA, homovanillic acid; MHPG, methoxylhydroxyphenylglycol; PLP, pyridoxal 5′-phosphate; PTP, 6-pyruvoyltetrahydropterin; VLA, vanillyllactic acid; VMA, vanillylmandelic acid; VMAT2, vesicular monoamine transporter 2. Adapted from Brennenstuhl H, Jung-Klawitter S, Assmann B, Opladen T. Inherited Disorders of Neurotransmitters: Classification ad Practical Approaches for Diagnosis and Treatment. Neuropediatrics. 2019 Feb;50(1):2–14.

to dystonic features, due to a dysregulation of serotonergic neurotransmission in the dysfunctional basal ganglia network involved in dystonia. The reduced availability of serotonin also contributes toward psychiatric symptoms such as increased irritability or sleep disturbances and depression, whereas catecholamine deficiency causes autonomous dysregulation, including profound sweating, nasal congestion, and hypotonia. Figure 21.2 shows an overview of the symptoms, their respective causal attribution, and their interdependency. Identification of these symptoms in pediatric patients should result in further testing, according to the proposed algorithm included in this chapter.

Table 21.1 Overview of inherited neurotransmitter deficiencies and their genetic background

Group	Enzyme deficiency	OMIM/ORPHA number	Genetic cause	Inheritance[a]
Biopterin synthesis/recycling defects	SPR	612716	*SPR*	AR
	AD-GTPCH1	233910	*GCH1*	AD
	AR-GTPCH1		*GCH1*	AR
	PTPS	261640	*PTPS*	AR
	DHPR	261630	*QDPR*	AR
	PCD	264070	*PCD*	AR
Primary neurotransmitter synthesis defects	TH	605407	*TH*	AR
	AADC	608643	*AADC*	AR
Monoamine transportopathies	SLC6A3 (DTDS)	613135	*SLC6A3*	AR
	SCL18A2 (VMAT2)	ORPHA: 352649	*SCL18A2*	AR
Monoamine catabolism disorders	MAO-A/MAO-B	309850	*MAOA/MAOB*	XL
	DBH	609312	*DBH*	AR
Co-chaperone defects[b]	DNAJC12	606060	*DNAJC12*	AR

[a] AR, autosomal-recessive; AD, autosomal-dominant; XL, X-linked. [b] See Chapter 22 for further details.

BH_4 Cofactor Deficiencies without HPA

Autosomal-Dominant GTPCH1 Deficiency (Segawa Disease, Dopa-Responsive Dystonia, DYT5a, DYT/PARK-GCH1)

GTPCH1 is a key enzyme of the BH_4 synthesis pathway. Genetic variants of the *GCH1* gene cause drastically reduced dopamine and serotonin levels due to the reduced availability of BH_4 [3]. GTPCH1 deficiency presents either in an autosomal-dominant (AD) or autosomal-recessive (AR) manner.

The clinical spectrum of AD-GTPCH1 deficiency is wide with symptom onset during the first decade of life, mainly comprised of dystonia of the lower extremity. Typically symptoms show worsening during the day with rapid improvement after sleep, referred to as diurnal or circadian fluctuation [4]. Additional symptoms include "parkinsonian" symptoms, e.g. tremor and bradykinesia. Impaired fine motor skills can develop later in the clinical course and may be attributable to poor disease control [5]. Only a small subset of patients show impaired intellectual development, while neuropsychiatric features such as sleep disturbance and anxiety are more common [6].

Supplementation of low-dose levodopa in combination with a decarboxylase inhibitor (carbidopa or benserazid) improves motor function drastically in AD-GTPCH1-deficient patients; therefore, a treatment trial can be used as a diagnostic tool. Concentrations of homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), biopterin, and neopterin are low in the CSF. Genetic testing is used to verify underlying variants in the *GCH1* gene [7].

Sepiapterin Reductase Deficiency (DYT/PARK-SPR)

Variants of the *SPR* gene cause sepiapterin reductase (SPR) deficiency, a very rare autosomal-recessive disorder [8]. SPR deficiency leads to early-onset axial hypotonia, delayed achievement of developmental motor milestones, and prominent psychiatric features such as irritability and behavioral problems [9]. A constellation of motor symptoms has been described in the early stages, with hypokinetic rigidity including impairment of postural reactions, spasmodic dystonia of the trunk

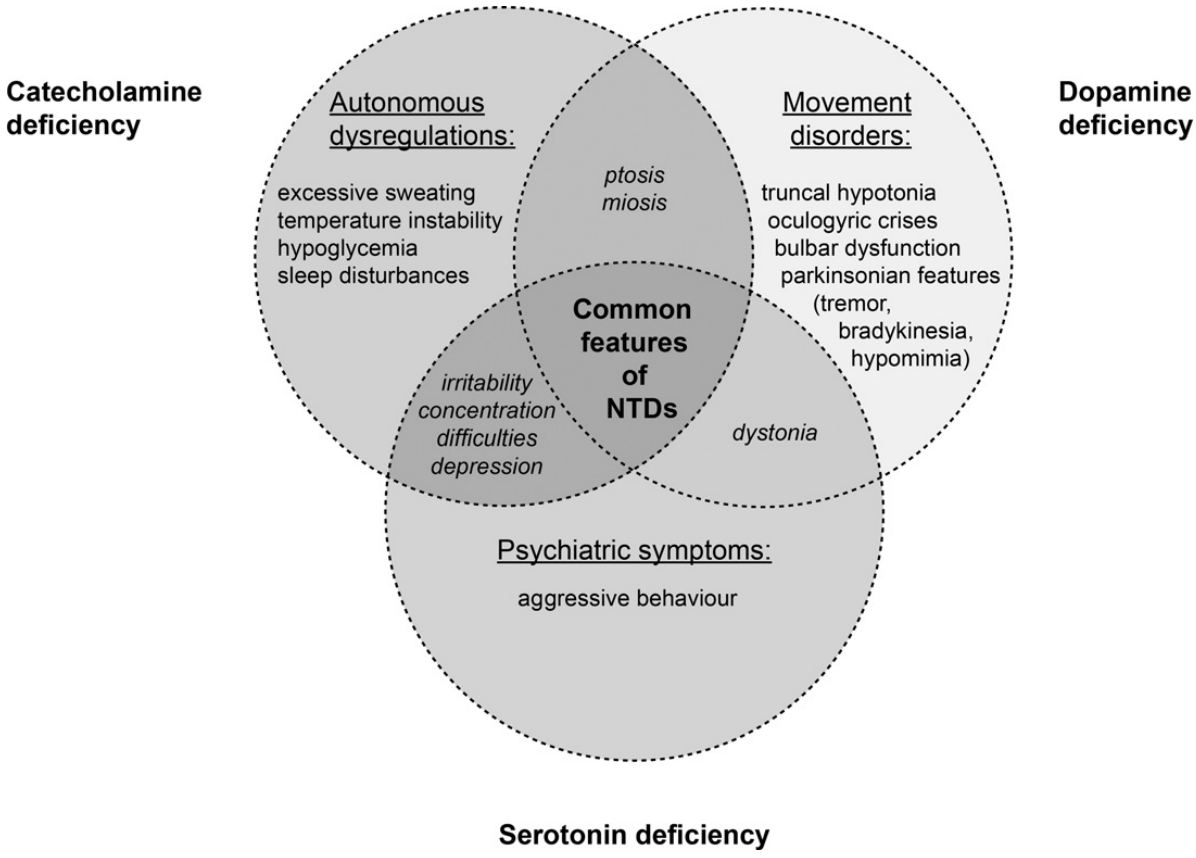

Figure 21.2 Overview of common features of inherited neurotransmitter deficiencies (NTDs) and the respective neurotransmitter systems involved in its pathophysiology.

with oculogyric crises, and resting tremor of the limbs and head that can be inhibited by contact or spontaneous movement [10]. Growth-hormone deficiency and hypoglycemia are attributed to dopamine depletion in SPR-deficient patients [11]. The majority of patients with SPR deficiency show cognitive impairment [12]. Diagnosis may be challenging due to non-specific symptoms. Dystonic spasms and oculogyric crises may mimic epilepsy, delaying diagnosis [12]. Diagnosis depends on the determination of neurotransmitter metabolites in CSF. Here, low concentrations of HVA and 5-HIAA with elevation of sepiapterin and 7,8-dihyrobiopterin (BH_2) are typical.

Treatment consists of the supplementation of neurotransmitter precursors, levodopa and 5-hydroxytryptophan (5-HTP), in combination with the blockage of peripheral decarboxylation, in order to increase the dosage that crosses the blood–brain barrier. This is usually done in a 4:1 ratio of levodopa/decarboxylase inhibitor. Selective serotonin reuptake inhibitors (SSRIs), dopaminergic agonists, monoamine oxidase inhibitors, and dopamine/noradrenaline reuptake inhibitors have shown effects in single cases; however, so far there is no controlled clinical study or guideline available for the treatment of this disease [12].

BH_4 Cofactor Deficiencies with HPA

Autosomal-Recessive GTPCH1 Deficiency (DYT/PARKGCH1)

Homozygous or compound heterozygous variants in *GCH1* are the genetic cause for AR-GTPCH1 deficiency. With early neonatal onset and an often complex neurological phenotype, this disorder

resembles the severe end of a continuous spectrum between the AR and AD form of GTPCH1 deficiency. Classic features at onset are neonatal rigidity, truncal hypotonia, and dystonia–parkinsonism, as well as oculogyric crises. Most cases present with HPA on newborn screening; however, this biochemical hallmark can be missing in rare cases of AR-GTPCH1 deficiency [13, 14].

Similar to AD-GTPCH1 deficiency, supplementation of levodopa/decarboxylase inhibitor represents the main treatment strategy. Compared to AD-GTPCH1 deficiency, the levodopa dose required to achieve an adequate treatment response is higher. 5-HTP can reduce neuropsychiatric symptoms. BH_4 supplementation can be used to normalize the HPA.

6-Pyruvoyltetrahydropterin Synthase Deficiency (DYT/PARK-PTS)

6-Pyruvoyltetrahydropterin synthase (PTPS) deficiency represents the most frequent disorder of BH_4 synthesis accompanied by HPA. It is caused by variants of the *PTPS* gene and comprises a highly variable clinical spectrum depending on the degree of residual enzyme activity [2]. The phenotype ranges from severe hypotonia with dystonia, dystonia–parkinsonism, cognitive impairment, and epileptic seizures to milder phenotypes with unaltered neurodevelopment [15]. HPA is usually present on newborn screening making it a key diagnostic marker for early diagnosis [13].

The treatment of patients with PTPS deficiency consists of the supplementation of neurotransmitter precursors and inhibition of peripheral decarboxylation. Similar to AR-GTPCH1 deficency, BH_4 supplementation helps control HPA. Some patients with PTPS deficiency benefit from BH_4 monotherapy. However, high doses need to be administered peripherally to achieve adequate concentrations in the central nervous system [2].

Dihydropteridine Reductase Deficiency (DYT/PARKQDPR)

BH_4 is continuously recycled by a regenerative pathway using DHPR and pterin-4a-carbinolamine dehydratase (PCD) to reduce BH_2 and prevent the accumulation of potentially harmful intermediates (see Figure 21.1) [16]. Variants in the *QDPR* gene cause DHPR deficiency [8], resulting in a variety of biochemical features, such as the accumulation of BH_2 with the subsequent reduction of catecholamine and serotonin synthesis, dysregulation of nitric oxide synthase activity, and reduced 5-methyltetrahydrofolate (5-MTHF) formation [15]. Symptoms appear in early childhood, most frequently starting in the neonatal period, with microcephaly and developmental delay. Later in life, motor function is highly impaired in untreated children, characterized by a dystonia–parkinsonism phenotype with tremor as well as seizures [2].

Usually, after identification of HPA in newborn screening, the pterin pattern in dried blood spots or urine can further differentiate the underlying BH_4 disorder. But since pterins are normal in DHPR deficiency, it is crucial to determine the DHPR enzyme activity in dried blood to confirm this defect. Treatment is similar to other BH_4 synthesis defects based on the supplementation of neurotransmitter precursors. Based on the hypothesis that BH_4 supplementation may lead to increased 7, 8-dihydrobiopterin (BH_2) production resulting in aggravation of disease severity by inhibiting the aromatic L-amino acid hydroxylases or by increasing nitric oxide (NO) uncoupling and oxidative stress, this treatment approach is currently controversial in DHPRD. However, literature evidence for these potential harmful effects is scarce and based on cell experiments only. Therefore, there is no reliable justification to withhold this therapeutic intervention from patients with DHPRD. Due to folate depletion in the CSF, the administration of folinic acid should be initiated, having a positive effect on dopamine levels in the brain [18].

Pterin-4a-Carbinolamine Dehydratase Deficiency

PCD deficiency is caused by genetic variants in *PCBD1*, which lead to a milder and more benign phenotype compared to other BH_4 deficiencies. In newborn screening, only mild HPA is noted, whereas high urine levels of 7-biopterin (primapterin) confirms the diagnosis [19]. Therefore, PCD deficiency is often referred to as a mild form of HPA rather than a neurotransmitter deficiency. Interestingly, PCD deficiency is described as a dimerization cofactor for hepatocyte nuclear factor 1 (HNF1) [20]. Mutations in *PCBD1* cause reduced transcriptional activity of HNF1 and are associated with the impaired development of liver and pancreatic cells causing early-onset diabetes [21, 22].

Treatment consists of dietary measures, and BH_4 is recommended to control HPA.

Primary Enzymatic Defects of Monoamine Metabolism

Tyrosine Hydroxylase Deficiency (TH-D, Dopa-Responsive Dystonia, DYT5b, DYT/PARK-TH)

TH catalyzes the rate-limiting step of dopamine synthesis, thus, TH deficiency leads to an isolated catecholamine deficiency (see Figure 21.1). TH deficiency is caused by genetic variants in the *TH* gene. Classic features of TH deficiency are caused by catecholamine depletion and include dystonia–parkinsonism, oculogyric crises, and non-specific features such as autonomic dysregulation and developmental impairment [23]. The phenotypic spectrum ranges from a mild form (type A) to a severe form (type B). The latter usually presents with early neonatal-onset encephalopathy and a hypokinetic–rigid movement disorder. In addition, severe developmental delay may be noted in type B patients [23]. CSF neurotransmitter measurements reveal reduced levels of HVA, normal 5-HIAA, and a low HVA:5-HIAA ratio [24].

Treatment is based on the supplementation of levodopa/decarboxylase inhibitor. Of note is that TH-deficient patients are highly sensitive to very low doses of levodopa. Furthermore, patients with long-standing dopaminergic deficiency are more likely to suffer from adverse medication-related effects, such as dyskinesia, nausea, or vomiting. This is not caused by a toxic effect of levodopa and should therefore not lead to the cessation of the medication. Reduced levodopa dosage is instead recommended until the side effects disappear [25].

Aromatic L-Amino Acid Decarboxylase Deficiency

Variants in the *DDC* gene cause aromatic L-amino acid decarboxylase (AADC) deficiency, which represents a rare disease with approximately 150 cases described in the medical literature, a fifth within an Asian subpopulation [26]. Similar to BH_4 disorders, a combined reduction of serotonin and dopamine-derived catecholamines leads to a complex movement disorder with predominating dystonia–parkinsonism and a progressive extrapyramidal movement disorder combined with autonomous dysregulation such as profuse sweating, nasal congestion, temperature instability, insomnia, and irritability. Many patients show signs of severe neurocognitive developmental delay [27, 28]. Diagnosis is established by reduced CSF concentrations of HVA and 5-HIAA in combination with elevated 3-orthomethyldopa, levodopa, and 5-HTP. Urine analysis of organic acids can reveal high concentrations of vanillylactate. The metabolic profile of pyridoxine-5'-phosphate oxidase (PNPO) deficiency can mimic the changes seen in AADC defciency, due to the role of pyridoxal 5'-phosphate (PLP) as an essential cofactor of AADC. However, the determination of AADC enzyme activity, vanillylactate concentration in the urine, or PLP concentrations in the CSF can be used to distinguish PNPO deficiency and AADC deficiency [27]. Due to high residual AADC activity in the renal parenchyma, the determination of catecholamine concentrations in the urine is not useful [29].

AADC deficiency represents the first neurotransmitter deficiency for which a consensus guideline was published [30]. This guideline suggests the first-line use of dopaminergic agonists as stand-alone therapy or in combination with monoamine oxidase (MAO) inhibitors to increase the availability of monoamine neurotransmitters. PLP can be used to increase the residual enzyme activity of the AADC enzyme [30]. A clinical trial is currently ongoing, which evaluates the use of adeno-associated viral-mediated gene therapy. Although the initial data reveal an improvement of motor function, long-term data evaluating the efficacy, safety, and stability of gene therapy are pending [31].

Disorders of Monoamine Catabolism

Monoamine Oxidase A and B Deficiency

The last step of dopamine degradation is the oxidative deamination of the catecholamines to vanillylmandelic acid (VMA) and methoxylhydroxyphenylglycol (MHPG) by the two isoenzymes, MAO-A and -B [32]. Both enzymes are located in secretory neurotransmitter vesicles. The respective genes are located at region Xp11.23, making this a rare X-linked condition. Isolated MAO-A deficiency is a cause of intellectual deficiency and behavioral abnormalities, such as repetitive aggressive behavior and violent outbursts [33]. A combined deficiency results in intellectual disability, autonomous dysregulation, hypotonia, stereotypies, and epilepsy [34]. Isolated MAO-B deficiency does not lead to a clinical phenotype.

The biochemical profile reveals high concentrations of MAO-A substrates (normetanephrine and

3-methoxytyramine) in the urine and reduced concentrations of HVA, MHPG, and 5-HIAA in the CSF [32]. There is little information available on clinical treatments. Mouse data exist, describing an effect of SSRIs to improve neuropsychiatric symptoms [35].

Dopamine Beta-Hydroxylase Deficiency

Dopamine beta-hydroxylase (DBH) is encoded by the *DBH* gene and serves as a membrane-bound intra-vesicular enzyme for the conversion of dopamine to norepinephrine. The prevalence of DBH deficiency is unknown. Clinical symptoms are caused by an imbalance of sympathetic and parasympathetic signaling: profound orthostatic hypotension, hypotonia, hypothermia, hypoglycemia, and ptosis [36, 37]. Classic laboratory findings of DBH deficiency are reduced concentrations of norepinephrine and epinephrine with high concentrations of dopamine in the blood [38]. In a recent study, two cases of orthostatic hypotension and a biochemical constellation similar to DBH deficiency, with regular enzymatic activity and no genetic alterations, were identified. Further genetic investigation revealed bi-allelic variants in the *CYB561* gene, encoding for a transmembrane electron carrier on catecholamine secretory vesicles, which is necessary for proper DBH function [39].

Monoamine Transporter Defects

Dopamine Transporter Deficiency Syndrome

The reuptake of neurotransmitters into the presynaptic neuron represents a way of terminating synaptic transmission. To achieve this complex process, the cell relies on transmembrane transporter proteins, such as solute carrier family 6, which is encoded by the *SLC6A3* gene, and serves as a dopamine transporter. Malfunction of this protein is called dopamine transporter deficiency syndrome (DTDS). Symptoms usually develop during the first years of life with axial hypotonia and a predominantly choreatic movement disorder. The clinical phenotype changes over time to more dystonia and parkinsonism, including hypomimia, tremor, or bradykinesia. Overall, patients show delayed achievement of neurodevelopmental milestones, especially involving motor functions [40]. Recently, late-onset DTDS was described, with a milder phenotype attributable to residual enzyme activity. Symptoms are predominantly motor impairment with dystonia, rigidity, and progressive bradykinesia [41].

Diagnostics show distinct findings with high concentrations of CSF HVA and normal 5-HIAA, resulting in an increased CSF HVA:5-HIAA ratio. The pterin profile does not usually reveal any abnormalities. Confirmation of the diagnosis can be done by genetic testing for *SLC6A3* variants [42].

Treatment of DTDS is difficult and is focused on the improvement of symptoms rather than reversing biochemical disturbances. Dopaminergic agonists with a high affinity toward presynaptic autoreceptors are recommended [42]. Classic treatment strategies for dystonia include trihexyphenidyl, oral baclofen, and benzodiazepines.

Vesicular Monoamine Transporter 2 Deficiency

SLC18A2 encodes for vesicular monoamine transporter 2 (VMAT2), an integral membrane protein that functions as a transporter of dopamine and catecholamines into presynaptic neurotransmitter vesicles. So far, eight individuals from one family have been reported. Each developed early childhood developmental delay, axial hypotonia with parkinsonism, oculogyric crises, and bulbar dysfunction [43]. Laboratory investigations, apart from low serotonin concentrations in full blood, did not reveal conclusive findings, and thus genetic testing is recommended for patients presenting with this phenotype and a high suspicion of a vesicular monoamine transporter defect. Treatment with pramipexole is preferred since levodopa worsens parkinsonian symptoms in these patients [44].

A Practical Approach to Diagnosis and Treatment

Useful Diagnostic Tools/Algorithms

The diagnosis of inherited deficiencies of neurotransmitters is challenging. Due to the lack of peripheral markers and inconclusive imaging studies, the diagnosis still relies on the determination of neurotransmitters and their metabolic precursors or degradation products, mainly in the CSF. The implementation of such measurements requires standardized procedures (material acquisition, storage and transport of CSF, etc.).

The determination of phenylalanine concentration in newborn screening dried blood spots is part of routine testing for phenylketonuria. Every detected

case of HPA needs to undergo measurement of pterins and DHPR enzyme activity. In case of a suspicious clinical presentation and the absence of HPA, urine analysis of sepiapterin concentrations can be considered [45]. Hyperprolactinemia can point towards a central dopaminergic deficiency; however, this parameter is susceptible to variability, even due to emotional or physical stress during sample collection [46]. Recently, whole blood serotonin emerged as a useful marker that reveals reduced concentrations in BH_4 disorders, namely AADC deficiency, SPR deficiency, and VMAT2 [47].

A lumbar puncture for measurement of neurotransmitter metabolites should always be performed under optimal clinical conditions following a standardized protocol. Subsequent handling of specimens, including direct freezing and storage of CSF on dry ice or liquid nitrogen, is essential to prevent the degradation of metabolites. A number of pterin species are unstable, especially when exposed to ultraviolet light. Therefore, samples need to be treated with antioxidant chemicals and stored in the absence of light. The concentrations of HVA and 5-HIAA follow a cranio-caudal gradient which requires standardized CSF sample volume fractions to limit pre-analytical errors [48]. Specific instructions should always be discussed with the respective laboratory to ensure proper sample handling.

Molecular genetic testing confirms the diagnosis. It is anticipated that next-generation sequencing techniques will change our diagnostic approach in the future; however, if genetic testing leads to a diagnosis (e.g. by whole-exome sequencing or following identification of an affected family member), metabolic profiling with enzymatic activity assays or the determination of neurotransmitter metabolites may still be used to confirm the underlying metabolic disturbance.

Treatment

Table 21.2 summarizes therapeutic approaches. Individual doses should be titrated carefully with close monitoring of side effects. Children presenting with classic symptoms of dopa-responsive dystonia, including lower limb dystonia with diurnal variation, should undergo a temporary levodopa trial, which is of diagnostic and therapeutic value. Despite recent advances in biochemical, radiological, and molecular genetic testing, such trials might be especially beneficial for regions where the above-mentioned diagnostics are not readily available. However, it is important to thoroughly assess and document the patient's motor performance, autonomous dysregulation, and physical activity status before starting any medical intervention.

Overall, levodopa should be started at 0.5–1 mg/kg per day and divided into at least four to five doses per day. The dosing can be increased, generally in increments of 2–7 days, according to individual tolerance, usually not exceeding 10 mg/kg per day. A combination of levodopa with a peripheral inhibitor of decarboxylation increases the intracerebral availability of levodopa and enhances the impact of the drug. The usual ratio of levodopa to the decarboxylase inhibitor is 4:1. Side effects of this medical treatment include choreiform movements, nausea, or vomiting. These side effects can be at least partly attributed to overreaction of highly upregulated dopamine receptors and can persist for hours or days but are completely reversible. In contrast to Parkinson disease, neurotransmitter-deficient patients do not develop drug habituation and can remain on an individually titrated dose for a long period of time. Slow-release preparations are associated with a higher chance to normalize prolactin levels and clinical symptoms [48]. An adequate levodopa trial should be at least 5–10 weeks because dystonia may require time for improvement. Premature cessation of a levodopa trial, whether due to side effects or the absence of immediate response, could produce false-negative results. A total duration of 2 months on the maximum tolerated dose or 10 mg/kg per day is recommended to produce reliable clinical results. In the case of an absent clinical response, a levodopa taper over approximately 4 weeks is recommended.

For serotonin deficiency, 5-HTP supplementation is generally recommended. Overall, the dose is approximately 2 mg/kg per day less than the dose of levodopa given and should not exceed 8 mg/kg per day. Side effects mostly comprise gastrointestinal discomfort.

HPA can either be controlled by dietary measures or, when necessary, it can be treated with BH_4 supplementation. The desired range of phenylalanine is below 6 mg/dL irrespective of patient age. Folinic acid supplementation is recommended (10–20 mg per day) when the CSF 5-MTHF concentration is low.

Table 21.2 Overview of selected inherited neurotransmitter disorders including biopterin synthesis defects, primary neurotransmitter synthesis defects, monoamine transportopathies, and co-chaperone defects

Disorder	Enzyme/protein deficiency	Therapy[a]
Biopterin synthesis/recycling defects	SPR	Levodopa starting at 1 mg/kg per day titrated up to 10 mg/kg per day combined with carbidopa in 4:1 ratio, 5-HTP starting at 1 mg/kg per day titrated up to 8 mg/kg per day, consider selegiline[b] 0.03–0.2 mg/kg per day
	AD-GTPCH1	Levodopa starting at 1 mg/kg per day titrated up to 10 mg/kg per day combined with carbidopa in 4:1 ratio
	AR-GTPCH1	Levodopa starting at 1 mg/kg per day titrated up to 10 mg/kg per day combined with carbidopa in 4:1 ratio, 5-HTP starting at 1 mg/kg per day titrated up to 6 mg/kg per day, BH4 1 to 10 mg/kg per day titrated according to Phe levels
	PTPS	Levoopa starting at 0.5–1 mg/kg per day titrated up to 10 mg/kg per day combined with carbidopa in 4:1 ratio, 5-HTP starting at 1 mg/kg per day titrated up to 8 mg/kg per day, BH4 1 to 10 mg/kg per day titrated according to Phe levels
	DHPR	Levoopa starting at 0.5–1 mg/kg per day titrated up to 10 mg/kg per day, 5-HTP starting at 3 mg/kg per day titrated up to 11 mg/kg per day phenylalanine level control only by dietary measures, folinic acid 10–20 mg per day
	PCD	Consider BH4 titrated according to Phe levels, early screening for diabetes
Primary neurotransmitter synthesis defects	TH	Levoopa starting at 0.5–1 mg/kg per day titrated up to 10 mg/kg per day combined with carbidopa in 4:1 ratio, selegeline[b] 0.1–0.4 mg/kg per day (max. dose 10 mg per day)
Monoamine transportopathies	AADC	*Dopamine agonists*: pramipexole base 5–10 µg/kg per day (max. 75 µg/kg per day), ropinirole 0.25 mg per day (max. 24 mg per day), transdermal rotigone 2 mg per day, increased weekly up to 8 mg per day, bromocriptine 0.1 mg/kg per day up to 0.5 mg/kg per day *MAO inhibitors*: selegeline[b] 0.1 mg/kg per day increase every 2 weeks up to 0.3 mg/kg per day, tranylcypromine 0.1 mg/kg per day increase every 2 weeks up to 30 mg per day *Cofactors*: pyridoxine 100 to 200 mg per day, pyridoxal 5'-phosphate 100–200 mg per day
	SLC6A3 (DTDS)	Pramipexole base 5–40 µg/kg per day, ropinirole 0.5 to 4 mg per day, transdermal rotigotine 6 mg/kg per day
	SLC18A2 (VMAT2)	Pramipexole base 5–40 µg/kg per day
Monoamine catabolism disorders	MAO-A/ MAO-B	SSRIs have shown beneficial effect in mice, no data for humans available
	DBH	Droxidopa used in adults as 100 mg 3 times daily to a maximum dose of 600 mg 3 times daily; no data for pediatric use available
Co-chaperone defects[c]	DNAJC12	BH4 1 to 10 mg/kg per day titrated according to Phe levels; levoopa starting at 1 mg/kg per day titrated up to 10 mg/kg per day combined with carbidopa in 4:1 ratio; consider 5-HTP starting at 1 mg/kg per day titrated up to 10 mg/kg per day

[a] **Please note**: The dosages given are the range which is usually applied and has been published. In individual patients, some adaptations and variations might be reasonable. For example, in AD-GTPCH1 deficiency usually between 4 mg/kg and 7 mg/kg per day of levodopa are sufficient to stop the movement disorder. In these cases, levoopa should not be increased further. On the other end of the spectrum, in severe dopamine deficiency, patients may not tolerate more than 5–7 mg/kg per day. Some more hints how to decide about dosage and pace of increments are given in the text. [Adapted from Brennenstuhl H, Jung-Klawitter S, Assmann B, Opladen T. Inherited Disorders of Neurotransmitters: Classification and Practical Approaches for Diagnosis and Treatment. Neuropediatrics. 2019 Feb;50(1):2–14.] [b] Dosing for sublingual selegeline preparation can differ. [c] See Chapter 22 for details.

Clinical Research on Neurotransmitter Disorders

The International Working Group on Neurotransmitter Related Disorders (iNTD) is a worldwide research network focused on primary and secondary neurotransmitter diseases. Currently there are more than 40 partners from 25 different countries. By combining results of basic research with clinical data, the network aims to improve our understanding of the complex nature of inborn errors of neurotransmitter metabolism and lead to optimized diagnostic tools and therapeutic approaches.

An Internet-based registry for inherited defects of biogenic amines, pterin, folate, serine, glycine, and GABA metabolism was established (www.intd-registry.org). It represents the first longitudinal registry for neurotransmitter disorders and enables systematic high-quality data gathering.

The network is highly interested in further partners, metabolic centers, patients, and families who wish to participate. For further information visit www.intd-online.org.

Key Points and Clinical Pearls

- The cardinal symptoms of deficiencies in the synthesis of monoamine neurotransmitters reflect dopamine deficiency as well as the imbalance of other neurotransmitters including serotonin, norepinephrine, or epinephrine in the central nervous system.
- While the clinical spectrum of neurotransmitter-related disorders overlaps with numerous other diseases, e.g. cerebral palsy, certain clinical features may raise the clinical suspicion for a disorder of impaired neurotransmission (e.g. early-onset parkinsonism, oculogyric crises, diurnal fluctuation of symptoms, or an unexplained cerebral palsy–like picture).
- The diagnosis of neurotransmitter-related disorders is achieved by the analysis of neurotransmitter metabolites in the urine, blood, and CSF or by molecular testing, depending on the resources available.
- The treatment of neurotransmitter-related disorders is commonly based on the supplementation of neurotransmitter precursors or cofactors to reinstate enzymatic function.

Directions for Future Research

- Patient-derived induced pluripotent stem cells, induced pluripotent stem-cell-derived neurons and three-dimensional neuronal tissues will help in the understanding of how neurotransmitter disorders impact neurodevelopment.
- Gene therapy using adeno-associated virus vectors is showing promising results.
- High-throughput drug screening might enable the identification of compound candidates for drug repurposing.

References

1. Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders: Clinical advances and future perspectives. Nat Rev Neurol. 2015;**11**(10):567–84.
2. Opladen T, Hoffmann GF, Blau N. An international survey of patients with tetrahydrobiopterin deficiencies presenting with hyperphenylalaninaemia. J Inherit Metab Dis. 2012;**35**(6):963–73.
3. Nygaard TG. Dopa-responsive dystonia. Delineation of the clinical syndrome and clues to pathogenesis. Adv Neurol. 1993;**60**:577–85.
4. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol. 2003;**54** Suppl 6:S32-45.
5. Bandmann O, Wood NW. Dopa-responsive dystonia: The story so far. Neuropediatrics. 2002;**33** (1):1–5.
6. Lopez-Laso E, Sanchez-Raya A, Moriana JA, et al. Neuropsychiatric symptoms and intelligence quotient in autosomal dominant Segawa disease. J Neurol. 2011;**258**(12):2155–62.
7. Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: Long-term treatment response and prognosis. Neurology. 1991;**41**(2 (Pt 1)):174–81.
8. Thöny B, Blau N. Mutations in the BH4-metabolizing genes GTP cyclohydrolase I, 6-pyruvoyl-tetrahydropterin synthase, sepiapterin reductase, carbinolamine-4a-dehydratase, and dihydropteridine reductase. Hum Mutat. 2006;**27** (9):870–8.
9. Friedman J, Hyland K, Blau N, MacCollin M. Dopa-responsive hypersomnia and mixed movement disorder due to sepiapterin reductase deficiency. Neurology. 2006;**67**(11):2032–5.

10. Leuzzi V, Carducci C, Tolve M, et al. Very early pattern of movement disorders in sepiapterin reductase deficiency. Neurology. 2013;**81**(24):2141–2.

11. Zielonka M, Makhseed N, Blau N, Dopamine-responsive growth-hormone deficiency and central hypothyroidism in sepiapterin reductase deficiency. JIMD Rep. 2015;**24**:109–13.

12. Friedman J, Roze E, Abdenur JE, et al. Sepiapterin reductase deficiency: A treatable mimic of cerebral palsy. Ann Neurol. 2012;**71**(4):520–30.

13. Horvath GA, Stockler-Ipsiroglu SG, Salvarinova-Zivkovic R, et al. Autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia: Evidence of a phenotypic continuum between dominant and recessive forms. Mol Genet Metab. 2008;**94**(1):127–31.

14. Opladen T, Hoffmann G, Horster F, et al. Clinical and biochemical characterization of patients with early infantile onset of autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia. Mov Disord. 2011;**26**(1):157–61.

15. Blau NTB, Cotton RGH. Disorders of tetrahydrobiopterin and related biogenic amines. In Scriver CR, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease: McGraw-Hill; 2001, pp. 1725–76.

16. Werner ER, Blau N, Thony B. Tetrahydrobiopterin: Biochemistry and pathophysiology. Biochem J. 2011;**438**(3):397–414.

17. Coughlin CR, 2nd, Hyland K, Randall R, Ficicioglu C. Dihydropteridine reductase deficiency and treatment with tetrahydrobiopterin: A case report. JIMD Rep. 2013;**10**:53–6.

18. Irons M, Levy HL, O'Flynn ME, et al. Folinic acid therapy in treatment of dihydropteridine reductase deficiency. J Pediatr. 1987;**110**(1):61–7.

19. Thöny B, Neuheiser F, Kierat L, et al. Mutations in the pterin-4alpha-carbinolamine dehydratase (*PCBD*) gene cause a benign form of hyperphenylalaninemia. Hum Genet. 1998;**103**(2):162–7.

20. Rhee KH, Stier G, Becker PB, Suck D, Sandaltzopoulos R. The bifunctional protein DCoH modulates interactions of the homeodomain transcription factor HNF1 with nucleic acids. J Mol Biol. 1997;**265**(1):20–9.

21. Mendel DB, Khavari PA, Conley PB, et al. Characterization of a cofactor that regulates dimerization of a mammalian homeodomain protein. Science. 1991;**254**(5039):1762–7.

22. Simaite D, Kofent J, Gong M, et al. Recessive mutations in *PCBD1* cause a new type of early-onset diabetes. Diabetes. 2014;**63**(10):3557–64.

23. Willemsen MA, Verbeek MM, Kamsteeg EJ, et al. Tyrosine hydroxylase deficiency: A treatable disorder of brain catecholamine biosynthesis. Brain. 2010;**133**(Pt 6):1810–22.

24. Marin-Valencia I, Serrano M, Ormazabal A, et al. Biochemical diagnosis of dopaminergic disturbances in paediatric patients: Analysis of cerebrospinal fluid homovanillic acid and other biogenic amines. Clin Biochem. 2008;**41**(16–17):1306–15.

25. Hoffmann GF, Assmann B, Brautigam C, et al. Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. Ann Neurol. 2003;**54** Suppl 6:S56-65.

26. Lee HF, Tsai CR, Chi CS, Chang TM, Lee HJ. Aromatic L-amino acid decarboxylase deficiency in Taiwan. Eur J Paediatr Neurol. 2009;**13**(2):135–40.

27. Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology. 2010;**75**(1):64–71.

28. Haavik J, Blau N, Thony B. Mutations in human monoamine-related neurotransmitter pathway genes. Hum Mutat. 2008;**29**(7):891–902.

29. Wassenberg T, Willemsen MA, Geurtz PB, et al. Urinary dopamine in aromatic L-amino acid decarboxylase deficiency: The unsolved paradox. Mol Genet Metab. 2010;**101**(4):349–56.

30. Wassenberg T, Molero-Luis M, Jeltsch K, et al. Consensus guideline for the diagnosis and treatment of aromatic L-amino acid decarboxylase (AADC) deficiency. Orphanet J Rare Dis. 2017;**12**:12.

31. Hwu WL, Muramatsu S, Tseng SH, et al. Gene therapy for aromatic L-amino acid decarboxylase deficiency. Sci Transl Med. 2012;**4**(134):134ra61.

32. Brunner HG, Nelen MR, van Zandvoort P, et al. X-linked borderline mental retardation with prominent behavioral disturbance: Phenotype, genetic localization, and evidence for disturbed monoamine metabolism. Am J Hum Genet. 1993;**52**(6):1032–9.

33. Cheung NW, Earl J. Monoamine oxidase deficiency: A cause of flushing and attention-deficit/ hyperactivity disorder? Arch Intern Med. 2001;**161**(20):2503–4.

34. Whibley A, Urquhart J, Dore J, et al. Deletion of *MAOA* and *MAOB* in a male patient causes severe developmental delay, intermittent hypotonia and stereotypical hand movements. Eur J Hum Genet. 2010;**18**(10):1095–9.

35. Godar SC, Bortolato M, Castelli MP, et al. The aggression and behavioral abnormalities associated with monoamine oxidase A deficiency are rescued by acute inhibition of serotonin reuptake. J Psychiatr Res. 2014;**56**:1–9.

36. Robertson D, Garland EM. Dopamine beta-hydroxylase deficiency. GeneReviews®. 2003;Sep 4 (updated Apr 25, 2019).

37. Arnold AC, Garland EM, Celedonio JE, et al. Hyperinsulinemia and insulin resistance in dopamine beta-hydroxylase deficiency. J Clin Endocrinol Metab. 2017;**102**(1):10–4.

38. Timmers HJ, Deinum J, Wevers RA, Lenders JW. Congenital dopamine-beta-hydroxylase deficiency in humans. Ann N Y Acad Sci. 2004;**1018**:520–3.

39. van den Berg MP, Almomani R, Biaggioni I, et al. Mutations in *CYB561* causing a novel orthostatic hypotension syndrome. Circ Res. 2018;**122** (6):846–54.

40. Kurian MA, Li Y, Zhen J, et al. Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: An observational cohort and experimental study. Lancet Neurol. 2011;**10**(1):54–62.

41. Ng J, Zhen J, Meyer E, et al. Dopamine transporter deficiency syndrome: Phenotypic spectrum from infancy to adulthood. Brain. 2014;**137**(Pt 4):1107–19.

42. Yildiz Y, Pektas E, Tokatli A, Haliloglu G. Hereditary dopamine transporter deficiency syndrome: Challenges in diagnosis and treatment. Neuropediatrics. 2017;**48**(1):49–52.

43. Rilstone JJ, Alkhater RA, Minassian BA. Brain dopamine–serotonin vesicular transport disease and its treatment. N Engl J Med. 2013;**368**(6):543–50.

44. Ng J, Heales SJ, Kurian MA. Clinical features and pharmacotherapy of childhood monoamine neurotransmitter disorders. Paediatr Drugs. 2014;**16** (4):275–91.

45. Carducci C, Santagata S, Friedman J, et al. Urine sepiapterin excretion as a new diagnostic marker for sepiapterin reductase deficiency. Mol Genet Metab. 2015;**115**(4):157–60.

46. Birnbacher R, Scheibenreiter S, Blau N, et al. Hyperprolactinemia, a tool in treatment control of tetrahydrobiopterin deficiency: Endocrine studies in an affected girl. Pediatr Res. 1998; **43** (4 Pt 1): 472–7.

47. Rath M, Korenke GC, Najm J, et al. Exome sequencing results in identification and treatment of brain dopamine–serotonin vesicular transport disease. J Neurol Sci. 2017;**379**:296–7.

48. Hoffmann GF, Blau N. Congenital Neurotransmitter Disorders: A Clinical Approach. Huppauge, NY: Nova Science Publishers; 2014.

Chapter

22

Neurotransmitter Disorders: DNAJC12-Deficient Hyperphenylalaninemia – An Emerging Neurotransmitter Disorder

Nenad Blau and Manuel Schiff

Introduction

DNAJC12 deficiency is a recently described form of hyperphenylalaninemia (HPA) [1]. HPA represents a metabolic condition caused by a deficiency in either phenylalanine (Phe) hydroxylase (PAH) or in one of the enzymes involved in the biosynthesis or regeneration of tetrahydrobiopterin (BH4) [2]. BH4 is the natural cofactor of PAH, tyrosine hydroxylase (TH), tryptophan hydroxylases (TPHs), and alkylglycerol monooxygenase, as well as all isoforms of nitric oxide synthase [3].

Variants in *DNAJC12* lead to mild HPA, biogenic amines deficiency in the central nervous system, causing intellectual disability, dystonia, and parkinsonism, thereby defining a new entity of HPA without PAH or BH4 deficiency [4]. This expands the clinical and metabolic spectrum of patients detected in the newborn screening for phenylketonuria (PKU) and changes our understanding of the differential diagnosis and management [5]. So far, more than 29 patients have been described in the literature, most of them diagnosed through whole-exome sequencing [1, 6–11]. All patients tested presented with low levels of the cerebrospinal fluid (CSF) neurotransmitter metabolites homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), but with normal CSF, urinary, or blood neopterin and biopterin. They all responded to oral loading with BH4 (20 mg/kg) by lowering their blood phenylalanine levels. Substitution with BH4 and/or neurotransmitter precursors levodopa/carbidopa and 5-hydroxytryptophan (5-HTP) had beneficial effects in preventing the neurodevelopmental phenotype in patients treated before the onset of symptoms.

Biochemical and Genetic Background

DNAJC12, a type III member of the HSP40/DNAJ family, has been identified as the specific co-chaperone of PAH, TH, and TPHs 1 and 2) [1], the last two being rate-limiting steps in the biosynthesis of catecholamines (dopamine, epinephrine, and norepinephrine) and serotonin, respectively. Dysfunction of the three hydroxylases results not only in HPA (PAH deficiency) but also in neurological and neuropsychiatric impairments (TH or the TPH deficiencies).

The function of the DNAJ proteins in the quality-control machinery is proposed to be the transfer of its specific protein clients to the molecular chaperone HSC70/HSP70–HSP90 network for proper folding [12]. This complex molecular chaperone machinery is essential to maintain the proteostasis in eukaryotic cells, not only by assisting in the folding of client proteins (e.g. PAH) but also in the intertwined triage decisions that affect the removal of misfolded proteins and thus prevent toxic aggregation and cellular damage [13].

A model of the DNAJC12/HSP70 machinery in the folding process of PAH is shown in Figure 22.1, based on [12]. DNAJC12 binds to the client protein (PAH) through its peptide-binding domain (1) and interacts with the HSP70–ATP complex through the HPD motif (conserved His, Pro, Asp signature, crucial for stimulation of HSP70's ATPase activity) in the N-terminal J domain (2). The unfolded PAH rapidly but transiently interacts with the "open" peptide-binding site (adenine nucleotide-binding cleft) of HSP70. ATP hydrolysis is stimulated by both the J domain and PAH, causing a conformational change in HSP70 that closes the cleft and stabilizes the PAH interaction. DNAJC12 then leaves the complex (3). A nucleotide exchange factor (NEF), which has a higher affinity for HSP70–ADP than HSP70–ATP, binds HSP70 (4). The ADP subsequently dissociates through the distortion of the ATP-binding domain (5), after which ATP binds to HSP70 (6). PAH is released because of its low affinity for HSP70–ATP (7). If the native state of PAH is not attained on

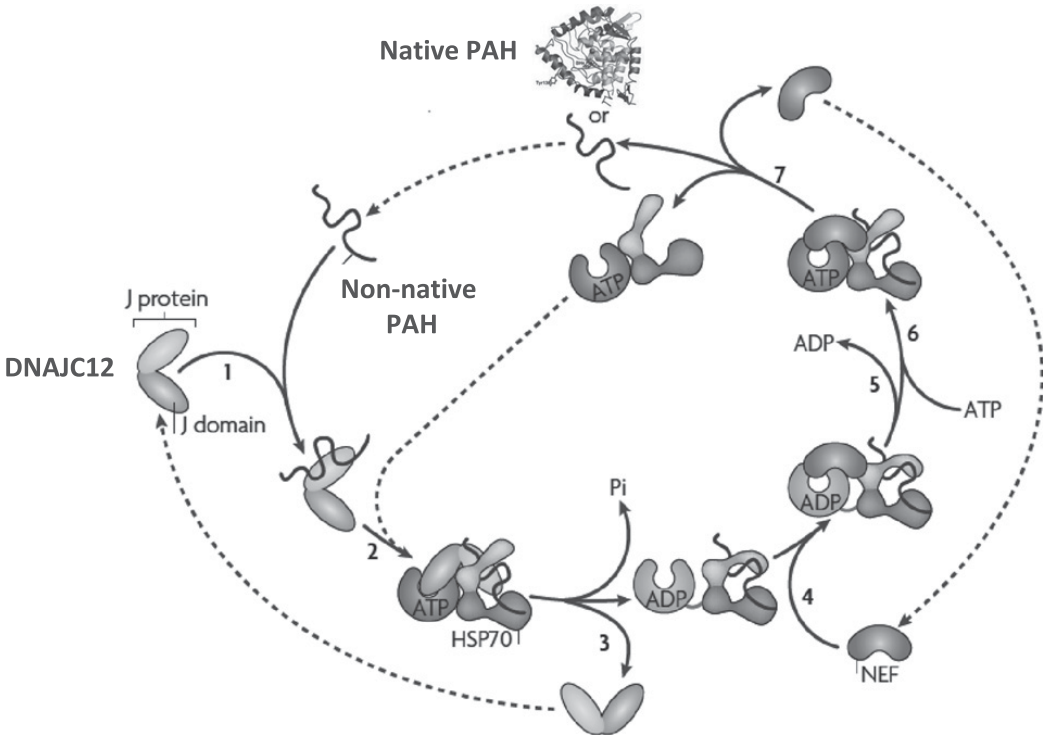

Figure 22.1 Proposed model for the interaction between co-chaperone DNAJC12, its client PAH, and the HSP70 chaperone machinery in the refolding process of PAH. For details see text. An identical model can be proposed for the interaction between DNAJC12 and TH and TPHs 1 and 2. Modified from Kampinga HH, Craig EA. The HSP70 chaperone machinery: J proteins as drivers of functional specificity. Nat Rev Mol Cell Biol. 2010;11(8):579–92. Abbreviations: HSP70, heat shock 70 KDa protein; NEF, nucleotide exchange factor; PAH, phenylalanine hydroxylase; Pi, inorganic phosphate.

release, DNAJC12 rebinds to exposed hydrophobic regions and the cycle begins again.

Beyond its function in protein refolding, DNAJC12 is responsible for protein degradation [12] (Figure 22.2). The ubiquitin-interacting motifs (UIMs) of the DNAJC12 recognize clients (e.g. PAH) that contain a monoubiquitin or polyubiquitin moiety (1). After transfer of the client to HSP70 (2), E3 ligases (such as CHIP, i.e. carboxy-terminus of HSC70 interacting protein) and the ubiquitin conjugation machinery (UBC) can associate with the HSP70–DNAJC12 complex (theoretical proposal), leading to further ubiquitylation of the bound client (3, 4). After the canonical ATP hydrolysis step (4) and NEF-mediated nucleotide exchange (5), the polyubiquitylated PAH released from HSP70 is transferred to the proteasome for degradation.

Different DNAJC-family members were previously reported to be associated with Parkinson disease, parkinsonism, and neurodegenerative diseases. Mutant *DNAJC5* leads to dominant adult-onset Kufs disease and parkinsonism [14], and the overexpression of DNAJC5 induces tau release in cells [15]. Also, deleterious variants in *DNAJC6* were associated with recessive juvenile parkinsonism [16], and *DNAJC13* variants lead to essential tremor [17] and were associated with Parkinson disease [18]. Furthermore, deletion variants of *DNAJC8* [19] and *DNAJC19* [20] lead to ataxia.

It has been shown in vitro that *DNAJC12* variants result in reduced PAH protein expression and activity in patients' fibroblasts [1]. At the same time, *PAH* variants found in PKU patients interact with DNAJC12 different from the wild-type PAH. The interaction of normal wild-type DNAJC12 with mutant PAH in cells expressing several *PAH* variants associated with different forms of HPA leads to severe protein instability and accelerated PAH degradation, thus supporting the role of DNAJC12 in the processing of misfolded ubiquitinated PAH

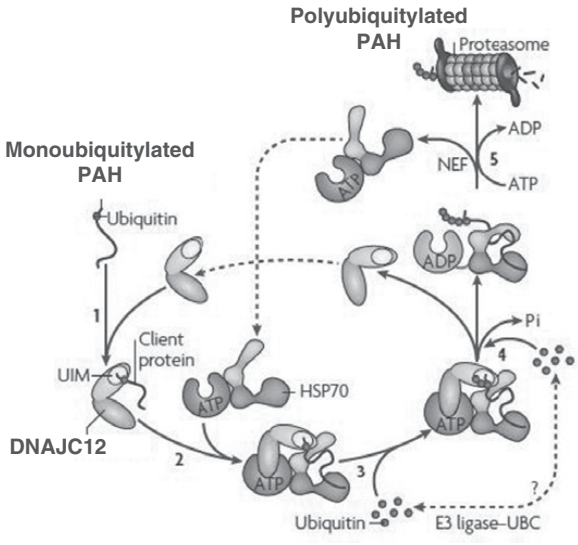

Figure 22.2 DNAJC12-targeted degradation of PAH. For details see text. Modified from Kampinga HH, Craig EA. The HSP70 chaperone machinery: J proteins as drivers of functional specificity. Nat Rev Mol Cell Biol. 2010;11(8):579–92. Abbreviations: HSP70, heat shock 70 KDa protein; NEF, nucleotide exchange factor; PAH, phenylalanine hydroxylase; Pi, inorganic phosphate; UBC, ubiquitin conjugation machinery; UIM, ubiquitin-interacting motif.

by the ubiquitin-dependent proteasome/autophagy systems [21, 22].

Clinical Phenotype

Variants in *DNAJC12* were recently described to lead to mild HPA (in two patients, the newborn screening blood Phe level was normal, but elevated at the time of diagnosis), central biogenic amine deficiency, intellectual disability, and movement disorders (see next section). The initial report was on six patients from four unrelated families with HPA who exhibited neurodevelopmental delay, dystonia, and a unique profile of dopamine and serotonin deficiencies without mutations in *PAH* or BH4 metabolism disorder-related genes [1]. Five additional patients from three unrelated Dutch and Saudi families with homozygosity and compound heterozygosity in *DNAJC12* were subsequently described with a very mild neurological phenotype (autistic features and hyperactivity), with subtle dystonia in one patient [6]. Homozygous *DNAJC12* null variants have also been identified in two families with early-onset parkinsonism. Both patients had mild intellectual disability, mild non-progressive motor symptoms, sustained benefit from a small dose of levodopa, and substantial worsening of symptoms after levodopa discontinuation. Neuropathology revealed no alpha-synuclein pathology, and substantia nigra depigmentation with moderate cell loss [7]. Furthermore, DNAJC12 deficiency has been elucidated in HPA cases from Spain, as well as one from Chile with no variants in *PAH* and excluded BH4 deficiency. Three novel nucleotide variations were identified in 11 cases. All cases presented with HPA at diagnosis and all are currently clinically asymptomatic, except one who presented with psychomotor delay and seizures. All of these cases are consuming a normal diet, and a number of them are being treated with BH4 with a favorable response [8]. Furthermore, four cases of infants with mild HPA and global developmental delay, intellectual disability, and dystonia were reported in the last few months [9–11], and we are aware of at least eight more unreported cases (personal communication). Some patients with a mild form of DNAJC12 deficiency may present without any clinical symptoms and might remain asymptomatic even in the absence of treatment, therefore questioning the need for therapy in these mildly-affected patients.

Movement Disorder Phenotype

Due to the recent identification of DNAJC12 deficiency, the natural history remains to be delineated. Regarding movement disorders, there seems to be a spectrum of severity independent from biochemical or molecular findings (no apparent genotype–phenotype correlation and no relation with blood phenylalanine and/or neurotransmitter metabolite CSF levels). This ranges from mild and subtle movement disorders [6] to severe dystonia and extrapyramidal movement disorders in early [1] or late [10, 11] childhood, and early-onset parkinsonism in children and adults [7] (Table 22.1). Clinical characteristics are however non-specific as they reflect dopamine deficiency in the central nervous system. In contrast with other neurotransmitter disorders, autonomic features such as temperature instability or lability of blood pressure or heart rate were not observed. Oculogyric crises

Table 22.1 Summary of biochemical and clinical features in 29 patients (aged 2–51 years) with DNAJC12 deficiency

Feature	Patients (*N* = 29)
Laboratory tests	
Blood Phe in newborn screening (μmol/L)	84–526
Blood Phe at diagnosis (μmol/L)	49[a]–595
BH4 loading test positive	13/13
CSF 5-HIAA low	12/12
CSF HVA low	11/12
CSF Neopterin elevated	2/7
CSF Biopterin elevated	3/8
Clinical signs and symptoms	
Intellectual disability	10/29
Dystonia	6/29
Axial hypotonia	4/29
Parkinsonism	4/29
Attention difficulties	4/29
Speech delay	3/29
Autistic features	2/29
Psychosis/depression	2/29
Fatigue	2/29
Hypertonia of extremities	1/29
Nystagmus	1/29
Oculogyric crisis	1/29
No symptoms	10/29[b]

[a] While on BH4 treatment. [b] Diagnosed in the first months of life.

were reported in one patient [1]. For details on the adult movement disorder phenotype, see videos in supplemental data [7].

Treatment

Though variable in terms of clinical severity, the natural course of DNAJC12 deficiency seems to be prevented by therapy aiming at correcting biochemical abnormalities, i.e. BH4 and neurotransmitter precursors (levodopa and 5-HTP). However, when applied late, or alternatively in mild forms, treatment benefits are questionable. Regardless, in line with neuropathology suggesting that DNAJC12 deficiency is not a neurodegenerative but rather a non-progressive disorder [7], treatment benefits in adult-diagnosed DNAJC12 deficiency patients with parkinsonism is unequivocal as a mean of limiting phenylalanine neurotoxicity on the one hand and an attempt to restore defective monoaminergic neurotransmission on the other. As detailed above, DNAJC12 interacts with PAH, TH, and TPHs 1 and 2, respectively, catalyzing the BH4-activated conversion of phenylalanine into tyrosine, tyrosine into levodopa, the precursor of dopamine, and tryptophan into 5-hydroxytryptophan, the precursor of serotonin [1]. This provides a pathophysiological rationale for the biogenic amine disorder-like phenotype in *DNAJC12*-defective individuals and a basis for therapy: BH4 being the common cofactor of the four above-mentioned aromatic amino acid hydroxylases could enhance their enzyme activities and/or target misfolding (chaperone function) and the neurotransmitter precursors could restore dopamine and serotonin deficiencies.

In terms of dosages, 10 mg/kg per day of each drug (BH4, levopa/carbidopa [10/1] and 5-HTP) is probably to be recommended. In the initially reported patients, this was sufficient to reduce Phe levels (<300 μmol/L) and normalize neurotransmitter metabolite CSF levels. In some patients, BH4 alone was also noted to improve the extrapyramidal movement phenotype [1, 11].

Conclusions

DNAJC12 deficiency appears to result in a more heterogeneous neurological phenotype than initially described (Table 22.1). While the early identification and institution of treatment with BH4 and neurotransmitter precursors are crucial to ensure optimal neurological outcomes in DNAJC12-deficient patients with a severe phenotype, the optimal treatment for patients with a milder phenotype remains to be defined. The molecular investigation of PAH needs to be added to the current scheme of differential diagnosis of HPAs (Figure 22.3). Every individual with HPA (particularly mild forms) and with genetically and biochemically excluded PAH or BH4 deficiency needs to be evaluated for variants in *DNAJC12*. One should, however, keep in mind that some DNAJC12-deficient patients may present with normal or borderline blood Phe levels and be missed by newborn screening, as reported for two patients [1, 11]. Thus, blood amino acid analysis may be indicated in individuals with developmental disability, movement disorders, hyperactivity, or autism.

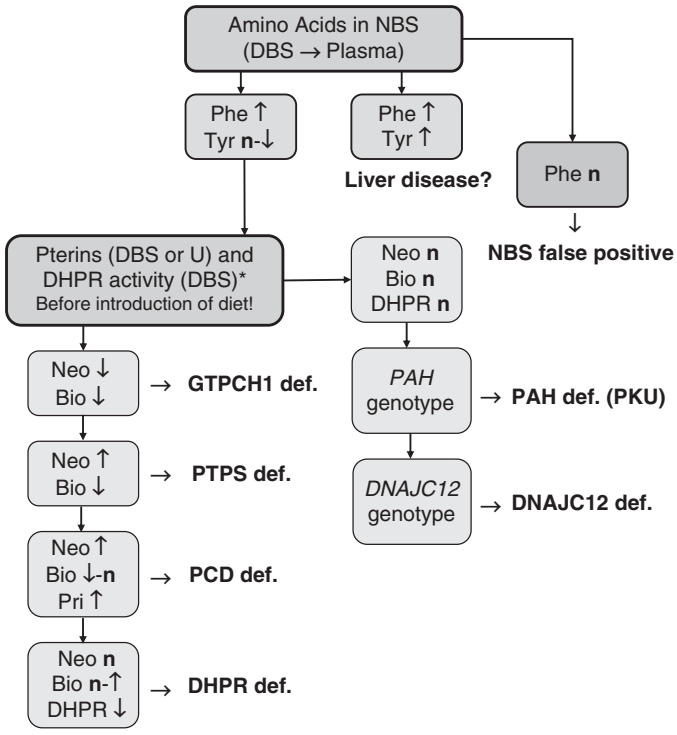

Figure 22.3 Flow-chart for the differential diagnosis of hyperphenylalaninemias. n: normal; def: deficiency; NBS: newborn screening; DBS: dried blood spot; U: urine; Neo: neopterin; Bio: biopterin; Pri: primapterin (7-biopterin); GTPCH1: GTP cyclohydrolase 1; PTPS: 6-pyruvoyltetrahydropterin synthase; PCD: pterin-4a-carbinolamine dehydratase; DHPR: dihdropteridine reductase; PAH: phenylalanine hydroxylase

Key Points and Clinical Pearls

- DNAJC12 deficiency presents with hyperphenylalaninemia (HPA) and can be detected through newborn screening for phenylketonuria.
- All patients reported to date present with CSF deficiency of biogenic amines even before the onset of clinical symptoms.
- In severe early-onset presentations, dystonia and developmental delay are clinically evident around 6 months of age.
- Very late diagnosed and untreated patients may present with non-progressive parkinsonism.
- Early treatment with tetrahydrobiopterin and neurotransmitter precursors is beneficial.

Directions for Future Research

- Generation of an animal model for DNAJC12 deficiency.
- In-depth studies of interactions between DNAJC12 and phenylalanine hydroxylase (PAH), tyrosine hydroxylase, and tryptophan hydroxylases 1 and 2.
- Interactions between PAH variant protein and DNAJC12.
- Natural history of DNAJC12 deficiency.

References

1. Anikster Y, Haack TB, Vilboux T, et al. Biallelic mutations in *DNAJC12* cause hyperphenylalaninemia, dystonia, and intellectual disability. Am J Hum Genet. 2017;**100**(2):257–66.
2. Blau N, Van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010;**376**:1417–27.
3. Werner ER, Blau N, Thöny B. Tetrahydrobiopterin: Biochemistry and pathophysiology. Biochem J. 2011;**438**:397–414.
4. Bouchereau J, Huttlin EL, Guarani V, et al. DNAJC12: A molecular chaperone involved in proteostasis, PKU, biogenic amines metabolism and beyond? Mol Genet Metab. 2018;**123**(3):285–6.
5. Blau N, Martinez A, Hoffmann GF, Thony B. DNAJC12 deficiency: A new strategy in the diagnosis of hyperphenylalaninemias. Mol Genet Metab. 2018;**123**:1–5.

6. van Spronsen FJ, Himmelreich N, Rufenacht V, et al. Heterogeneous clinical spectrum of DNAJC12-deficient hyperphenylalaninemia: From attention deficit to severe dystonia and intellectual disability. J Med Genet. 2017; doi:10.1136/jmedgenet-2017-104875.
7. Straniero L, Guella I, Cilia R, et al. DNAJC12 and dopa-responsive non-progressive parkinsonism. Ann Neurol. 2017;**82**(4):640–6.
8. Leal F, Navarrete R, Castro M, et al. Spanish hyperphenylalaninemia cases bearing a high frequent mutation in the *DNAJC12* gene. J Inborn Error Metab Screen. 2017;**5**:131.
9. Feng Y, Liu S, Tang C, et al. Identification of an inherited pathogenic *DNAJC12* variant in a patient with hyperphenylalalinemia. Clin Chim Acta. 2018; doi:10.1016/j.cca.2018.09.002.
10. Veenma D, Cordeiro D, Sondheimer N, Mercimek-Andrews S. *DNAJC12*-associated developmental delay, movement disorder, and mild hyperphenylalaninemia identified by whole-exome sequencing re-analysis. Eur J Hum Genet. 2018;**26**(12):1867–70.
11. de Sain-van der Velden MGM, Kuper WFE, Kuijper MA, et al. Beneficial effect of BH4 treatment in a 15-year-old boy with biallelic mutations in *DNAJC12*. JIMD Rep. 2018;**42**:99–103.
12. Kampinga HH, Craig EA. The HSP70 chaperone machinery: J proteins as drivers of functional specificity. Nat Rev Mol Cell Biol. 2010;**11** (8):579–92.
13. Dekker SL, Kampinga HH, Bergink S. DNAJs: More than substrate delivery to HSPA. Front Mol Biosci. 2015;**2**:35.
14. Cadieux-Dion M, Andermann E, Lachance-Touchette P, et al. Recurrent mutations in *DNAJC5* cause autosomal dominant Kufs disease. Clin Genet. 2013;**83** (6):571–5.
15. Fontaine SN, Zheng D, Sabbagh JJ, et al. DNAJ/HSC70 chaperone complexes control the extracellular release of neurodegenerative-associated proteins. EMBO J. 2016;**35**(14):1537–49.
16. Edvardson S, Cinnamon Y, Ta-Shma A, et al. A deleterious mutation in *DNAJC*6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism. PLoS One. 2012;**7**(5):e36458.
17. Rajput A, Ross JP, Bernales CQ, et al. *VPS35* and *DNAJC13* disease-causing variants in essential tremor. Eur J Hum Genet. 2015;**23**(6):887–8.
18. Gustavsson EK, Trinh J, Guella I, et al. *DNAJC13* genetic variants in parkinsonism. Mov Disord. 2015;**30** (2):273–8.
19. Ito N, Kamiguchi K, Nakanishi K, et al. A novel nuclear DNAJ protein, DNAJC8, can suppress the formation of spinocerebellar ataxia 3 polyglutamine aggregation in a J-domain independent manner. Biochem Biophys Res Commun. 2016;**474**(4):626–33.
20. Ojala T, Polinati P, Manninen T, et al. New mutation of mitochondrial *DNAJC19* causing dilated and noncompaction cardiomyopathy, anemia, ataxia, and male genital anomalies. Pediatr Res. 2012;**72**(4):432–7.
21. Himmelreich N, Hoffmann GF, Blau N. Expression pattern of phenylalanine hydroxylase variants is regulated by co-chaperone DNAJC12. Mol Genet Metab. 2018;**123**:210.
22. Jung-Kc K, Himmelreich N, Prestegard K. S, et al. Phenylalanine hydroxylase variants interact with the co-chaperone DNAJC12. Hum Mutat. 2019;**40**:483–494.

Chapter

23 Neurotransmitter Disorders: Disorders of GABA Metabolism and Movement Disorders

Phillip L. Pearl, Melissa DiBacco, K. Michael Gibson, and Jean-Baptiste Roullet

Introduction

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. The primary precursor of GABA is glutamate, the major excitatory neurotransmitter in the brain. Glutamate is converted into GABA via glutamate decarboxylase (GAD). GABA-transaminase (GABA-T) metabolizes GABA to succinic semialdehyde, which is rapidly metabolized to succinic acid by succinic semialdehyde dehydrogenase (SSADH) and then enters the tricarboxylic acid (TCA) cycle (Figure 23.1). The TCA cycle regenerates a molecule of glutamate from each molecule of GABA catabolized. Clinical disorders known to affect GABA metabolism are autosomal-recessively inherited SSADH deficiency and GABA-T deficiency. Abnormal MRI signals of the globus pallidi, subthalamic nuclei, and cerebellar dentate nuclei are common features in SSADH deficiency. Movement disorders are a cardinal feature of GABA-T deficiency and have also been described in a subset of patients with SSADH deficiency.

Succinic Semialdehyde Dehydrogenase Deficiency

Background

SSADH is an autosomal-recessive disorder that has a range of presentations, but typically manifests with a relatively non-progressive encephalopathy characterized

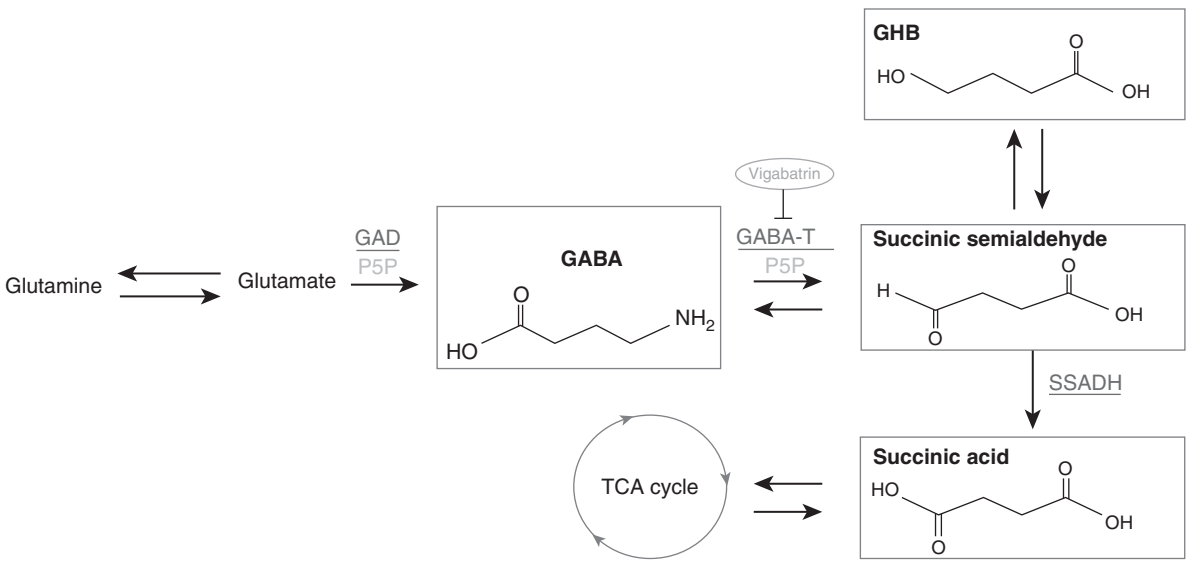

Figure 23.1 GABA degradation pathway. GABA is normally converted via GABA-transaminase (GABA-T) into succinate semialdehyde, which is then broken down to succinic acid by succinate semialdehyde dehydrogenase (SSADH). In the absence of SSADH, succinate semialdehyde is converted to gamma-hydroxybutyric acid (GHB) rather than succinic acid, and this leads to increased endogenous GABA and GHB in brain. Abbreviation: P5P, pyridoxal-5′-phosphate.

by developmental delay, hypotonia, and a prominent expressive language deficit presenting in the first 2 years of life. Originally described in 1983 [1], a recent literature survey identified 182 confirmed published cases from 40 countries [2]. Based on laboratory experience, it is estimated that approximately 500 people have been diagnosed worldwide, and the disorder may well be underdiagnosed. SSADH is a mitochondrial protein in the aldehyde dehydrogenase family (subfamily 5A1), and encoded by *ALDH5A1* on chromosome 6p22. At least 45 *ALDH5A1* mutations have been published as pathogenic for SSADH deficiency [3]. In the absence of SSADH, the breakdown of GABA to succinic acid is altered. The result is a build-up of GABA, as well as gamma-hydroxybutyric acid (GHB; 4-hydroxybutyric acid), a neurotoxic agent that may contribute to the clinical manifestations. GHB is elevated in all physiological fluids, with the cerebral spinal fluid (CSF) showing up to a three-fold increase in GABA and 230-times increase in GHB in patients [4]. Although the excess GHB in all physiological fluids is the hallmark of the disease, there is no correlation between the severity of clinical features and GHB levels [5]. Recent longitudinal studies revealed a significant negative age correlation with GHB and GABA, with attainment of a nadir in GHB levels in red blood cells by 10 years of age and in GABA at 30–40 years of age [6]. Hair samples quantified for GHB levels from ten patients with SSADH deficiency showed significantly elevated concentrations in patients ages 3–7 years, with levels reaching the control range by 12–13 years [7]. Thus, the imbalance in GABA and GHB concentrations in this disorder fluctuate with age.

Clinical Manifestations

Detection is typically by urine organic acids for an elevated level, followed by confirmation using *ALDH5A1* gene sequencing. Clinical features include developmental delay, intellectual disability with prominent impairment of expressive language, motor dysfunction, hypotonia, hyporeflexia, and non-progressive ataxia (Table 23.1). As patients enter adolescence and adulthood, more disabling symptoms tend to be behavioral and psychiatric manifestations, with a high prevalence of attention deficit hyperactivity disorder, anxiety disorder, autistic features, obsessive–compulsive disorder, and sometimes aggression and hallucinations [4, 8–10].

Sleep disturbances with excessive daytime somnolence have been reported, with polysmonography showing a reduced sleep latency as well as a prolonged latency to stage rapid eye movement (REM) with a reduced percentage of stage REM [11]. This is consistent with animal models demonstrating a reduction of REM-stage sleep, associated with hyperGABAergic states via inhibition of GABA transaminase [12]. Epilepsy is present in about half of affected individuals, and appears to be more prevalent over time [13]. There is a paradox of epilepsy in hyperGABAergic disorders, as GABA is the major inhibitory neurotransmitter of the brain. Our cohort of 128 patients demonstrates a 69% incidence of epilepsy in subjects of ages 12 and older, compared to 50% of the total population ($p < 0.01$) (Table 23.2). Generalized tonic–clonic and absence are the most common seizure types. We have observed a tendency to see more absence seizures in the younger patients compared to tonic–clonic in the older cohorts, which may correlate with the aforementioned age-related changes in GABA and GHB concentrations as well as the natural history of seizures in the null mouse model [14]. Sudden unexpected death in epilepsy patients (SUDEP) has occurred in four adult patients to our knowledge, which corresponds to a premature mortality rate of 13% in the adult population contained in our registry. The most common abnormal electrographic findings are generalized epileptiform discharges and diffuse background slowing [8, 9]. Electrographic status epilepticus of sleep and photosensitivity have also been observed in patients.

Movement disorders are not described universally in SSADH-deficient patients, although they are certainly reported and were even described in the index case report of gamma-hydroxybutyric aciduria as "short episodes of abnormal movements" between the ages of 6 months and 12 months, as well as ocular apraxia and a significant ataxia of the trunk and limbs by 20 months

Table 23.1 Clinical manifestations of SSADH ($N = 133$) (based on parent questionnaire data in registry) [53].

Clinical feature	Number (*n*)	Percent
Intellectual disability	76	57
Fine motor delay	93	70
Gross motor delay	98	74
Speech delay	103	77
Behavioral problems	70	53
Seizures	65	49
Hypotonia	95	71
Ataxia	69	52

Data from DiBacco ML, Roullet JB, Kapur K, et al. Age-related phenotype and biomarker changes in SSADH deficiency. Ann Clin Transl Neurol. 2018;6(1):114–20.

Table 23.2 SSADH deficiency features by age group (in years; *N* = 133) (based on parent questionnaire data in registry) [53].

	Birth–3, *n* = 40	Child (4 – 11), *n* = 43	Adolescent (12 – 17), *n* = 19	Adult (18+), *n* = 31
Intellectual disability	19 (48%)	28 (65%)	11 (58%)	18 (58%)
Fine motor delay	25 (63%)	30 (70%)	14 (74%)	24 (77%)
Gross motor delay	30 (75%)	30 (70%)	14 (74%)	24 (77%)
Speech delay	29 (73%)	34 (79%)	15 (79%)	25 (81%)
Behavioral problems	12 (30%)	28 (65%)	10 (53%)	20 (65%)
Seizures	8 (20%)	23 (53%)	12 (63%)	22 (71%)
Sleep disturbance	11 (28%)	17 (40%)	12 (63%)	19 (61%)
Hypotonia	32 (80%)	33 (77%)	11 (58%)	19 (61%)
Obsessive-compulsive	5 (13%)	12 (28%)	11 (58%)	18 (58%)
Ataxia	16 (40%)	30 (70%)	10 (53%)	13 (42%)

Data from DiBacco ML, Roullet JB, Kapur K, et al. Age-related phenotype and biomarker changes in SSADH deficiency. Ann Clin Transl Neurol. 2018;6(1):114–20.

[15]. Although intermittent decompensation as seen in other metabolic disorders is not characteristic in the majority of patients, there is a subgroup (10%) with a more severe phenotype characterized by regression as well as prominent extrapyramidal manifestations [16, 17]. Basal ganglia signs, including choreoathetosis, dystonia, and myoclonus, as well as clinical onset in the first 6 months of life, are reported in these patients [18]. About half of the patients in this subgroup may show a progressive course with deterioration over time [17]. The varying degrees of severity have not been explained by genotype–phenotype correlation; in fact, there have been cases within the same family where the disorder in one sibling presents as an acute infantile encephalopathy with severe choreoathetosis and in another sibling with a more typical non-progressive appearance (Video 23.1) [19]. In addition, paroxysmal exertional dystonia has been described in SSADH deficiency, with clinical benefit from vigabatrin intervention [20]. The latter report revealed a prominent lurching gait. We have seen the same exertional lurching gait in a similarly aged adolescent with SSADH deficiency (Video 23.2). Alternatively, vigabatrin has been associated with basal ganglia, thalamic, and brainstem T2 hyperintensities on MRI [21] in addition to hyperkinetic movement disorders [22].

Imaging Findings

MRI demonstrates a fairly consistent pattern of distribution that may be characterized as a dentato-pallidoluysian pattern with increased T2-weighted and fluid-attenuated inversion recovery (FLAIR) signals involving the cerebellar dentate nuclei, globus pallidi (interna and externa), and subthalamic nuclei (Figure 23.2). This is usually, but not always, bilateral and symmetrical. Cerebral atrophy, cerebellar atrophy, delayed myelination and T2 hyperintensities in the subcortical white matter, thalami, and brainstem have also been found. MRS using single- and multivoxel-studies show normal spectra except for elevations of GABA and related compounds (including GHB and homocarnosine) on special editing techniques in affected patients, but not obligate heterozygotes [23]. Fluorodeoxyglucose brain positron emission tomography (PET) has demonstrated a decreased cerebellar glucose metabolism in patients with cerebellar atrophy on structural MRI [24]. PET using flumazenil to image the distribution of GABA-A receptors demonstrated a substantial reduction in binding in multiple regions in subjects compared to both parent heterozygote and healthy controls, consistent with overuse-dependent downregulation of GABA-A receptors (Figure 23.3) [25].

Treatment Strategies and Clinical Trials

Treatment for SSADH deficiency remains symptomatic, typically for seizure control and psychiatric manifestations. Options include targeted antiseizure drug therapy, anxiolytic agents, neuroleptics, and selective serotonin reuptake inhibitors. Antiseizure medications are generally selected to target generalized seizures, although valproate is typically avoided due to its ability to inhibit any residual SSADH enzymatic activity [26]. Lamotrigine, levetiracetam, topiramate,

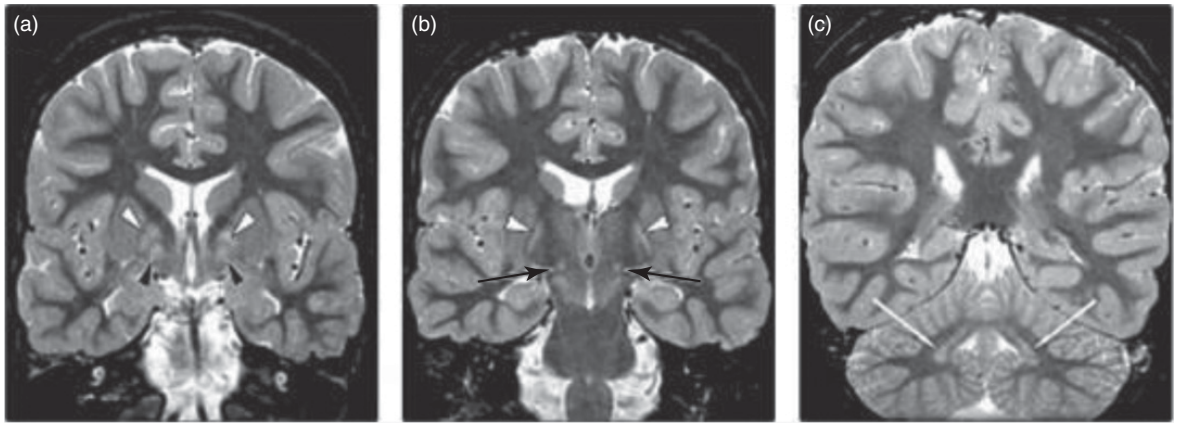

Figure 23.2 Dentato-pallido-luysian pattern in SSADH deficiency. Coronal short tau inversion recovery sections from MRI in a patient with SSADH deficiency showing bilateral symmetrical homogenous signal abnormalities in the globus pallidus (internal portion [black arrows, a], external portion [white arrows, a and b]), subthalamic nucleus (black arrows, b), and dentate nucleus (white arrows, c). Reproduced with permission from Pearl PL, Gibson KM, Quezado Z, Dustin I, Taylor J, Trzcinski S, et al. Decreased GABA-A binding on flumazenil PET in succinic semialdehyde dehydrogenase deficiency. Neurology. 2009;73(6):423–9.

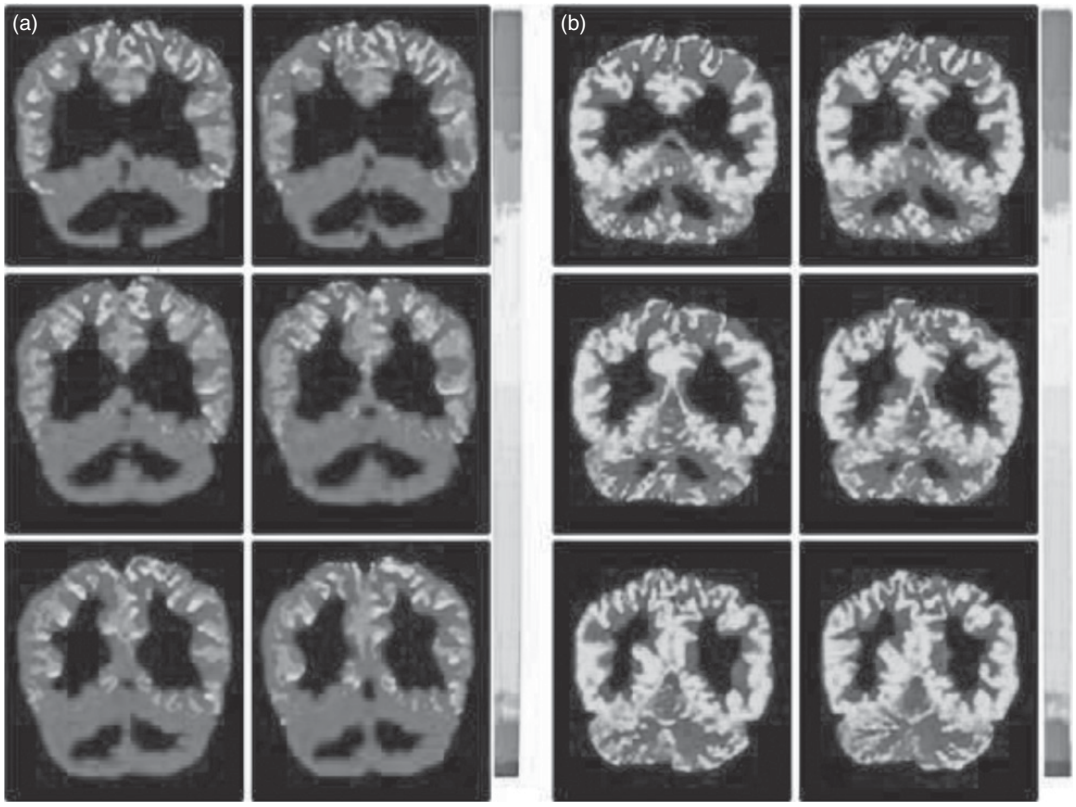

Figure 23.3 Decreased GABA-A binding on flumazenil PET in SSADH deficiency. Flumazenil PET shows a marked reduction of cortical binding potential of ^{11}C-flumazenil in (a) a patient with SSADH deficiency versus (b) a heterozygote control. Reproduced with permission from Pearl PL, Gibson KM, Quezado Z, Dustin I, Taylor J, Trzcinski S, et al. Decreased GABA-A binding on flumazenil PET in succinic semialdehyde dehydrogenase deficiency. Neurology. 2009;73(6):423–9.

and zonisamide have been successful medications for maintenance therapy.

Vigabatrin, an irreversible inhibitor of GABA-T, is potentially a rational choice because it inhibits the conversion of GABA to GHB, yet exacerbates an already elevated GABA level [27–29]. In clinical use, vigabatrin has not been a reliable therapeutic, with many reports of a lack of effect, or worsening of symptoms, ranging from seizure control to alertness. In addition, other concerns regarding vigabatrin use include retinal toxicity with visual-field defects [30–32], MRI signal changes in the GABA-rich thalamus and basal ganglia [21], and a recent report of white matter spongiosis on a post-mortem study in a patient with polymicrogyria who died of SUDEP [33].

Therapeutic strategies in the animal model of SSADH deficiency have led to clinical trials that are ongoing [34]. Early promising results using taurine, based on the observation that suckling mice developed seizures as they weaned and that taurine was a principal component of murine breast milk, were followed by a single non-blinded, uncontrolled case report of improved gait, coordination, and energy in a 2-year-old boy with SSADH deficiency [35]. This was followed by an open-label study in 18 patients (age range 0.5–28 years, mean 12 years) without clinically meaningful improvement on the Adaptive Behavior Assessment Scale [36]. A crossover open-label study of seven patients (age range 12–33 years) on and off taurine assessed biomarkers, such as transcranial magnetic stimulation (TMS), CSF metabolites, and neuropsychological evaluations did not identify significant changes [37].

Benefit in the animal model from SGS 742, a GABA-B receptor antagonist, led to a current phase 2 double-blinded, placebo-controlled clinical trial in progress [38]. Preclinical work suggests potential efficacy and safety utilizing GHB antagonist NCS-382 [39–41].

GABA-Transaminase Deficiency

Background

GABA-T is the initial key enzyme involved in GABA degradation. Deficiency of this enzyme is inherited in an autosomal-recessive pattern and was initially reported in 1984, with two cases reported in the same family suggesting mortality within the first 2 years of life [42]. Only a small number of affected individuals have been published although more cases are being identified with increasing use of phenotype-specific gene panels and whole-exome sequencing. The initial reports described neonatal or early-infantile onset encephalopathy although other phenotypes are emerging with increased recognition, including survival through the first decade [43]. Other common features are hypotonia, hyperreflexia, hypersomnolence, high pitched cry, and accelerated linear growth (Table 23.3) [42, 43]. The accelerated linear growth has been attributed to the growth hormone promoting effects of GABA.

Table 23.3 Clinical manifestations GABA-T ($N = 10$)

Clinical feature	Number	Percent
Developmental delay	10	100
Hypotonia	10	100
Hypersomnolence	10	100
Seizures	6	60
Accelerated growth	4	40
Choreoathetosis	3	30
Failure to thrive	6	60

Data from Koenig MK, Hodgeman R, Riviello JJ, Chung W, Bain J, Chiriboga CA, et al. Phenotype of GABA-transaminase deficiency. Neurology. 2017;88(20):1919–24.

Movement disorders may be very prominent when present, with choreoathetosis reported in one-third of patients [43]. A combined presentation of hypersomnolence and hyperkinetic movement disorder of distal extremities during wakefulness, superimposed upon hypotonia and impaired response to auditory and visual stimuli has been described [44]. Virtually constant choreoathetosis and myoclonus have been seen (Video 23.3); less excessive adventitious movements were observed in this patient after treatment with the GABA-receptor benzodiazepine-binding site antagonist, flumazenil [43].

GABA-T locates to the 4-aminobutyrate aminotransferase (*ABAT*) gene at chromosome 16p13.2. The concentration of free GABA in the CSF has been shown to be as high as 60 times greater (in the index case) than in controls. Diagnosis may be predicated on the measurement of CSF amino acid concentrations, with elevations in free and total GABA and beta-alanine. There is no CSF elevation of GHB. Metabolomic profiling may be informative by the detection of the GABA keto-analogue 2-pyrrolidinone in plasma, urine, or CSF [45]. The rarity of this disorder may be due to in utero death or the infrequency of recessive alleles, but diagnosis is likely impeded by the general lack of availability of CSF testing for GABA concentrations. Alternatively, the

increasing use of MRS with special editing for small molecules and molecular testing will lead to more diagnosed cases [43, 46].

The ABAT enzyme has recently been discovered to have a dual function. ABAT deficiency results in both a neurometabolic disorder as described, as well as a mitochondrial genome depletion syndrome where there is a marked loss of mitochondrial genome (mtDNA) copy number. ABAT plays an essential role in mitochondrial nucleoside salvage by aiding in the production of deoxynucleotide triphosphate (dNTP) from deoxynucleotide diphosphate (dNDP) in the mitochondria, the building block for DNA [47].

Electroencephalography shows severe abnormalities including burst-suppression, modified hypsarrhythmia, multifocal spike discharges, generalized spike and wave, and diffuse background slowing and disorganization. Imaging has shown hypomyelination, T2- and diffusion-weighted hyperintensities involving the white matter including the internal and external capsules, and progressive cerebral atrophy (Figure 23.4) [48].

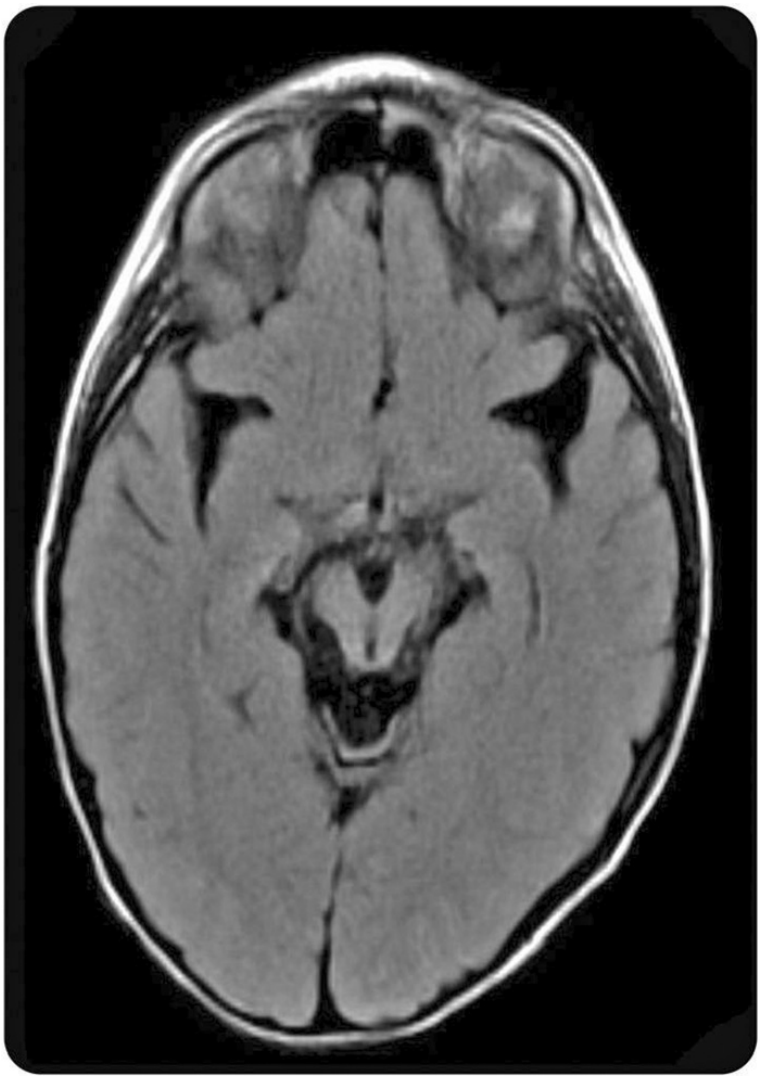

Figure 23.4 MRI in GABA-T deficiency. Axial MRI, FLAIR sequence, with prominent enlargement of the Sylvian fissures and pontomesencephalic cisterns. Reproduced with permission from Koenig MK, Hodgeman R, Riviello JJ, Chung W, Bain J, Chiriboga CA, et al. Phenotype of GABA-transaminase deficiency. Neurology. 2017;88(20):1919–24.

Treatment Strategies and Clinical Trials

Therapeutic interventions are aimed to provide symptomatic treatment of motor difficulties and seizures. Treatment with continuous flumazenil, the GABA-A benzodiazepine receptor antagonist, was initiated in two patients. The aforementioned patient began flumazenil at 21 months and continued this for 2 years at the time of this writing with improved alertness, interactions, and less excessive adventitious movements. The EEG background improved after the first infusion and continued to improve in the organization of the background with some persistent generalized epileptiform discharges (Figure 23.5). The second patient, age 7 years at time of initiation, with

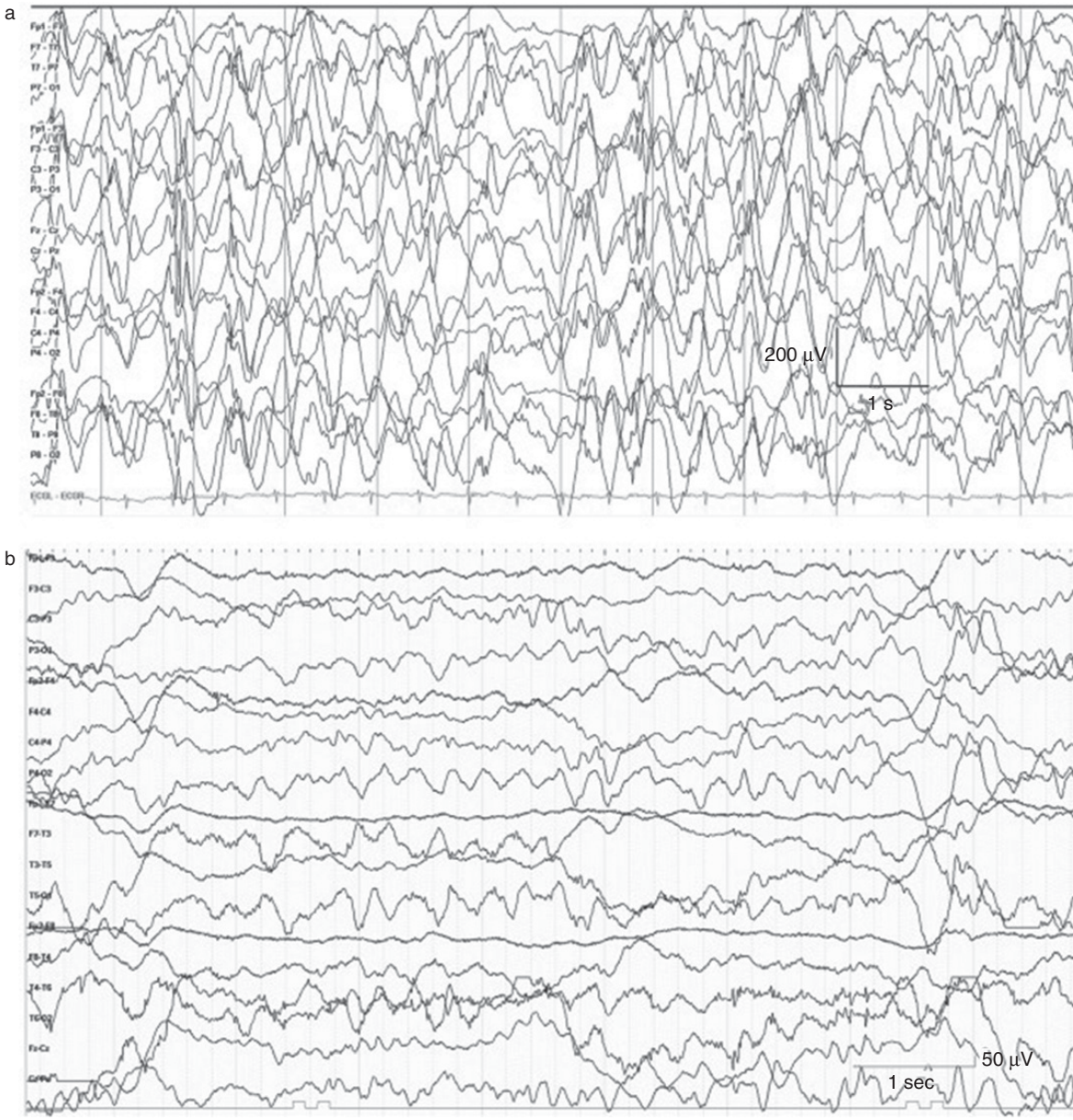

Figure 23.5 (a) EEG pre flumazenil. Patient at 21 months of age, with high-voltage polymorphic delta and multifocal and generalized spike-wave; and (b) EEG post flumazenil. Patient at 26 months, with improved background organization but some persistence of generalized epileptiform activity (settings in all figures: HFF 70 Hz, LFF 1 Hz, sensitivity 10 µV/mm). Reproduced with permission from Koenig MK, Hodgeman R, Riviello JJ, Chung W, Bain J, Chiriboga CA, et al. Phenotype of GABA-transaminase deficiency. Neurology. 2017;88(20):1919–24.

a more severe phenotype, was not continued due to lack of benefit [43].

Conclusions and Overview of Movement Disorders in Inherited Disorders of GABA Metabolism

SSADH deficiency appears to affect a number of neurotransmitter systems, including decreased glutamine with a high elevation of GABA appearing to affect the glial-neuronal shuttle with disturbances in glutamate–glutamine and GABA–glutamate homeostasis [49, 50]. A correlation of GHB with dopamine and serotonin metabolites suggests an increased turnover of both dopamine and serotonin [4, 51]. Hence, alterations in neurotransmitters and their metabolites are implicated in an array of debilitating signs and symptoms, including aggression, hallucinations, sleep disturbances, hyperactivity, and, potentially, movement disorders. Extrapyramidal signs have been associated with the condition, including choreoathetosis, paroxysmal exertional dyskinesias including dystonia, and myoclonus [16–20].

Ataxia, typically mild and non-progressive, and hypotonia are common clinical manifestations of SSADH deficiency and implicate cerebellar dysfunction. While imaging features usually emphasize the involvement of the basal ganglia and white matter, there is a similar increased signal intensity of the cerebellar dentate nuclei as well as prominent and, in some cases, progressive cerebellar atrophy [52]. Accordingly, fluorodeoxyglucose PET has demonstrated a marked decrease in cerebellar metabolism in association with cerebellar vermian atrophy on structural imaging [24].

In the case of GABA-T (ABAT) deficiency, choreoathetosis may be very prominent and a phenotype of hypersomnolence–hyperkinetic movement disorder may be typical. The phenotypic spectrum appears to be widening as new cases are reported via the increasing use of molecular diagnostics and potentially metabolomic screening.

Key Points and Clinical Pearls

- Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. Deficiencies of enzymes in GABA metabolism appear to affect a number of neurotransmitter systems.
- Succinic semialdehyde dehydrogenase (SSADH) deficiency manifests typically as a non-progressive encephalopathy with prominent expressive language deficit, intellectual deficiency, hypotonia, hyporeflexia, epilepsy, and psychiatricmorbidity. Choreoathetosis, exertional dyskinesias, and ataxia may be present.
- GABA transaminase deficiency (*ABAT* mutations) presents in its classic form with early-onset encephalopathy having prominent epilepsy and extrapyramidal manifestations.
- High levels of gamma-hydroxybutyric acid (GHB), associated with myoclonus following exogenous use, are endogenous in SSADH deficiency. Evidence suggests that high GHB increases the turnover of dopamine and serotonin.
- Neuroimaging shows increased signal abnormalities in the globus pallidus, subthalamic nucleus, and cerebellar dentate nucleus in SSADH deficiency, and spectroscopy shows elevated GABA in the basal ganglia in both SSADH and GABA-T deficiencies.

Directions for Future Research

- The natural history of both SSADH deficiency and GABA transaminase require further study for successful implementation of clinical trials.
- Biomarkers using TMS, high-density EEG, and magnetoencephalography are under study to assess abnormalities in GABAergic transmission in these disorders.
- GABA receptor antagonism is under current study for the treatment of SSADH deficiency.
- Enzyme-replacement therapy is being assessed for SSADH deficiency.
- Induced pluripotent stem cells and organoid development are being studied in SSADH deficiency as well as the prospect of viral-mediated gene therapy.

References

1. Gibson KM, Sweetman L, Nyhan WL, et al. Succinic semialdehyde dehydrogenase deficiency: An inborn error of gamma-aminobutyric acid metabolism. Clin Chim Acta. 1983;**133**(1):33–42.
2. Attri SV, Singhi P, Wiwattanadittakul N, et al. Incidence and geographic distribution of succinic semialdehyde dehydrogenase (SSADH) deficiency. JIMD Rep. 2017;**34**:111–5.
3. Pearl PL, Parviz M, Vogel K, et al. Inherited disorders of gamma-aminobutyric acid metabolism and advances in *ALDH5A1* mutation identification. Dev Med Child Neurol. 2015;**57**(7):611–7.
4. Gibson KM, Gupta M, Pearl PL, et al. Significant behavioral disturbances in succinic semialdehyde dehydrogenase (SSADH) deficiency (gamma-hydroxybutyric aciduria). Biol Psychiatry. 2003;**54**(7):763–8.
5. Akaboshi S, Hogema BM, Novelletto A, et al. Mutational spectrum of the succinate semialdehyde dehydrogenase (*ALDH5A1*) gene and functional analysis of 27 novel disease-causing mutations in patients with SSADH deficiency. Hum Mutat. 2003;**22**(6):442–50.
6. Jansen EE, Vogel KR, Salomons GS, et al. Correlation of blood biomarkers with age informs pathomechanisms in succinic semialdehyde dehydrogenase deficiency (SSADHD), a disorder of GABA metabolism. J Inherit Metab Dis. 2016;**39**(6):795–800.
7. Johansen SS, Wang X, Sejer Pedersen D, et al. Gamma-hydroxybutyrate (GHB) content in hair samples correlates negatively with age in succinic semialdehyde dehydrogenase deficiency. JIMD Rep. 2017;**36**:93–8.
8. Pearl PL, Novotny EJ, Acosta MT, Jakobs C, Gibson KM. Succinic semialdehyde dehydrogenase deficiency in children and adults. Ann Neurol. 2003;**54** Suppl 6: S73-80.
9. Pearl PL, Gibson KM, Acosta MT, et al. Clinical spectrum of succinic semialdehyde dehydrogenase deficiency. Neurology. 2003;**60**(9):1413–7.
10. Pearl PL, Capp PK, Novotny EJ, Gibson KM. Inherited disorders of neurotransmitters in children and adults. Clin Biochem. 2005;**38**(12):1051–8.
11. Pearl PL, Shamim S, Theodore WH, et al. Polysomnographic abnormalities in succinic semialdehyde dehydrogenase (SSADH) deficiency. Sleep. 2009;**32**(12):1645–8.
12. Scherschlicht R. Role for GABA in the control of the sleep–wakefulness cycle. In Wauquier A, Gaillard J, Monti JM, Radulovacki M, editors. Sleep: Neurotransmitters and Neuromodulators. New York, NY: Raven Press; 1985, pp. 237–49.
13. Lapalme-Remis S, Lewis EC, De Meulemeester C, et al. Natural history of succinic semialdehyde dehydrogenase deficiency through adulthood. Neurology. 2015;**85**(10):861–5.
14. Pearl PL, Gibson KM, Cortez MA, et al. Succinic semialdehyde dehydrogenase deficiency: Lessons from mice and men. J Inherit Metab Dis. 2009;**32**(3):343–52.
15. Jakobs C, Bojasch M, Monch E, et al. Urinary excretion of gamma-hydroxybutyric acid in a patient with neurological abnormalities. The probability of a new inborn error of metabolism. Clin Chim Acta. 1981;**111**(2–3):169–78.
16. Pearl PL, Acosta MT, Theodore WH, et al. Human SSADH deficiency: Phenotype and treatment strategies. *In* Hoffmann GF, editor. Diseases of Neurotransmission: From Bench to Bed. Heilbronn: SPS Publications; 2004, pp. 187–98.
17. Pearl PL, Acosta MT, Wallis DD, et al. Dyskinetic features of succinate semialdehyde dehydrogenase deficiency, a GABA degradative defect. In Fernandez-Alvarez E, Arzimanoglou A, Tolosa E, editors. Paediatric Movement Disorders: Progress in Understanding. Esher: John Libbey Eurotext; 2005, pp. 203–12.
18. Rahbeeni Z, Ozand PT, Rashed M, et al. 4-Hydroxybutyric aciduria. Brain Dev. 1994;**16** Suppl:64–71.
19. Zeiger WA, Sun LR, Bosemani T, Pearl PL, Stafstrom CE. Acute infantile encephalopathy as presentation of succinic semialdehyde dehydrogenase deficiency. Pediatr Neurol. 2016;**58**:113–5.
20. Leuzzi V, Di Sabato ML, Deodato F, et al. Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency. Neurology. 2007;**68**(16):1320–1.
21. Pearl PL, Vezina LG, Saneto RP, et al. Cerebral MRI abnormalities associated with vigabatrin therapy. Epilepsia. 2009;**50**(2):184–94.
22. Dill P, Datta AN, Weber P, Schneider J. Are vigabatrin induced T2 hyperintensities in cranial MRI associated with acute encephalopathy and extrapyramidal symptoms? Eur J Paediatr Neurol. 2013;**17**(3):311–5.
23. Novotny EJ, Jr., Fulbright RK, Pearl PL, Gibson KM, Rothman DL. Magnetic resonance spectroscopy of neurotransmitters in human brain. Ann Neurol. 2003;**54** Suppl 6:S25-31.
24. Al-Essa MA, Bakheet SM, Patay ZJ, Powe JE, Ozand PT. Clinical, fluorine-18 labeled 2-fluoro-2-deoxyglucose positron emission tomography (FDG PET), MRI of the brain and biochemical observations in a patient with 4-hydroxybutyric aciduria: A progressive neurometabolic disease. Brain Dev. 2000;**22**(2):127–31.

25. Pearl PL, Gibson KM, Quezado Z, et al. Decreased GABA-A binding on FMZ-PET in succinic semialdehyde dehydrogenase deficiency. Neurology. 2009;**73**(6):423–9.
26. Shinka T, Ohfu M, Hirose S, Kuhara T. Effect of valproic acid on the urinary metabolic profile of a patient with succinic semialdehyde dehydrogenase deficiency. J Chromatogr B Analyt Technol Biomed Life Sci. 2003;**792**(1):99–106.
27. Escalera GI, Ferrer I, Marina LC, et al. Succinic semialdehyde dehydrogenase deficiency: Decrease in 4-OH-butyric acid levels with low doses of vigabatrin. An Pediatr (Barc). 2010;**72**(2):128–32.
28. Pearl PL, Gropman A. Monitoring gamma-hydroxybutyric acid levels in succinate-semialdehyde dehydrogenase deficiency. Ann Neurol. 2004;**55**(4):599;author reply
29. Ergezinger K, Jeschke R, Frauendienst-Egger G, et al. Monitoring of 4-hydroxybutyric acid levels in body fluids during vigabatrin treatment in succinic semialdehyde dehydrogenase deficiency. Ann Neurol. 2003;**54**(5):686–9.
30. Krauss GL, Johnson MA, Miller NR. Vigabatrin-associated retinal cone system dysfunction: Electroretinogram and ophthalmologic findings. Neurology. 1998;**50**(3):614–8.
31. Spence SJ, Sankar R. Visual field defects and other ophthalmological disturbances associated with vigabatrin. Drug Saf. 2001;**24**(5):385–404.
32. Vanhatalo S, Nousiainen I, Eriksson K, et al. Visual field constriction in 91 Finnish children treated with vigabatrin. Epilepsia. 2002;**43**(7):748–56.
33. Pearl PL, Poduri A, Prabhu SP, et al. White matter spongiosis with vigabatrin therapy for infantile spasms. Epilepsia. 2018;**59**(4):e40-e4.
34. Gupta M, Greven R, Jansen EE, et al. Therapeutic intervention in mice deficient for succinate semialdehyde dehydrogenase (gamma-hydroxybutyric aciduria). J Pharmacol Exp Ther. 2002;**302**(1):180–7.
35. Saronwala A, Tournay A, Gargus JJ. Taurine treatment of succinate semialdehyde dehydrogenase (SSADH) deficiency reverses MRI-documented globus lesions and clinical syndrome (abstract). Proceedings of the 15th Annual Clinical Genetics Meeting. Phoenix, AZ: American College of Medical Genetics; 2008, p. 103.
36. Pearl PL, Schreiber J, Theodore WH, et al. Taurine trial in succinic semialdehyde dehydrogenase deficiency and elevated CNS GABA. Neurology. 2014;**82**(11):940–4.
37. Schreiber JM, Pearl PL, Dustin I, et al. Biomarkers in a taurine trial for succinic semialdehyde dehydrogenase deficiency. JIMD Rep. 2016;**30**:81–7.
38. Phase 2 clinical trial of sgs-742 therapy in succinic semialdehyde dehydrogenase deficiency: National Library of Medicine; 2013–2019. Available from: https://clinicaltrials.gov/ct2/show/NCT02019667 (accessed December 2019).
39. Vogel KR, Ainslie GR, Roullet JB, McConnell A, Gibson KM. In vitro toxicological evaluation of NCS-382, a high-affinity antagonist of gamma-hydroxybutyrate (GHB) binding. Toxicol In Vitro. 2017;**40**:196–202.
40. Vogel KR, Ainslie GR, Walters DC, et al. Succinic semialdehyde dehydrogenase deficiency, a disorder of GABA metabolism: An update on pharmacological and enzyme-replacement therapeutic strategies. J Inherit Metab Dis. 2018;**41**(4):699–708.
41. Vogel KR, Ainslie GR, McConnell A, Roullet JB, Gibson KM. Toxicologic/transport properties of NCS-382, a gamma-hydroxybutyrate (GHB) receptor ligand, in neuronal and epithelial cells: Therapeutic implications for SSADH deficiency, a GABA metabolic disorder. Toxicol In Vitro. 2018;**46**:203–12.
42. Jaeken J, Casaer P, de Cock P, et al. Gamma-aminobutyric acid-transaminase deficiency: A newly recognized inborn error of neurotransmitter metabolism. Neuropediatrics. 1984;**15**(3):165–9.
43. Koenig MK, Hodgeman R, Riviello JJ, et al. Phenotype of GABA-transaminase deficiency. *Neurology*. 2017;**88**(20):1919–24.
44. Nagappa M, Bindu PS, Chiplunkar S, et al. Hypersomnolence–hyperkinetic movement disorder in a child with compound heterozygous mutation in 4-aminobutyrate aminotransferase (*ABAT*) gene. Brain Dev. 2017;**39**(2):161–5.
45. Koenig MK, Bonnen PE. Metabolomics profile in ABAT deficiency pre- and post-treatment. JIMD Rep. 2019;**43**:13–7.
46. Tsuji M, Aida N, Obata T, et al. A new case of GABA transaminase deficiency facilitated by proton MR spectroscopy. J Inherit Metab Dis. 2010;**33**(1):85–90.
47. Besse A, Wu P, Bruni F, et al. The GABA transaminase, ABAT, is essential for mitochondrial nucleoside metabolism. Cell Metab. 2015;**21**(3):417–27.
48. Ichikawa K, Tsuji M, Tsuyusaki Y, et al. Serial magnetic resonance imaging and (1)H-magnetic resonance spectroscopy in GABA transaminase deficiency: A case report. JIMD Rep. 2019;**43**:7–12.
49. Gibson KM, Schor DS, Gupta M, et al. Focal neurometabolic alterations in mice deficient for succinate semialdehyde dehydrogenase. J Neurochem. 2002;**81**(1):71–9.
50. Chowdhury GM, Gupta M, Gibson KM, Patel AB, Behar KL. Altered cerebral glucose and acetate metabolism in succinic semialdehyde dehydrogenase-

deficient mice: Evidence for glial dysfunction and reduced glutamate/glutamine cycling. J Neurochem. 2007;**103**(5):2077–91.

51. Knerr I, Pearl PL, Bottiglieri T, et al. Therapeutic concepts in succinate semialdehyde dehydrogenase (SSADH; ALDH5A1) deficiency (gamma-hydroxybutyric aciduria). Hypotheses evolved from 25 years of patient evaluation, studies in Aldh5a1-/- mice and characterization of gamma-hydroxybutyric acid pharmacology. J Inherit Metab Dis. 2007;**30**(3):279–94.
52. Acosta MT, Munasinghe J, Pearl PL, et al. Cerebellar atrophy in human and murine succinic semialdehyde dehydrogenase deficiency. J Child Neurol. 2010;**25**(12):1457–61.
53. DiBacco ML, Roullet JB, Kapur K, et al. Age-related phenotype and biomarker changes in SSADH deficiency. Ann Clin Transl Neurol. 2018;6(1):114–20.

Chapter

24 Vitamin-Responsive Disorders: Ataxia with Vitamin E Deficiency and Movement Disorders

Krisztina K. Johansen and Jan O. Aasly

Background

Ataxia with vitamin E deficiency (AVED) was first described in 1981 by Burck et al. [1] as a progressive cerebellar ataxia in a 12-year-old boy with low vitamin E levels and without any alternative diagnosis. A few more reports presented similar cases resembling Friedreich ataxia (FA), all with low vitamin E levels but with variable severity of symptoms. In 1993, two consanguineous Tunisian families were reported with the same characteristics but there was no linkage to the locus on chromosome 9q as expected in FA [2]; instead, the genetic locus was mapped to proximal chromosome 8q [3]. Two years later, the alpha-tocopherol transfer protein (TTPA) gene was identified and the condition was termed AVED [4]. The identification of the gene led to therapeutic opportunities by supplementation of vitamin E in these patients.

Vitamin E

Vitamin E is a fat-soluble antioxidant which prevents lipid oxidation in membranes. There are various forms of tocopherols and tocotrienols. Alpha-tocopherol is probably the most important. It is absorbed in the small intestine and transported to the liver where it is incorporated into very low-density lipid proteins and then enters the circulation. Vitamin E is reported to have an anti-inflammatory effect and modulates DNA repair. Several studies have examined the effect of supplemental therapy using tocopherols and tocotrienols in aging populations. Immune-enhancing effects were attributed to the inhibition of cyclooxygenase (COX) activity, neutralizing reactive oxygen species-mediated damage, modulating T-cell function, and influencing the activities of several enzymes involved in signaling pathways related to immune response and inflammation. Numerous clinical trials reported a beneficial effect of vitamin E supplementation on cardiovascular disease, diabetes, cancer, and neurodegenerative diseases [5]. Adequate alpha-tocopherol is essential for normal cell function, especially in the central nervous system. Vitamin E deficiency presents primarily as a neurological disorder with spinocerebellar ataxia as a result of cerebellar Purkinje cell loss [6].

Etiology

AVED is caused by bi-allelic mutations in the *TTPA* gene on chromosome 8q13. *TTPA* codes for the protein TTPA, which mediates the integration of vitamin E from chylomicrons to the very low-density lipoprotein (VLDL) in the liver and enables its systemic circulation. Patients with AVED have normal absorption of vitamin E from the gut and uptake into chylomicrons but the incorporation of alpha-tocopherol to the VLDL by the cytosolic protein TTPA is impaired. This leads to the rapid elimination and deficient recycling of vitamin E.

Genetics

The causative gene, *TTPA*, is localized to chromosome 8q [7]. The majority of cases originate from populations in North Africa with high rates of consanguinity [8–11]. A common haplotype in the North African families suggested an increased frequency in the region with a possible founder effect [12]. The majority of cases are reported from Tunisia and Morocco but some rare cases were also reported from other geographic regions.

Over 20 mutations have been identified covering all five exons of the gene. The 744delA mutation is the most common [10, 11, 13–16] and was first described in 1995 in North African and southern Italian patients [4]. Two other mutations, 530AG>GTAAGT and 513insTG, were found in a northern German family and in a US family with Danish and English ancestry [4]. In Japanese patients, three further mutations were detected: 486delT, R192H [17], and H101Q [18].

In North African patients the 744delA is the most common mutation while in the European countries the 513insTT seems to be the most frequent disease-causing mutation [10, 15, 16, 19].

A genotype–phenotype correlation has been described. Truncating gene mutations seem to lead to an earlier onset and more severe form, while missense mutations might cause a more benign form. Semiconservative missense mutations H101Q, A120T, and R192H may cause a milder type, and non-conservative mutations R59W, E141K, and R221W have been described with a severe, early-onset disease. The homozygous truncating mutations 530AG>GTAAGT, 744delA, 486delT, and R134X are reported to lead to a more severe phenotype [15, 19]. Table 24.1 presents the known mutations in the *TTPA* gene.

Prevalence

The prevalence of AVED varies between geographic regions and ethnic groups. Only a few population-based studies have been performed. AVED is a rare movement disorder in most countries with an estimated prevalence of 0.5–3.5 in 1,000,000 in Europe. In Mediterranean and North African countries, and particularly in those with high rates of consanguinity, the prevalence may be much higher [10, 11].

A Moroccan study reported similar frequency of FA and AVED. In Rabat, 29 patients with symptoms resembling FA were admitted to the local department of neurology between 1987 and 1997; 16 had FA and 13 AVED [13].

An Algerian study examined 166 patients with cerebellar ataxia, segregating in an autosomal-recessive pattern. Nineteen patients had a genetically confirmed diagnosis of AVED, the second most common autosomal-recessive cerebellar ataxia after FA. Twelve of the 19 patients belonged to families with clear consanguinity [20].

A Japanese study found one homozygous and 21 heterozygous carriers for a mutation in *TTPA* in a population of 821 inhabitants of an isolated island outside of the main island of Japan but none of these mutations were found in 150 probands from Tokyo [18].

An epidemiological study from Italy reported a prevalence of 3.5 in 1,000,000 for AVED in the province of Padua [21]. A French study reported 102 cases with autosomal-recessive progressive cerebellar ataxia with only one subject identified as AVED. The overall prevalence of AVED in the Alsace region was 1 in 1,800,000 (0.6 per million) [22], similar to a Norwegian study which estimated an AVED prevalence of 0.6 in 1,000,000 [23].

Clinical Symptoms

Most AVED cases manifest in childhood or early adolescence, usually before the age of 20 years. A few Japanese cases had a later onset, which seemed more common in male patients. The clinical presentation is similar to FA although symptoms are heterogeneous and there is heterogeneity within the same family and among carriers of the same mutation [10, 11, 15, 16, 20]. The main symptoms are progressive spinocerebellar ataxia accompanied by neuropathy, head titubation and vision impairment. In a few cases, other neurological symptoms like torticollis might be the initial sign. A careful individual evaluation is needed in all cases.

The most common initial signs are gait impairment, clumsiness, and cerebellar ataxia affecting both lower and upper extremities. Ataxia persists throughout the disease course. Dysarthria, head tremor, and neuropathy are common. Sensory deficits combined with weak or absent tendon reflexes in the lower extremities with inverted plantar reflexes are found in most of the cases. Spasticity is rare [16]. Skeletal deformities may be present and may manifest as kyphoscoliosis, pes cavus, or hammertoes [10, 16, 20]. Distal lower limb amyotrophy may be seen [10, 24].

Dystonia has been reported [9, 15, 25–29]. Becker et al. reported two siblings manifesting with cervical and bilateral arm dystonia as the initial symptoms, and one of them progressed to develop generalized dystonia [30]. Another case with severe generalized dystonia was found to be unresponsive to vitamin E supplementation, requiring treatment with botulinum toxin injections [31].

Ophthalmological manifestations consist of reduced visual acuity and retinitis pigmentosa [10, 11, 13, 16]. Retinitis pigmentosa seems to be more common in Japanese patients [18, 32–36]. Other eye symptoms are rare but oculomotor apraxia and exotropia have both been reported [10]. A recent case report described macular degeneration [37]. Deafness is uncommon, only reported in three cases [34, 35, 38].

Urinary urgency and incontinence is rare [10, 35]. A male patient was examined and normal seminal parameters and normal fertility was found [39].

Table 24.1 Mutations in the *TTPA* gene

Exon	Mutations	Effect	Clinical phenotype*	References
5′UTR	c. -1 C>T		Severe	[35]
1	c. 2 T>C		n.d.	[32]
1	c.161_164del	R54fs		[30]
1	c.173 C>A	A58D		[49]
1	c.175 C>T	R59W	Severe	[15, 45]
1	c.191 A>G	D64G	Severe	[35]
Intron1	c.205-1 G>C	R68fs	n.d.	[15]
2	c.219insAT		Severe	[16]
2	c.303 T>G	H101Q	Mild	[9, 15, 18, 33, 36, 43]
2	c.306 A>G		Mild	[15]
2	c.358 G>A	A120T	Mild	[15, 23, 50]
3	c.400 C>T	R134X	n.d.	[15, 23, 50, 51]
3	c.421 G>T		n.d.	[48]
3	c.412 G>A	E141K	Severe	[15]
3	c.437delT		Severe	[45]
3	c.457 G>A	G153R		[49]
3	c.485delT		Severe	[17]
3	c.486delT		Severe	[15, 17, 31]
3	c.487delT	W163fs		[30]
3	c.513insTT		Severe	[4, 15–17, 23, 26, 51, 52]
3	c.530AG>GTAAGT		Severe	[1, 4, 15, 25]
3	c.552 G>A		Severe	[25, 48, 53]
4	c.548 T>C	L183P	Severe	[34]
4	c.575 T>C	R192H	Mild	[15, 17]
4	c.661 C>T c.706del	R221W H236fs	Severe	[15] [24]
5	c.717delC	D239EfsX25		[37]
5	c.736 G>C	G246 R	Mild	[16]
5	c.744delA		Severe	[11, 13, 15, 16, 20, 26]

* n.d., not determined.

Arrhythmia and cardiomyopathy are rare features; however, cardiac abnormalities have been reported in up to 31% of Moroccan patients [11, 15]. This is an important feature that might help to distinguish AVED from FA. Diabetes mellitus is rare [11].

Growth retardation was observed in all 16 Moroccan patients [11]. Cognitive decline and learning difficulties requiring special education services is not often seen and behavioral changes are rare [30, 40]. Seizures have been reported in four cases [20, 41].

Diagnostic Studies

The diagnosis is based on clinical features in association with low serum vitamin E levels. Genetic testing confirms the diagnosis and excludes other conditions.

Blood Tests

Plasma alpha-tocopherol (vitamin E) levels are low, typically <1.7 mg/L (4.0 μmol/L) [15, 16]. Normal lipid profiles, blood glucose, and vitamin A levels should be present. The concentration of vitamin

E depends on the test method and varies among laboratories. Caution should be taken because alpha-tocopherol oxidizes when exposed to air, which might influence results. Alpha-fetoprotein should be assessed, and is normal, ruling out ataxia–telangiectasia.

Imaging

Brain MRI may show mild vermian and hemispheric cerebellar atrophy [16] but most cases have normal MRI [16]. ECG and echocardiography are mostly normal but in a few cases tachyarrhythmia and cardiomyopathy are detected [10, 11, 42].

Nerve Conduction Studies

El Euch-Fayache et al. reported nerve conduction studies in 45 AVED patients: 88% had axonal neuropathy; 42%, sensorimotor; 34%, purely sensory; and 24% had pure motor neuropathy. In most cases, mild to moderate neuropathy was found, 9% had normal neuropathy, and 17% had severe neuropathy [10].

Nerve and Muscle Biopsies

Degenerated axons and some demyelinated segments of the superficial peroneal nerve have been reported. The density of large myelinated fibers is slightly reduced.

Histopathological Findings

Only two cases have been examined thus far. In a Tunisian patient with severe cardiomyopathy, who died at age 29 years from heart failure, demyelination with neuronal atrophy, axonal spheroids, and corpora amylacea were discovered. Accumulation of neuronal lipofuscin was detected in the cerebral cortex, thalamus, lateral geniculate body, and nucleus ambiguous, spinal horns, and dorsal root ganglia [42].

In a Japanese AVED patient who died at age 73 years, autopsy showed marked atrophy of the brainstem and the spinal cord. The posterior column was degenerated with astrocytic proliferation. Numerous corpora amylacea and axonal spheroids were seen. Hyalinization and thickening of the vascular walls were described. The posterior roots were also affected. The sural nerve had normal myelinated axons. In the cerebellum, Purkinje cell loss was observed. The cerebral cortex was normal and the retina was atrophic [43].

Differential Diagnosis

Vitamin E deficiency may be caused by malnutrition, malabsorption secondary to liver dysfunction, cholestasis, pancreatic insufficiency, or other diseases of the gastrointestinal tract. These disorders must be evaluated and ruled out. Primary lipid malabsorption is seen in abetalipoproteinemia, and might present with similar symptoms, but in this condition both vitamins E and A are usually low.

Autosomal-recessive cerebellar ataxias (ARCAs) include numerous subgroups with overlapping clinical manifestations. The most common ARCA is FA, thus it is important to exclude GAA expansion repeats in the *frataxin* gene. Other types of early-onset ARCAs have mostly genetic causes; however, in those with onset after age 20 years a genetic cause is less common [22]. The main clinical symptoms, cerebellar ataxia, dysarthria, pyramidal sign, deep sensory disturbances, absence of tendon reflexes, and skeletal deformities are overlapping with FA. Head tremor is more common in AVED compared to FA, and in Japanese cases retinitis pigmentosa is more prevalent. Dystonia is an uncommon feature but might be present in AVED. Cardiomyopathy and diabetes mellitus on the other hand are more common in FA patients and neuropathy is much more severe compared to AVED [22, 44].

Benomar et al. compared seven AVED families (13 patients) carrying the 744del mutation in *TTPA* gene with eight FA families (16 patients) with GAA expansions in the *frataxin* gene. All families originated from Morocco. The clinical presentation of these two conditions was very similar; however, there were some differences: Head titubation (8/11 vs. 1/15), visual acuity (8/11 vs. 1/15), and retinitis pigmentosa (3/11 vs. 0/15) were more often seen in AVED families. Severe demyelinating neuropathy was more frequent in FA families (4/7 vs. 2/8) and the disease progressed more rapidly in FA patients compared to AVED [13].

Treatment

Early normalization of vitamin E levels is crucial for optimal outcomes. High-dose vitamin E supplementation should be initiated ideally even before patients develop neurological symptoms, as many of these tend to be irreversible [23, 45]. During early disease stages, vitamin E supplementation allows stabilization of the neurological symptoms [15, 16], and in the very early stages may lead to improvement [46, 47].

The course of the disease is variable but most patients are stabilized on vitamin E supplementation; however, it is important to point out that some might worsen [15, 16]. Overall, patients monitored for a year on oral supplementation of vitamin E to maintain serum levels within normal ranges showed mild improvement [47]. In an 8-year old child with symptoms since age 3 years and homozygous 744delA mutations, 1,200–1,500 mg/day vitamin E supplementation led to a complete remission of truncal and limb ataxia and sensory symptoms after 6 months of therapy [46]. Another study reported a case of a 9-year old patient whose behavioral symptoms and cognitive function improved rapidly, but the neurological symptoms, including ataxia, recovered incompletely [48]. In patients with initial worsening on vitamin E supplementation, higher doses (>1,000 mg/day of vitamin E) are sometimes required [16]. Patients with no supplementation progress to become wheelchair-bound [4, 8, 13, 15–17, 47]. Marzouki et al. reported improvements in patients in early disease after 13 months of vitamin E supplementation. In asymptomatic patients, no worsening or any abnormalities in visual acuity were observed and ECG findings remained unchanged during the study period [11]. Vitamin E supplementation should be given with meals to allow the efficient absorption of this fat-soluble vitamin.

Conclusions

AVED is an important cause of cerebellar ataxia and mimics the phenotype of FA. Early diagnosis is imperative as treatment with high doses of vitamin E can halt disease progression or even reverse some manifestations. Primary prevention is possible and treatment should be continued lifelong. Plasma vitamin E levels should be monitored in regular intervals.

Key Points and Clinical Pearls

- Ataxia with isolated vitamin E deficiency (AVED) is an important cause of cerebellar ataxia and mimics the phenotype of Friedreich ataxia.
- Early diagnosis and treatment with high-dose vitamin E is imperative, to halt disease progression or even reverse some manifestations.
- Primary prevention is possible and treatment should be continued lifelong.
- Plasma vitamin E levels should be monitored in regular intervals.

Directions for Future Research

- Establish the prevalence of AVED in different populations.
- Establish the optimal regimen for supplementing vitamin E.
- Investigate the natural history of AVED on supplementation with vitamin E.

References

1. Burck U, Goebel HH, Kuhlendahl HD, Meier C, Goebel KM. Neuromyopathy and vitamin E deficiency in man. Neuropediatrics. 1981;**12**(3):267–78.
2. Ben Hamida M, Belal S, Sirugo G, et al. Friedreich's ataxia phenotype not linked to chromosome 9 and associated with selective autosomal recessive vitamin E deficiency in two inbred Tunisian families. Neurology. 1993;**43**(11):2179–83.
3. Ben Hamida C, Doerflinger N, Belal S, et al. Localization of Friedreich ataxia phenotype with selective vitamin E deficiency to chromosome 8q by homozygosity mapping. Nat Genet. 1993;**5**(2):195-200.
4. Ouahchi K, Arita M, Kayden H, et al. Ataxia with isolated vitamin E deficiency is caused by mutations in the alpha-tocopherol transfer protein. Nat Genet. 1995;**9**(2):141–5.
5. Mocchegiani E, Costarelli L, Giacconi R, et al. Vitamin E–gene interactions in aging and inflammatory age-related diseases: Implications for treatment. A systematic review. Ageing Res Rev. 2014;**14**:81–101.
6. Ulatowski L, Parker R, Warrier G, et al. Vitamin E is essential for Purkinje neuron integrity. Neuroscience. 2014;**260**:120–9.
7. Arita M, Sato Y, Miyata A, et al. Human alpha-tocopherol transfer protein: cDNA cloning, expression and chromosomal localization. Biochem J. 1995;**306** (Pt 2):437–43.
8. Harding AE, Matthews S, Jones S, et al. Spinocerebellar degeneration associated with a selective defect of vitamin E absorption. N Engl J Med. 1985;**313**(1):32–5.
9. Yokota T, Wada Y, Furukawa T, et al. Adult-onset spinocerebellar syndrome with idiopathic vitamin E deficiency. Ann Neurol. 1987;**22**(1):84–7.
10. El Euch-Fayache G, Bouhlal Y, Amouri R, Feki M, Hentati F. Molecular, clinical and peripheral neuropathy study of Tunisian patients with ataxia with vitamin E deficiency. Brain. 2014;**137**(Pt 2):402–10.
11. Marzouki N, Benomar A, Yahyaoui M, et al. Vitamin E deficiency ataxia with (744 del A)

mutation on alpha-TTP gene: Genetic and clinical peculiarities in Moroccan patients. Eur J Med Genet. 2005;**48**(1):21–8.

12. Doerflinger N, Linder C, Ouahchi K, et al. Ataxia with vitamin E deficiency: Refinement of genetic localization and analysis of linkage disequilibrium by using new markers in 14 families. Am J Hum Genet. 1995;**56**(5):1116–24.
13. Benomar A, Yahyaoui M, Meggouh F, et al. Clinical comparison between AVED patients with 744 del A mutation and Friedreich ataxia with GAA expansion in 15 Moroccan families. J Neurol Sci. 2002; **198** (1–2): 25–9.
14. Bouhlal Y, Zouari M, Kefi M, et al. Autosomal recessive ataxia caused by three distinct gene defects in a single consanguineous family. J Neurogenet. 2008;**22**(2):139-48.
15. Cavalier L, Ouahchi K, Kayden HJ, et al. Ataxia with isolated vitamin E deficiency: Heterogeneity of mutations and phenotypic variability in a large number of families. Am J Hum Genet. 1998;**62** (2):301–10.
16. Mariotti C, Gellera C, Rimoldi M, et al. Ataxia with isolated vitamin E deficiency: Neurological phenotype, clinical follow-up and novel mutations in *TTPA* gene in Italian families. Neurol Sci. 2004;**25**(3):130–7.
17. Hentati A, Deng HX, Hung WY, et al. Human alpha-tocopherol transfer protein: Gene structure and mutations in familial vitamin E deficiency. Ann Neurol. 1996;**39**(3):295–300.
18. Gotoda T, Arita M, Arai H, et al. Adult-onset spinocerebellar dysfunction caused by a mutation in the gene for the alpha-tocopherol-transfer protein. N Engl J Med. 1995;**333**(20):1313–8.
19. Di Donato I, Bianchi S, Federico A. Ataxia with vitamin E deficiency: Update of molecular diagnosis. Neurol Sci. 2010;**31**(4):511–5.
20. Hamza W, Ali Pacha L, Hamadouche T, et al. Molecular and clinical study of a cohort of 110 Algerian patients with autosomal recessive ataxia. BMC Med Genet. 2015;**16**:36.
21. Zortea M, Armani M, Pastorello E, et al. Prevalence of inherited ataxias in the province of Padua, Italy. Neuroepidemiology. 2004;**23**(6):275–80.
22. Anheim M, Fleury M, Monga B, et al. Epidemiological, clinical, paraclinical and molecular study of a cohort of 102 patients affected with autosomal recessive progressive cerebellar ataxia from Alsace, Eastern France: Implications for clinical management. Neurogenetics. 2010;**11**(1):1–12.
23. Elkamil A, Johansen KK, Aasly J. Ataxia with vitamin E deficiency in Norway. J Mov Disord. 2015;**8**(1):33–6.
24. Bonello M, Ray P. A case of ataxia with isolated vitamin E deficiency initially diagnosed as Friedreich's ataxia. Case Rep Neurol Med. 2016;**2016**:8342653.
25. Schuelke M, Finckh B, Sistermans EA, et al. Ataxia with vitamin E deficiency: Biochemical effects of malcompliance with vitamin E therapy. Neurology. 2000;**55**(10):1584–6.
26. Angelini L, Erba A, Mariotti C, et al. Myoclonic dystonia as unique presentation of isolated vitamin E deficiency in a young patient. Mov Disord. 2002;**17** (3):612–4.
27. Amiel J, Maziere JC, Beucler I, et al. Familial isolated vitamin E deficiency. Extensive study of a large family with a 5-year therapeutic follow-up. J Inherit Metab Dis. 1995;**18**(3):333–40.
28. Krendel DA, Gilchrist JM, Johnson AO, Bossen EH. Isolated deficiency of vitamin E with progressive neurologic deterioration. Neurology. 1987;**37** (3):538–40.
29. Stumpf DA, Sokol R, Bettis D, et al. Friedreich's disease: V. Variant form with vitamin E deficiency and normal fat absorption. Neurology. 1987;**37** (1):68–74.
30. Becker AE, Vargas W, Pearson TS. Ataxia with vitamin E deficiency may present with cervical dystonia. Tremor Other Hyperkinet Mov (NY). 2016;**6**:374.
31. Roubertie A, Biolsi B, Rivier F, et al. Ataxia with vitamin E deficiency and severe dystonia: Report of a case. Brain Dev. 2003;**25**(6):442–5.
32. Hoshino M, Masuda N, Ito Y, et al. Ataxia with isolated vitamin E deficiency: A Japanese family carrying a novel mutation in the alpha-tocopherol transfer protein gene. Ann Neurol. 1999;**45**(6):809–12.
33. Pang J, Kiyosawa M, Seko Y, et al. Clinicopathological report of retinitis pigmentosa with vitamin E deficiency caused by mutation of the alpha-tocopherol transfer protein gene. Jpn J Ophthalmol. 2001;**45**(6):672–6.
34. Shimohata T, Date H, Ishiguro H, et al. Ataxia with isolated vitamin E deficiency and retinitis pigmentosa. Ann Neurol. 1998;**43**(2):273.
35. Usuki F, Maruyama K. Ataxia caused by mutations in the alpha-tocopherol transfer protein gene. J Neurol Neurosurg Psychiatry. 2000;**69**(2):254–6.
36. Yokota T, Shiojiri T, Gotoda T, et al. Friedreich-like ataxia with retinitis pigmentosa caused by the His101Gln mutation of the alpha-tocopherol transfer protein gene. Ann Neurol. 1997;**41**(6):826–32.
37. Iwasa K, Shima K, Komai K, et al. Retinitis pigmentosa and macular degeneration in a patient with ataxia with isolated vitamin E deficiency with a novel c.717 del C mutation in the *TTPA* gene. J Neurol Sci. 2014; **345** (1-2): 228–30.

38. Kara B, Uzumcu A, Uyguner O, et al. Ataxia with vitamin E deficiency associated with deafness. Turk J Pediatr. 2008;**50**(5):471–5.

39. Rossato M, Mariotti C. Normal spermatogenesis and sperm function in a subject affected by cerebellar ataxia due to congenital vitamin E deficiency. Andrologia. 2014;**46**(3):322–4.

40. Mansoor S, Ahmad A. Progressive ataxia due to alpha-tocopherol deficiency in Pakistan. Iran J Neurol. 2016;**15**(2):103–5.

41. Muller KI, Bekkelund SI. Epilepsy in a patient with ataxia caused by vitamin E deficiency. BMJ Case Rep. 2011;doi:10.1136/bcr.01.2011.3728.

42. Larnaout A, Belal S, Zouari M, et al. Friedreich's ataxia with isolated vitamin E deficiency: A neuropathological study of a Tunisian patient. Acta Neuropathol. 1997;**93**(6):633–7.

43. Yokota T, Uchihara T, Kumagai J, et al. Postmortem study of ataxia with retinitis pigmentosa by mutation of the alpha-tocopherol transfer protein gene. J Neurol Neurosurg Psychiatry. 2000;**68**(4):521–5.

44. Durr A, Cossee M, Agid Y, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. N Engl J Med. 1996;**335**(16):1169–75.

45. Ponten SC, Kwee ML, Wolters E, Zijlmans JC. First case of ataxia with isolated vitamin E deficiency in the Netherlands. Parkinsonism Relat Disord. 2007;**13**(5):315–6.

46. Doria-Lamba L, De Grandis E, Cristiani E, et al. Efficacious vitamin E treatment in a child with ataxia with isolated vitamin E deficiency. Eur J Pediatr. 2006;**165**(7):494–5.

47. Gabsi S, Gouider-Khouja N, Belal S, et al. Effect of vitamin E supplementation in patients with ataxia with vitamin E deficiency. Eur J Neurol. 2001;**8**(5):477–81.

48. Schuelke M, Mayatepek E, Inter M, et al. Treatment of ataxia in isolated vitamin E deficiency caused by alpha-tocopherol transfer protein deficiency. J Pediatr. 1999;**134**(2):240–4.

49. Zelante G, Patti F, Vinciguerra L, Gellera C, Zappia M. Ataxia with vitamin E deficiency caused by a new compound heterozygous mutation. Neurol Sci. 2016;**37**(9):1571–2.

50. Koht J, Bjornara KA, Jorum E, Tallaksen CM. Ataxia with vitamin E deficiency in southeast Norway, case report. Acta Neurol Scand Suppl. 2009(189):42–5.

51. Cellini E, Piacentini S, Nacmias B, et al. A family with spinocerebellar ataxia type 8 expansion and vitamin E deficiency ataxia. Arch Neurol. 2002;**59**(12):1952–3.

52. Martinello F, Fardin P, Ottina M, et al. Supplemental therapy in isolated vitamin E deficiency improves the peripheral neuropathy and prevents the progression of ataxia. J Neurol Sci. 1998;**156**(2):177–9.

53. Tamaru Y, Hirano M, Kusaka H, et al. Alpha-tocopherol transfer protein gene: Exon skipping of all transcripts causes ataxia. Neurology. 1997;**49**(2):584–8.

Chapter 25

Vitamin-Responsive Disorders: Biotin–Thiamine-Responsive Basal Ganglia Disease and Movement Disorders

Albert L. Misko and Florian S. Eichler

Introduction

Biotin–thiamine-responsive basal ganglia disease (BTBGD) is a reversible neurodegenerative disorder that is widely underdiagnosed. Though found in a pan-ethnic distribution, it was first recognized as an inherited disorder among a cluster of Saudi Arabian families that presented with subacute encephalopathy, seizures, dystonia, dysarthria, dysphagia, supranuclear facial palsy, and external ophthalmoplegia [1]. Brain MRI consistently demonstrates cytotoxic and vasogenic edema affecting regions of cortex, subcortical white matter, basal ganglia, brainstem, and cerebellum [2]. Importantly, patients rapidly respond to biotin and thiamine administration, with resolution of neurological symptoms and long-term protection with maintenance treatment. Failure to expediently diagnose and initiate treatment results in severe and irreversible neurological disabilities, highlighting the necessity to understand the spectrum of clinicoradiological presentations, pertinent diagnostic testing, and appropriate treatment.

First described in 1998, BTBGD was initially named "biotin-responsive basal ganglia disease," as biotin but not thiamine had been recognized as the critical metabolite to which patients responded. Two years later, the disorder was linked to inactivating mutations in *SLCA19A3*, the gene encoding the thiamine transporter THTR2 [3]. This raised questions about the biotin-responsive nature and the need for thiamine supplementation. Since that time, patients responsive to thiamine but not biotin have been identified and, along with radiographic similarities to Wernicke encephalopathy (a nutritional deficit in thiamine), it has been established that intracellular depletion of thiamine is the main pathophysiological mechanism. This has led to the renaming of the disorder as BTBGD.

A spectrum of clinical phenotypes is now recognized [4]. These phenotypes range from more severe cases in infancy to milder phenotypes in adulthood. The clinical heterogeneity is likely related to the age at onset and may be due to age-specific changes in energy metabolism during early development. Though variably effective among phenotypic subgroups, thiamine and biotin supplementation remains the standard of care, and expedient diagnosis remains paramount.

Clinicoradiographic Spectrum

The disease course in BTBGD falls into one of three major categories defined by the age at onset [4]: (1) an early-infantile syndrome; (2) classic childhood-onset BTBGD; and (3) an adult-onset Wernicke-like encephalopathy. Table 25.1 summarizes cases and phenotypes reported to date.

In early infancy, two distinct presentations of BTBGD are described: a Leigh-like syndrome and atypical infantile spasms [5, 6]. Collectively, BTBGD in early infancy has only been reported in ~30 patients. The Leigh-like syndrome in this age group presents with poor feeding, vomiting, acute encephalopathy, and severe lactic acidosis. Brain MRI shows elevated T2 signal and vasogenic edema involving the perirolandic area, bilateral putamen, and medial thalamic nuclei with MRS showing lactate peaks [2]. Several patients also displayed restricted diffusion in several areas of the cerebral cortex and white matter, corpus callosum, basal ganglia, thalamus, brainstem, and cerebellum. These lesions develop into rarefaction or cystic degeneration of the white matter and, finally, progressive cerebral, cerebellar, and brainstem atrophy. Biotin and thiamine supplementation appear to have a limited efficacy, although two reported infants showed favorable responses [2]. Another presentation of BTBGD in early infancy was reported in four Japanese patients (age range 2–11 months) who developed atypical infantile spasms with multifocal spike discharges on EEG without hypsarrhythmia

Table 25.1 Summary of published cases and their phenotypes

Phenotype	Number of cases	Origin	Male: female ratio	Age of onset	References
Infantile	29	Japan, Canada, Europe, North Africa, Central America	19:4	1–3 months	[1], [4], [18], [24–31]
Childhood	103	Saudi, Europe, India, Japan	48:55	3–7 years	[2], [5–7], [22], [23], [32], [33]
Adult	2	Japan	2:0	Adult	[8]

[7]. Neuroimaging in all cases demonstrated bilateral T2 hyperintensities in the thalami and basal ganglia, with subsequent development of diffuse cerebral atrophy on follow-up imaging. All patients developed severe developmental delay and spastic quadriplegia. Biotin supplementation was attempted in one patient at 8 months after onset of symptoms and was without benefit, but the timing of treatment and additional supplementation of thiamine remain untested in this subpopulation.

The classic presentation of BTBGD occurs in later childhood and is characterized by subacute encephalopathy, epilepsy, external ophthalmoplegia, dysarthria, dysphagia, and dystonia that progresses to severe rigidity and spastic quadriparesis. Initial symptoms typically emerge in developmentally normal children who experience a progressive course punctuated by episodic deterioration. In acute crises of the classic form, brain MRI shows bilateral and symmetrical lesions in the basal ganglia, particularly the head of the caudate and putamen, in addition to cortical gray and subcortical white matter involvement (Figure 25.1). Though less frequently reported, the thalami and cerebellum can also be involved. The affected brain areas show a mix of cytotoxic and vasogenic edema, which is an important diagnostic clue. In the acute phase, a ribbon of cortical and some subcortical involvement is frequently seen but there is sparing of the central white matter. In the chronic phase, atrophy and necrosis of the basal ganglia are evident, with mineralization on follow-up imaging. Patients with classic BTBGD are typically responsive to biotin and thiamine supplementation with resolution of symptoms within days of treatment. The rapid initiation of treatment and lifelong supplementation can lead to favorable outcomes while delayed treatment after the onset of irreversible brain damage results in severe neurological disability or death.

Adult-onset disease has been reported in two Japanese males [8], who presented in their second decade of life with status epilepticus, diplopia, nystagmus, ptosis, ophthalmoplegia, and ataxia. MRI of the brain showed high-intensity FLAIR signal in the bilateral medial thalamus and periaqueductal gray region, similar to findings in Wernicke encephalopathy. A dramatic response to high-dose thiamine was reported in both patients.

Movement Disorders Associated with BTBGD

In the most common form of childhood BTBGD, the neurological symptomology is predominated by dystonia, a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements and/or postures. The movements are typically twisted, patterned, or tremulous in quality and may involve the extremities, neck, or facial muscles. The pattern of dystonia in BTBGD is often generalized, but segmental and focal presentations may also manifest. The onset of dystonia during acute decompensations is temporally associated with vasogenic edema of the basal ganglia. The persistence of these imaging changes in the acute period is predictive of the extent of ensuing atrophy and subsequent dystonia. If treatment is initiated early in the course of the disease, before irreversible damage of the basal ganglia has occured, dystonia usually resolves within days of biotin and/or thiamine treatment.

Ataxia may also be prominent in the initial acute presentation and has been reported in up to 70–80% of cases [4]. Interestingly, explicit involvement of the cerebellum is less frequently reported but has been identified as swelling of the cerebellar cortex during the acute presentation and subsequent development of atrophy. The mechanism underlying the radio-

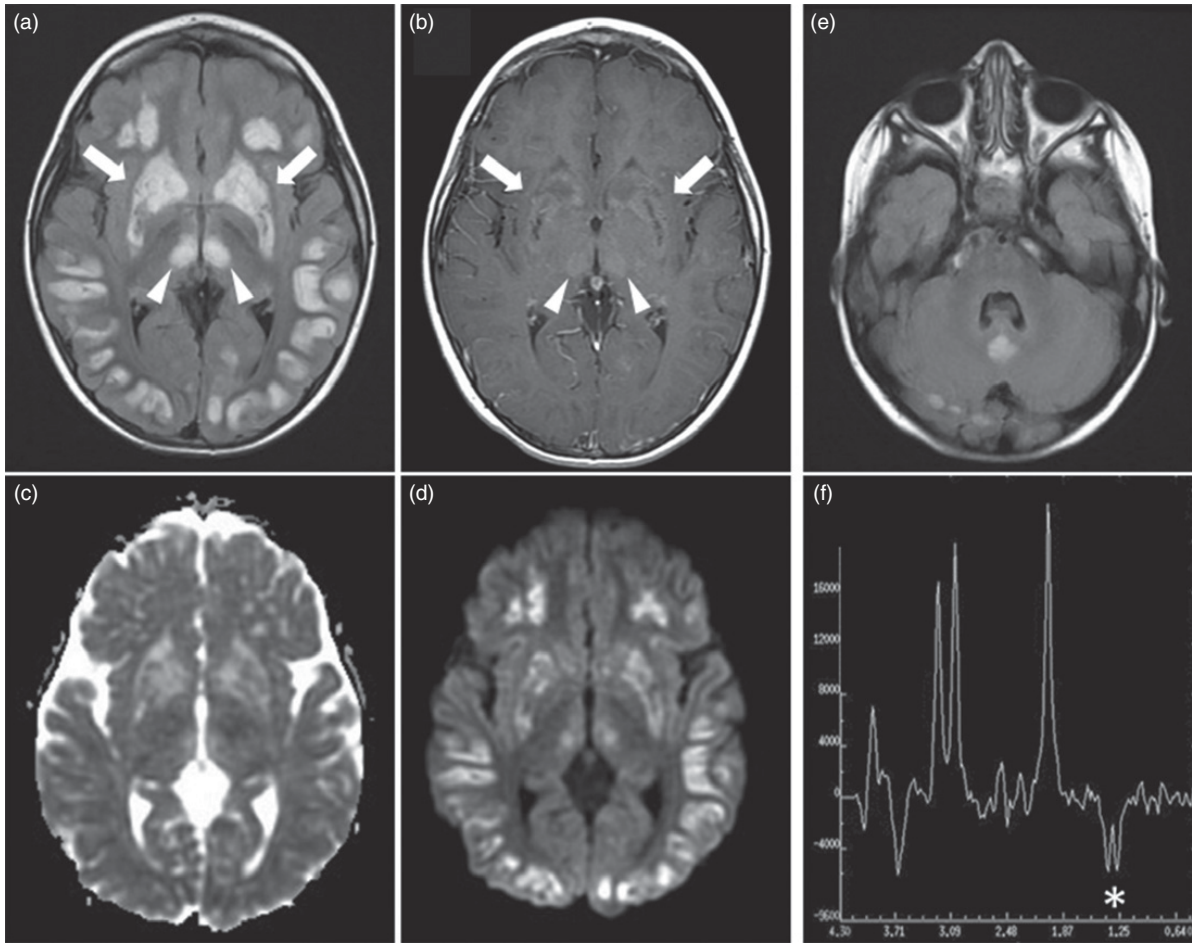

Figure 25.1 Brain MRI findings in a 26-year-old adult with BTBGD. On (a) fluid-attenuated inversion recovery images, symmetrical hyperintense lesions are present in the lenticular nuclei (arrows), medial thalamus (arrow heads), and in numerous discrete areas of subcortical white matter and cortex. (b) T1-weighted imaging with contrast demonstrated a blush of contrast in the basal ganglia and medial thalamus, consistent with vascular tight junction dysregulation. (c) Apparent diffusion coefficient and (d) diffusion-weighted imaging show vasogenic edema in the basal ganglia. Diffusion restriction is not present indicating that the hyperintense signal on diffusion-weighted imaging is an artifact from T2 shine-through. (f) On MRS, a lactate doublet (asterisk) is present on a voxel placed over the basal ganglia.

clinical dissociation seen in most patients, however, is uncertain but may relate to subtle injuries within the cerebellum not readily identified by standard imaging protocols. Alternatively, the involvement of the efferent cerebellar tracts in their course through the brainstem or targets in the thalamus may produce ataxia in patients, without overt cerebellar involvement. The appearance of vasogenic edema and responsiveness to biotin and/or thiamine are congruent with basal ganglia manifestations and consistent with a common pathomechanism.

Dysarthria is a motor speech disorder frequently reported in BTBGD. While not considered a movement disorder, it will often coincide with dystonia and may involve dystonia of the bulbar muscles. Some cases of BTBGD have been reported to progress to aphonia and aphagia [9]. It is unclear whether dysarthria is similarly responsive to biotin and thiamine treatment.

Eye movement abnormalities observed in BTBGD range from nystagmus to roving eye movements and ophthalmoplegia [5]. In older patients with a Wernicke-like encephalopathy, diplopia, ptosis, and ophthalmoplegia have been reported [8].

Differential Diagnosis

As the clinicoradiographic spectrum of disease varies across developmental period, so does the differential

diagnosis. In early infancy, the presentation may mimic infantile spasms or Leigh syndrome. In the case of infantile spasms, a complete work-up with EEG and brain MRI should be pursued. A distinguishing feature of BTBGD in this time period may be the lack of hypsarrhythmia expected in typical cases of infantile spasms. Initiation of biotin and thiamine treatment should be started concurrent with adrenocorticotrophic hormone or other standard therapy for epileptic spasms, while brain imaging along with metabolic and genetic work-up are pursued.

Leigh syndrome, or subacute necrotizing encephalomyelopathy, is a neuropathological entity characterized by variable foci of spongiform degeneration in the basal ganglia, thalamus, brainstem, cerebellum, spinal cord, and optic nerves, with a clinical picture reflecting the anatomical location of the lesions. Children frequently present with poor feeding, vomiting, acute encephalopathy, and severe lactic acidosis. If the clinical presentation and brain imaging are suggestive of Leigh syndrome, biotin and thiamine treatment should be considered while confirmation of the genetic defect is awaited.

In childhood and adolescence, a patient presenting with acute or subacute dystonia raises an extensive differential diagnosis. Among the dystonia plus disorders, we generally first consider treatable diseases such as inherited defects of dopamine synthesis and Wilson disease. A trial of carbidopa/levodopa treatment or screening for abnormal serum copper or ceruloplasmin levels can distinguish these disorders from BTBGD. Ophthalmological evaluation for Kayser–Fleischer rings or other ocular abnormalities can also be helpful. Another category of disorders that symmetrically affects the basal ganglia is that of neurodegeneration with brain iron accumulation [10]. Generally these show low T2 signal, and not high T2 signal, in the caudate, putamen, and thalamus, which can be a helpful differentiator (see also Chapter 16).

If the appropriate clinical and radiographic picture emerges to suggest BTBGD, the differential diagnosis should center on mitochondrial disorders that can present at the age of the patient in question. Like BTBGD, mitochondrial disorders frequently present with a episodic fluctuation of symptoms [11] during which patients exhibit seizures, extrapyramidal signs, basal ganglia involvement on brain MRI, and the presence of lactate on MRS. In contrast to BTBGD, however, mitochondrial diseases more commonly display hearing and vision impairment.

Among the mitochondrial disorders, those that most closely mimic BTBGD include pyruvate dehydrogenase deficiency and disorders of mitochondrial DNA (mtDNA) depletion. Pyruvate dehydrogenase deficiency presents with developmental delay, seizures, choreoathetosis, dystonia, episodic ataxia, lactate accumulation, and basal ganglia damage. The age at presentation can vary from infancy through childhood. Disorders that cause mtDNA depletion, such as *SUCLA2*- and *SUCLG1*-associated syndromes, can show T2 hyperintensity in the caudate and putamen, and a lactate peak on MRS [12]. Problems in overall growth, vision, and hearing are commonly noted and are generally not seen in BTBGD.

Apart from the inherited disorders, the symmetrical involvement of the basal ganglia can be seen in intoxication syndromes such as intoxication with methanol, carbon monoxide, and cyanide. Diagnosis centers on a history concerning for intoxication.

Genetics of BTBGD

This autosomal recessive disorder is caused by mutations in *SLC19A3*, which encodes the thiamine transporter THTR2 [13]. Despite an increasingly broad phenotypic spectrum associated with mutations in *SLC19A3*, no genotype–phenotype correlation has emerged. It seems that the founder mutation in the Middle East is associated with the milder phenotype and later onset (i.e. the classic childhood BTBGD form). Also, if the index case is a compound heterozygote for one missense variant and the other variant is a deletion, duplication, or nonsense type, then the classic childhood BTBGD form is the most likely phenotype. If a patient carries a homozygous nonsense mutation, homozygous deletion, or duplication, the syndrome is more likely to present early and develop a severe Leigh-like phenotype.

In humans, THTR2 and its homologue THTR1, which share a 53% amino acid identity, serve as the main transporters of thiamine across cell membranes [14]. While both are present in a wide range of tissues, expression in the brain has only been explicitly demonstrated for THTR2 [3, 15, 16]. In accordance, the loss of THTR1 leads to thiamine-responsive megaloblastic anemia, sensorineural deafness, and diabetes mellitus, but it has no appreciable effects on the nervous system [17]. The pattern of THTR2 expression across brain regions and cell types is currently unknown; however, THTR2 presumably plays

a role in transporting thiamine: (1) across endothelial cells of the blood–brain barrier, (2) from the choroid plexus into the cerebrospinal fluid (CSF), and/or (3) into neural cells. Interestingly, THTR2 does not facilitate the transport of biotin, highlighting the puzzling benefit of biotin supplementation in BTBGD.

Treatment of BTBGD

Currently the treatment of BTBGD consists of lifelong supplementation of biotin and thiamine. Reported dosages have been variable and appear to be arbitrary; however, biotin and thiamine are water-soluble B vitamins and have no known toxicity or side effects. A recent randomized controlled trial concluded that the combination of biotin plus thiamine was not superior to thiamine alone [18].

Both biotin and thiamine should be used in the treatment of acute disease, but only thiamine for chronic disease. We recommend a daily dose of biotin between 5 mg/kg and 10 mg/kg, and thiamine between 300 mg and 900 mg per day or 10–40 mg/kg per day in all phenotypes, except the adult form where thiamine at 600 mg per day is reported to be effective and sufficient in acute and chronic stages.

Thiamine pyrophosphate, the active form of thiamine, is a critical cofactor for a number of enzymes that are involved in energy metabolism, including the alpha-ketoacid dehydrogenase complexes (for mitochondrial energy metabolism), transketolase (through the pentose phosphate pathway), and 2-hydroxyacyl-coenzyme A (CoA) lyase (for peroxisome alpha-oxidation) [19]. While THRT2 actively transports thiamine across the cell membrane at low extracellular concentrations, thiamine is likely transported by passive diffusion at higher concentrations, consistent with the therapeutic benefit observed in patients.

Biotin metabolites are involved in the expression of multiple enzymes in glucose metabolism which may support cellular energy production when thiamine levels are depleted. However, other mechanisms by which biotin supports cellular metabolism may underlie its therapeutic efficacy in BTBGD, particularly in situations that involve catabolic states [20]. Some studies have shown that marginal biotin levels result in downregulation of SLC19A3 expression [21].

Unfortunately, in patients harboring *SLC19A3* mutations who present in infancy, treatment may be less effective [22]. The clinical severity of the encephalopathy and imaging findings may help assess whether the disease has advanced too far for treatment to be effective. While some infants still respond to treatment [23], long-term data are not yet available.

Given that BTBGD overlaps phenotypically with other causes of Leigh syndrome and given the risk of missing a treatable metabolic encephalopathy in the context of a prolonged diagnostic process, next-generation panel testing or exome sequencing, performed in parallel with mitochondrial genomic sequencing, is the best approach to ensure a rapid and accurate diagnosis. In rare situations in which there is an increased incidence of specific founder mutations in a given population, targeted Sanger sequencing remains a feasible and cost-effective alternative.

Key Points and Clinical Pearls

- Biotin–thiamin-responsive basal ganglia disease (BTBGD) is a reversible neurodegenerative disorder, inherited in an autosomal recessive pattern, and caused by inactivating mutations in *SLC19A3*, which encodes the thiamine transporter THTR2.
- The disease course in BTBGD falls into one of three major categories defined by the age at onset: (1) an early-infantile form presenting as a Leigh-like syndrome or atypical infantile spasms; (2) classic childhood-onset BTBGD, often triggered by febrile illness, presenting with encephalopathy, seizures, external ophthalmoplegia, dysarthria, dysphagia, and dystonia; and (3) an adult-onset Wernicke-like encephalopathy.
- Identification of disease-causing mutations in the *SLC19A3* gene definitively establishes the diagnosis; however, treatment should not be delayed in the setting of high clinical suspicion as favorable outcomes are correlated with early initiation of treatment.
- In acute disease, we recommend a daily dose of biotin between 5 mg/kg and 10 mg/kg, and thiamine between 300 mg and 900 mg per day or 10–40 mg/kg per day in all phenotypes, except the adult form where thiamine at 600 mg per day is reported to be effective and sufficient.

Directions for Future Research

- The expression and selective importance of THTR2 function across different brain regions and cell types remain poorly understood.
- The mechanism by which biotin supplementation is effective in treating a disorder of thiamine transport remains unexplained.
- Further research is needed to clarify the optimal dose and duration of thiamine and biotin therapy for BTBGD.

References

1. Ozand PT, Gascon GG, Al Essa M, et al. Biotin-responsive basal ganglia disease: A novel entity. Brain. 1998;**121** (Pt 7):1267–79.
2. Perez-Duenas B, Serrano M, Rebollo M, et al. Reversible lactic acidosis in a newborn with thiamine transporter-2 deficiency. Pediatrics. 2013;**131**(5):e1670–5.
3. Eudy JD, Spiegelstein O, Barber RC, et al. Identification and characterization of the human and mouse *SLC19A3* gene: A novel member of the reduced folate family of micronutrient transporter genes. Mol Genet Metab. 2000;**71**(4):581–90.
4. Alfadhel M, Almuntashri M, Jadah RH, et al. Biotin-responsive basal ganglia disease should be renamed biotin–thiamine-responsive basal ganglia disease: A retrospective review of the clinical, radiological and molecular findings of 18 new cases. Orphanet J Rare Dis. 2013;**8**:83.
5. Gerards M, Kamps R, van Oevelen J, et al. Exome sequencing reveals a novel Moroccan founder mutation in *SLC19A3* as a new cause of early-childhood fatal Leigh syndrome. Brain. 2013;**136**(Pt 3):882–90.
6. Sremba LJ, Chang RC, Elbalalesy NM, Cambray-Forker EJ, Abdenur JE. Whole exome sequencing reveals compound heterozygous mutations in *SLC19A3* causing biotin–thiamine responsive basal ganglia disease. Mol Genet Metab Rep. 2014;**1**:368–72.
7. Yamada K, Miura K, Hara K, et al. A wide spectrum of clinical and brain MRI findings in patients with *SLC19A3* mutations. BMC Med Genet. 2010;**11**:171.
8. Kono S, Miyajima H, Yoshida K, et al. Mutations in a thiamine-transporter gene and Wernicke's-like encephalopathy. N Engl J Med. 2009;**360**(17):1792–4.
9. Flones I, Sztromwasser P, Haugarvoll K, et al. Novel SLC19A3 promoter deletion and allelic silencing in biotin–thiamine-responsive basal ganglia encephalopathy. PLoS One. 2016;**11**(2):e0149055.
10. Kruer MC, Boddaert N, Schneider SA, et al. Neuroimaging features of neurodegeneration with brain iron accumulation. AJNR Am J Neuroradiol. 2012;**33**(3):407–14.
11. Morava E, van den Heuvel L, Hol F, et al. Mitochondrial disease criteria: Diagnostic applications in children. Neurology. 2006;**67**(10):1823–6.
12. Valayannopoulos V, Haudry C, Serre V, et al. New *SUCLG1* patients expanding the phenotypic spectrum of this rare cause of mild methylmalonic aciduria. Mitochondrion. 2010;**10**(4):335–41.
13. Zeng WQ, Al-Yamani E, Acierno JS, Jr., et al. Biotin-responsive basal ganglia disease maps to 2q36.3 and is due to mutations in *SLC19A3*. Am J Hum Genet. 2005;**77**(1):16–26.
14. Spector R, Johanson CE. Vitamin transport and homeostasis in mammalian brain: Focus on Vitamins B and E. J Neurochem. 2007;**103**(2):425–38.
15. Dutta B, Huang W, Molero M, et al. Cloning of the human thiamine transporter, a member of the folate transporter family. J Biol Chem. 1999;**274** (45):31925–9.
16. Fleming JC, Tartaglini E, Steinkamp MP, et al. The gene mutated in thiamine-responsive anaemia with diabetes and deafness (TRMA) encodes a functional thiamine transporter. Nat Genet. 1999;**22**(3):305–8.
17. Diaz GA, Banikazemi M, Oishi K, Desnick RJ, Gelb BD. Mutations in a new gene encoding a thiamine transporter cause thiamine-responsive megaloblastic anaemia syndrome. Nat Genet. 1999;**22**(3):309–12.
18. Tabarki B, Al-Shafi S, Al-Shahwan S, et al. Biotin-responsive basal ganglia disease revisited: Clinical, radiologic, and genetic findings. Neurology. 2013;**80** (3):261–7.
19. Brown G. Defects of thiamine transport and metabolism. J Inherit Metab Dis. 2014;**37**(4):577–85.
20. Rodriguez-Melendez R, Zempleni J. Regulation of gene expression by biotin (review). J Nutr Biochem. 2003;**14** (12):680–90.
21. Vlasova TI, Stratton SL, Wells AM, Mock NI, Mock DM. Biotin deficiency reduces expression of SLC19A3, a potential biotin transporter, in leukocytes from human blood. J Nutr. 2005;**135** (1):42–7.
22. Kevelam SH, Bugiani M, Salomons GS, et al. Exome sequencing reveals mutated *SLC19A3* in patients with an early-infantile, lethal encephalopathy. Brain. 2013;**136**(Pt 5):1534–43.
23. Haack TB, Klee D, Strom TM, et al. Infantile Leigh-like syndrome caused by *SLC19A3* mutations is a treatable disease. Brain. 2014;**137**(Pt 9):e295.

24. Adhisivam B, Mahto D, Mahadevan S. Biotin responsive limb weakness. Indian Pediatr. 2007;**44** (3):228–30.

25. El-Hajj TI, Karam PE, Mikati MA. Biotin-responsive basal ganglia disease: Case report and review of the literature. Neuropediatrics. 2008;**39** (5):268–71.

26. Bindu PS, Noone ML, Nalini A, Muthane UB, Kovoor JM. Biotin-responsive basal ganglia disease: A treatable and reversible neurological disorder of childhood. J Child Neurol. 2009;**24** (6):750–2.

27. Debs R, Depienne C, Rastetter A, et al. Biotin-responsive basal ganglia disease in ethnic Europeans with novel *SLC19A3* mutations. Arch Neurol. 2010;**67** (1):126–30.

28. Serrano M, Rebollo M, Depienne C, et al. Reversible generalized dystonia and encephalopathy from thiamine transporter 2 deficiency. Mov Disord. 2012;**27**(10):1295–8.

29. Fassone E, Wedatilake Y, DeVile CJ, et al. Treatable Leigh-like encephalopathy presenting in adolescence. BMJ Case Rep. 2013;**2013**:200838.

30. Schanzer A, Doring B, Ondrouschek M, et al. Stress-induced upregulation of SLC19A3 is impaired in biotin-thiamine-responsive basal ganglia disease. Brain Pathol. 2014;**24**(3):270–9.

31. Distelmaier F, Huppke P, Pieperhoff P, et al. Biotin-responsive basal ganglia disease: A treatable differential diagnosis of Leigh syndrome. JIMD Rep. 2014;**13**:53–7.

32. Ygberg S, Naess K, Eriksson M, et al. Biotin and thiamine responsive basal ganglia disease: A vital differential diagnosis in infants with severe encephalopathy. Eur J Paediatr Neurol. 2016;**20**(3):457–61.

33. Pronicka E, Piekutowska-Abramczuk D, Ciara E, et al. New perspective in diagnostics of mitochondrial disorders: Two years' experience with whole-exome sequencing at a national paediatric centre. J Transl Med. 2016;**14**(1):174.

Chapter 26

Disorders of Cholesterol Metabolism: Cerebrotendinous Xanthomatosis and Movement Disorders

Fanny Mochel and Emmanuel Roze

Cerebrotendinous Xanthomatosis

Metabolic and Biochemical Aspects

Bile acids are synthesized via the classic pathway initiated by cholesterol 7-alpha-hydroxylase (CYP7A1) or via alternate pathways, one of which is initiated by sterol 27-hydroxylase (CYP27). Cerebrotendinous xanthomatosis (CTX) is due to bi-allelic pathogenic variants in the *CYP27A1* gene, which encodes the mitochondrial cytochrome P-450 enzyme sterol 27-hydroxylase. Deficiency in this enzyme interferes with sterol intermediates in the alternative bile acid pathway. More specifically, CTX is associated with the reduced synthesis of 27-hydroxycholesterol (27-OHC) and chenodeoxycholic acid (CDCA), as well as the shunting of sterol intermediates into the microsomal pathway for cholic acid formation [1]. CTX is also characterized by the high production of cholestanol, which accumulates in various tissues, as well as increased levels of bile alcohols in the urine [2]. Evidence that cholestanol may be neurotoxic is supported by the finding of cholestanol deposition and apoptosis in neuronal cells, most notably Purkinje cells, in the cerebellum of rats fed a 1% cholestanol diet [3]. As the influx of 27-OHC may be involved in brain cholesterol homeostasis, the lack of 27-OHC may also impact cholesterol synthesis in the brain [4].

Clinical Description and Diagnosis

Patients with CTX typically manifest both systemic and neuropsychiatric symptoms. Systemic manifestations may include infantile cholestasis or liver dysfunction, juvenile-onset cataracts, Achilles tendon xanthomas, chronic diarrhea, osteoporosis, premature arteriosclerosis, and cardiovascular disease [5]. Neurological symptoms encompass learning disabilities and/or autism spectrum disorder, spastic paraplegia, cerebellar ataxia, peripheral neuropathy, bulbar palsy, epilepsy, parkinsonism, dementia, and psychiatric disturbances [5]. Wong et al. conducted a meta-analysis of 91 publications reporting on 194 CTX patients [6]. The study revealed that corticospinal tract abnormalities (59.8%) and ataxia (58.8%) were the most common neurological alterations followed by cognitive decline (46.4%), gait difficulties (38.1%), and cognitive delay (35.0%) [6]. In a natural history study, we highlighted that diarrhea often develops within the first year of life, cataract and school difficulties between 5 years and 15 years of age, usually preceding motor or psychiatric symptoms by about a decade [7]. Although some patients may have autistic features early in the disease course [8], there is a critical therapeutic window in most CTX patients before the onset of disabling neuropsychiatric symptoms [9]. Furthermore, the possibility to reverse the pathophysiological process in patients with CTX stresses that the disease must be diagnosed as early as possible. To help with this, a clinical suspicion index has been proposed [10]. In addition to the characteristic finding of tendon xanthomas, we propose to evaluate for CTX in all patients presenting with any of the following: infantile chronic diarrhea and/or jaundice, juvenile cataracts, a learning disability and/or autism spectrum disorder, pyramidal signs, cerebellar signs, parkinsonism, or peripheral neuropathy.

The most common biochemical diagnostic marker of CTX is increased plasma cholestanol. Two other plasma metabolites are of particular interested for the diagnosis of CTX: decreased 27-OHC and increased 7-alpha-hydroxy-4-cholesten-3-one (7αC4) [4]. Cholestanol and 7αC4 are good biomarkers to monitor the response to treatment. Because of the favorable outcome of CTX patients treated at an early stage of the disease, expert groups are advocating for newborn screening for CTX, based on the detection of bile alcohol glucuronides [11, 12]. The diagnosis of CTX is confirmed by the identification of two

pathogenic bi-allelic variants (compound heterozygous or homozygous) in *CYP27A1*.

Management

CDCA remains the treatment of choice in CTX as it downregulates CYP7A, restores the imbalance between CDCA and cholic acid, and is the only drug that has shown beneficial effects on neurological symptoms so far [5, 13]. The exogenous supply of CDCA may act by restoring a negative feedback in the endogenous acid bile and cholestanol synthesis. This drastically lowers plasma cholestanol concentrations in patients and prevents its accumulation in tissues [2, 5]. CDCA nearly normalizes the aberrant sterols profile found in patients with CTX [4]. While initial studies with CDCA reported a clear short-term clinical improvement in most patients [2, 14], long-term studies have rather reported clinical stabilization [9, 15, 16] and, sometimes, neurological deterioration [17]. In fact, Stelten et al. emphasized that the response to treatment strongly depends on when CDCA is initiated [18]. In a cohort of 56 Dutch CTX patients treated by CDCA with a median follow-up time of 8 years (6 months to 31.5 years), they showed that neurological symptoms, assessed by the modified Rankin Scale and Expanded Disability Status Scale (EDSS) scores, disappeared in all patients who were diagnosed before the age of 24 and treated since [18]. Furthermore, treatment prevented the development of new neurological symptoms during the follow-up period. In contrast, 61% of the patients diagnosed and treated after the age of 24 showed deterioration of the neurological symptoms, with parkinsonism as a prominent treatment-resistant feature [18]. A similar observation was made in a cohort of 43 CTX patients in the USA [19].

Electrophysiological studies using transcranial magnetic stimulation or electromyoneurography have highlighted that the effect of therapy may depend on the extent of irreversible structural damage to axons [15, 20]. Few studies have evaluated the effect of CDCA on quantitative brain structural metrics in CTX [21, 22]. In a series of 14 French patients with CTX treated by CDCA over a mean period of 5 years, we observed a significant clinical improvement on the EDSS and the Scale for the Assessment and Rating of Ataxia in patients up to 25 years old, whose treatment was initiated less than 15 years after the onset of neurological symptoms [23]. Eleven patients presented with a length-dependent peripheral neuropathy. Electrophysiological parameters improved significantly under CDCA [23]. On neuroimaging, volumetric analyses in a subset of patients showed no overt volume loss on CDCA. Moreover, diffusion-weighted imaging showed improved fiber integrity of the pontocerebellar connections and the internal capsule with CDCA [23].

Genetic Counseling

CTX is an autosomal-recessive disease. Parents are usually heterozygous carriers of one *CYP27A1* pathogenic variant and are asymptomatic. At conception, each sibling of a CTX patient has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Presymptomatic testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if both *CYP27A1* pathogenic variants in the family are known. Because CTX is treatable, and even more so when treatment is initiated in the early stage of the disease, it is important to advocate for testing of siblings from CTX patients, in line with guidelines for presymptomatic testing, especially in minors [24].

Movement Disorders in Cerebrotendinous Xanthomatosis

A broad range of movement disorders can be observed in CTX. As with other metabolic diseases, movement disorders are rarely "pure" but rather mixed, and are often combined with various motor disorders. Among these, cerebellar and pyramidal features are the most frequent. The spectrum of CTX-related movement disorders consists of parkinsonism, dystonia, myoclonus, and tremor. Neurologists should be aware of these possible manifestations of CTX, as movement disorders may be the presenting complaint of a patient with CTX seeking medical attention for the first time. In such cases, movement disorders represent the leading complaint: clues from the past medical history along with neurological and systemic findings from clinical examination usually raise the probability of CTX.

Cerebellar and Pyramidal Syndrome

Cerebellar and pyramidal involvement are frequent in CTX and often start between the second and fourth decade so that the majority of patients have cerebellar and pyramidal features before age 40 [6, 13, 15, 25].

Gait ataxia is the most frequent cerebellar manifestation and is often associated with ataxic dysarthria or dysmetria. Rarely, a low-frequency kinetic tremor of

cerebellar origin may also be present. Cerebellar abnormalities seen on MRI may include cerebellar atrophy as well as abnormalities of the dentate nucleus and surrounding white matter [26]. Interestingly, the clinical expression of ataxia is linked to the presence and extent of these abnormalities. Typically, corticospinal tract dysfunction results in a slowly progressive spastic paraparesis, with spasticity predominating over weakness. Pyramidal features likely reflect white matter lesions of the spinal cord [27]. In such cases, increased central motor conduction times on neurophysiological examination and abnormal signal intensity of the lateral corticospinal tracts on spine MRI can be detected [15, 27]. Occasionally, patients have a spinal form of CTX with an isolated and chronic myelopathy [27, 28]. Early treatment with CDCA may prevent worsening of cerebellar and corticospinal tract manifestations or even allow some degree of recovery [2, 23]. In addition to this treatment, management of spasticity and cerebellar manifestations in CTX is symptomatic. The treatment approach should involve a proactive and goal-centered multidisciplinary strategy [29, 30]. Rehabilitation, particularly physical and occupational therapies, are the mainstay of treatment. Oral anti-spasticity medications are usually of limited benefit. Targeted botulinum toxin injections can be useful in patients with disabling spasticity. Intrathecal baclofen can relieve disability in patients with severe spasticity.

Parkinsonism

CTX patients can occasionally develop parkinsonism late in the disease course, usually after the age of 40 [31, 32]. The typical picture is one of a progressive, asymmetric, akinetic–rigid parkinsonism. Resting tremor is sometimes present. The presence of additional neurological manifestations early in the course of parkinsonism, such as ataxia, spasticity, or cognitive deterioration, suggest atypical parkinsonism and can be a helpful clue. A case of pure corticobasal syndrome with no additional clinical features of CTX has previously been reported [31]. Findings from dopamine transporter imaging have consistently shown features of presynaptic dysfunction in patients with CTX-related parkinsonism [31, 32]. A reduced homovanilic acid level has also been found in the CSF of such patients (n = 3/3) [32]. Together, these findings suggest substantia nigra degeneration or dysfunction as an important pathogenic mechanism. Rarely, signal changes in the subtantia nigra or striatum have been reported in patients with parkinsonism. Levodopa responsiveness and early motor fluctuations have been observed in some patients, which supports the presynaptic denervation hypothesis [31–33]. However, the effect of levodopa is usually mild or transient, suggesting more diffuse lesions or dysfunction and possible postsynaptic dysfunction. Unlike most neurological manifestations of CTX, parkinsonism usually has a poor response to CDCA, even when treated early. Two possible explanations may account for this. First, parkinsonism may reflect irreversible lesions (neuronal loss) so that restoring the metabolism has no effect on these symptoms. Second, pathogenic mechanisms unrelated to cholestanol accumulation may be involved in CTX-related parkinsonism.

Dystonia and Myoclonus

Dystonia and myoclonus are rare manifestations of CTX. They are usually mild to moderate and therefore do not represent the most disabling features of the disease. Dystonia, when present, is usually focal or multifocal and mainly affects the limbs or craniofacial area [32]. It can be isolated or mixed with subcortical myoclonus, resulting in myoclonic dystonia [34]. The movement disorder can also appear as an isolated distal myoclonus either because the myoclonus is genuinely isolated or because upper limb dystonia (particularly limb dystonia) is usually restricted to mild abnormal postures and may go unnoticed. In CTX patients, there is little evidence for lesions or dysfunction within the striato-pallido-thalamo-cortical network, an area frequently involved in dystonia. It has been speculated that, in these patients, dystonia and subcortical myoclonus are mainly linked to the lesions of the cerebellum (particularly the dentate nucleus), with the subsequent dysfunction of cerebello-thalamo-cortical pathways. A similar pathogenesis has been described in myoclonus–dystonia due to a mutation in the *SGCE* gene, another disorder with dystonia and subcortical myoclonus [35]. Symptomatic treatment of CTX-related dystonia is non-specific, and mainly involves botulinum toxin injections. Pharmacological treatments of subcortical myoclonus are usually disappointing, with a poor benefit:side effect ratio, but a few drugs can be considered including zonisamide, benzodiazepines, gabapentin, and levetiracetam [36]. To date, the effect of CDCA treatment on dystonia and myoclonus has not been determined.

Tremor

Upper limb action tremor (both postural and kinetic tremor) has rarely been reported in CTX patients. In the absence of detailed clinical and neurophysiological characterization, we can only speculate as to the nature of this tremor. The most plausible hypotheses are: (1) tremor resembling essential tremor associated with CTX-related cerebellar lesions, resulting in a similar dysfunction of the cerebello-cortical pathways as is observed in essential tremor [37]; (2) dystonic tremor in which exacerbation by actions or attempts to maintain a certain posture is frequent and the associated dystonic posture can be difficult to detect; (3) mild distal myoclonus of subcortical origin that may be mis-attributed to tremor. Taking into account the uncertainty about the exact pathogenesis, treatment is mostly based on empirical knowledge. In our experience, propranolol may help in some patients and could be considered a first-line option. Very rarely, low-frequency palatal tremor can be part of the clinical picture of CTX [38]. This reflects a disruption of the dentato-rubro-olivary circuits likely due to dentate nuclei and/or olivary lesions observed in CTX. Depending on the associated manifestations, CTX-related palatal tremor can sometimes present as a "progressive ataxia palatal tremor" (PAPT) syndrome, which has been described in other conditions and metabolic disorders with cerebellar involvement [39]. Treatment of palatal tremor is not always warranted since patients often cope with it and the tremor may sometimes disappear without any treatment. If necessary, the most efficient treatment is likely botulinum toxin injections to the levator and tensor veli palatini muscles [39]. To date, the effect of CDCA treatment on tremor has not been determined.

Conclusions

CTX is an important treatable inherited metabolic disease that is often diagnosed late. Plasma cholestanol levels are elevated and, together with low levels of bile alcohols in the plasma or urine, are usually diagnostic. Confirmation is obtained by sequencing of *CYP27A1*. While treatment with CDCA can lower cholestanol levels and can prevent progression, the effect on existing symptoms is variable.

Key Points and Clinical Pearls

- Cerebrotendinous xanthomatosis (CTX) is a treatable inherited metabolic disease.
- Measuring plasma cholestanol levels is key to reaching a diagnosis.
- Measurement of plasma cholestanol should be pursued in any child with infantile chronic diarrhea or jaundice, cataracts, a learning disability and/or autism spectrum disorder.
- Motor symptoms tend to appear later in the disease course and cerebellar and pyramidal features are the most frequent. Peripheral neuropathy is also common in adults.
- CTX-related movement disorders comprise parkinsonism, dystonia, myoclonus, and tremor, and may occasionally be the presenting complaint.
- Early treatment with chenodeoxycholic acid is critical for long-term outcomes.

Directions for Future Research

- Develop a low-cost newborn screening test.
- Increase awareness among pediatricians and neurologists that CTX is a treatable disorder.
- Perform large prospective studies to investigate predictors of outcomes in treated patients.
- Develop add-on therapies to restore cholesterol homeostasis in the nervous system.

References

1. Salen G, Shefer S, Berginer V. Biochemical abnormalities in cerebrotendinous xanthomatosis. Dev Neurosci. 1991;**13**(4–5):363–70.
2. Berginer VM, Salen G, Shefer S. Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. N Engl J Med. 1984;**311**(26):1649–52.
3. Inoue K, Kubota S, Seyama Y. Cholestanol induces apoptosis of cerebellar neuronal cells. Biochem Biophys Res Commun. 1999;**256**(1):198–203.
4. Mignarri A, Magni A, Del Puppo M, et al. Evaluation of cholesterol metabolism in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2016;**39**(1):75–83.

5. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: A comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;**9**:179.
6. Wong JC, Walsh K, Hayden D, Eichler FS. Natural history of neurological abnormalities in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2018;**41**(4):647–56.
7. Degos B, Nadjar Y, Amador Mdel M, et al. Natural history of cerebrotendinous xanthomatosis: A paediatric disease diagnosed in adulthood. Orphanet J Rare Dis. 2016;**11**:41.
8. Stelten BML, Bonnot O, Huidekoper HH, et al. Autism spectrum disorder: An early and frequent feature in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2018;**41**(4):641–6.
9. Yahalom G, Tsabari R, Molshatzki N, et al. Neurological outcome in cerebrotendinous xanthomatosis treated with chenodeoxycholic acid: Early versus late diagnosis. Clin Neuropharmacol. 2013;**36**(3):78–83.
10. Mignarri A, Gallus GN, Dotti MT, Federico A. A suspicion index for early diagnosis and treatment of cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2014;**37**(3):421–9.
11. Vaz FM, Bootsma AH, Kulik W, et al. A newborn screening method for cerebrotendinous xanthomatosis using bile alcohol glucuronides and metabolite ratios. J Lipid Res. 2017;**58**(5):1002–7.
12. DeBarber AE, Kalfon L, Fedida A, et al. Newborn screening for cerebrotendinous xanthomatosis is the solution for early identification and treatment. J Lipid Res. 2018;**59**(11):2214–22.
13. Salen G, Steiner RD. Epidemiology, diagnosis, and treatment of cerebrotendinous xanthomatosis (CTX). J Inherit Metab Dis. 2017;**40**(6):771–81.
14. van Heijst AF, Verrips A, Wevers RA, et al. Treatment and follow-up of children with cerebrotendinous xanthomatosis. Eur J Pediatr. 1998;**157**(4):313–6.
15. Mignarri A, Rossi S, Ballerini M, et al. Clinical relevance and neurophysiological correlates of spasticity in cerebrotendinous xanthomatosis. J Neurol. 2011;**258**(5):783–90.
16. Mondelli M, Sicurelli F, Scarpini C, Dotti MT, Federico A. Cerebrotendinous xanthomatosis: 11-year treatment with chenodeoxycholic acid in five patients. An electrophysiological study. J Neurol Sci. 2001;**190** (1–2):29–33.
17. Pilo B, de Blas G, Sobrido MJ, et al. Neurophysiological study in cerebrotendinous xanthomatosis. Muscle Nerve. 2011;**43**(4):531–6.
18. Stelten BML, Huidekoper HH, van de Warrenburg BPC, et al. Long-term treatment effect in cerebrotendinous xanthomatosis depends on age at treatment start. Neurology. 2019;**92**(2):e83–e95.
19. Duell PB, Salen G, Eichler FS, et al. Diagnosis, treatment, and clinical outcomes in 43 cases with cerebrotendinous xanthomatosis. J Clin Lipidol. 2018;**12**(5):1169–78.
20. Ginanneschi F, Mignarri A, Mondelli M, et al. Polyneuropathy in cerebrotendinous xanthomatosis and response to treatment with chenodeoxycholic acid. J Neurol. 2013;**260**(1):268–74.
21. Catarino CB, Vollmar C, Kupper C, et al. Brain diffusion tensor imaging changes in cerebrotendinous xanthomatosis reversed with treatment. J Neurol. 2018;**265**(2):388–93.
22. Guerrera S, Stromillo ML, Mignarri A, et al. Clinical relevance of brain volume changes in patients with cerebrotendinous xanthomatosis. J Neurol Neurosurg Psychiatry. 2010;**81**(11):1189–93.
23. Amador MDM, Masingue M, Debs R, et al. Treatment with chenodeoxycholic acid in cerebrotendinous xanthomatosis: Clinical, neurophysiological, and quantitative brain structural outcomes. J Inherit Metab Dis. 2018;**41**(5):799–807.
24. Borry P, Evers-Kiebooms G, Cornel MC, et al. Genetic testing in asymptomatic minors: Background considerations towards ESHG recommendations. Eur J Hum Genet. 2009;**17**(6):711–9.
25. Verrips A, Hoefsloot LH, Steenbergen GC, et al. Clinical and molecular genetic characteristics of patients with cerebrotendinous xanthomatosis. Brain. 2000;**123** (Pt 5):908–19.
26. Mignarri A, Dotti MT, Federico A, et al. The spectrum of magnetic resonance findings in cerebrotendinous xanthomatosis: Redefinition and evidence of new markers of disease progression. J Neurol. 2017;**264** (5):862–74.
27. Verrips A, Nijeholt GJ, Barkhof F, et al. Spinal xanthomatosis: A variant of cerebrotendinous xanthomatosis. Brain. 1999;**122** (Pt 8):1589–95.
28. Abe R, Sekijima Y, Kinoshita T, et al. Spinal form cerebrotendinous xanthomatosis patient with long spinal cord lesion. J Spinal Cord Med. 2016;**39** (6):726–9.
29. Fonteyn EM, Keus SH, Verstappen CC, et al. The effectiveness of allied health care in patients with ataxia: A systematic review. J Neurol. 2014;**261** (2):251–8.
30. Nair KP, Marsden J. The management of spasticity in adults. BMJ. 2014;**349**:g4737.
31. Rubio-Agusti I, Kojovic M, Edwards MJ, et al. Atypical parkinsonism and cerebrotendinous xanthomatosis: Report of a family with corticobasal syndrome and a literature review. Mov Disord. 2012;**27**(14):1769–74.

32. Stelten BML, van de Warrenburg BPC, Wevers RA, Verrips A. Movement disorders in cerebrotendinous xanthomatosis. Parkinsonism Relat Disord. 2019;**58**:12–6.

33. Grandas F, Martin-Moro M, Garcia-Munozguren S, Anaya F. Early-onset parkinsonism in cerebrotendinous xanthomatosis. Mov Disord. 2002;**17**(6):1396–7.

34. Lagarde J, Roze E, Apartis E, et al. Myoclonus and dystonia in cerebrotendinous xanthomatosis. Mov Disord. 2012;**27**(14):1805–10.

35. Roze E, Lang AE, Vidailhet M. Myoclonus–dystonia: Classification, phenomenology, pathogenesis, and treatment. Curr Opin Neurol. 2018;**31**(4):484–90.

36. Hainque E, Vidailhet M, Cozic N, et al. A randomized, controlled, double-blind, crossover trial of zonisamide in myoclonus–dystonia. Neurology. 2016;**86**(18):1729–35.

37. Gallea C, Popa T, Garcia-Lorenzo D, et al. Intrinsic signature of essential tremor in the cerebello-frontal network. Brain. 2015;**138**(Pt 10):2920–33.

38. Rossi M, Cesarini M, Gatto EM, Cammarota A, Merello M. A treatable rare cause of progressive ataxia and palatal tremor. Tremor Other Hyperkinet Mov (NY). 2018;**8**:538.

39. Mongin M, Delorme C, Lenglet T, et al. Progressive ataxia and palatal tremor: Think about *POLG* mutations. Tremor Other Hyperkinet Mov (NY). 2016;**6**:382.

Chapter

27

Purine Metabolism Defects: The Movement Disorder of Lesch–Nyhan Disease

Jasper E. Visser and Hyder A. Jinnah

Purine Metabolism

Purine metabolism encompasses the metabolic pathways involved in the synthesis, interconversion, salvage, and degradation of purine-based nucleosides and nucleotides. These metabolic pathways are involved in many essential cellular processes, including energy transfer, oxidative phosphorylation, synthesis of DNA and RNA, and signal transduction. A nucleoside is a nitrogenous base linked to a 5-carbon sugar (either ribose or deoxyribose). For purines, this nitrogenous base is either adenine, guanine, or hypoxanthine. When nucleosides are covalently linked to one or more phosphate groups, they are referred to as nucleotides.

In the purine biosynthetic ("de novo") pathway, the high-energy compound phosphoribosyl pyrophosphate (PRPP) is first converted to inosine monophosphate (IMP) in 10 steps (Figure 27.1). Subsequently, IMP can be interconverted to either adenosine monophosphate (AMP) or guanosine monophosphate (GMP). These ribonucleotide monophosphates may be converted to their di- and triphosphate counterparts by nucleoside mono- and diphosphate kinase, to form adenosine diphosphate (ADP) and adenosine triphosphate (ATP) as well as guanosine diphosphate (GDP) and guanosine triphosphate (GTP), respectively. The deoxyribonucleotides, i.e. deoxyadenosine diphosphate (dADP) and deoxyguanosine diphosphate (dGDP), can be formed by converting the ribose of ADP and GDP to deoxyribose. This reaction is catalyzed by the enzyme ribonucleotide reductase.

In purine catabolism, the nucleotides are hydrolyzed and phosphorolyzed to their nucleosides, and ultimately converted to xanthine, which is oxidized to uric acid (Figure 27.1). For salvaging purine bases, two phosphoribosyltransferases catalyze the transfer of a ribose-5-phosphate from PRPP to the base, yielding the respective nucleotide. As such, adenine phosphoribosyltransferase (APRT) salvages adenine to AMP, while hypoxanthine–guanine phosphoribosyltransferase (HGPRT) regenerates IMP and GMP from hypoxanthine and guanine, respectively (Figure 27.1). In humans, adenine is only produced in small amounts, as AMP and adenosine are catabolized mainly through interconversion to IMP first. Therefore, HGPRT is also important in the recycling of adenine nucleosides.

Purine Functions

Purines are key players in multiple fundamental cellular processes that are ubiquitously present in cells of the human body. For example, the adenine-based nucleotide ATP is the principal cellular carrier of free energy and is essential for muscle contraction and other cellular movements, active transport of molecules, and biosynthesis of (macro-) molecules from simple precursors [1]. It should be noted, however, that in addition to being synthesized and salvaged through the metabolic pathways described above, ATP is primarily synthesized during cellular respiration. Second, the purinergic ribonucleotides (i.e. ATP and GTP) and deoxyribonucleotides (i.e. dATP and dGTP) are two of the four substrates for RNA and DNA synthesis, respectively. Third, GTP and GDP are essential in signal transduction, particularly pathways involving G proteins coupled with a cell-membrane-bound receptor [2]. In this mechanism, binding of a ligand to the G-protein-coupled receptor complex triggers an allosteric change in the G protein, causing a bound GDP to be replaced by GTP. Subsequently, the GTP activates the alpha subunit of the G protein, causing it to dissociate from the G protein and act as a downstream effector. A final generic function of purines has been proposed for the purine breakdown product, uric acid, which may act as an endogenous antioxidant.

Obviously, these universal purine functions are important for the nervous system as well. For example, the brain's energy demand is disproportionally

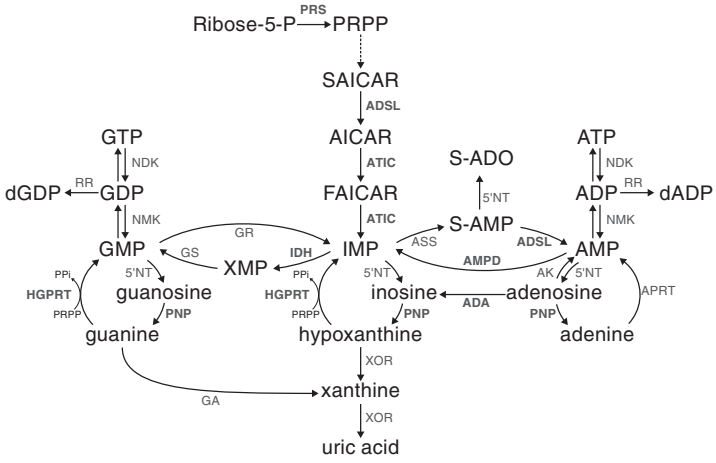

Figure 27.1 Overview of purine metabolism. Abbreviations: 5′NT, 5′-nucleotidase; AICAR, aminoimidazolecarboxamide ribotide; ADA, adenosine deaminase; AK, adenosine kinase; ADP, adenosine diphosphate; ADSL, adenylosuccinate lyase; AMP, adenosine monophosphate (or adenylic acid); AMPD, adenylate deaminase; AMPRT, amidophosphoribosyltransferase; APRT, adenine phosphoribosyltransferase; ASS, adenylosuccinate synthetase; ATIC, AICAR transformylase–IMP cyclohydrolase; ATP, adenosine triphosphate; FAICAR, 5-formamidoimidazole-4-carboxamide ribotide; GA, guanase; GDP, guanosine diphosphate; GMP, guanosine monophosphate (or guanylic acid) ; GR, GMP reductase; GS, GMP synthase; GTP, guanosine triphosphate; HGPRT, hypoxanthine–guanine phosphoribosyltransferase; IDH, IMP dehydrogenase; IMP, inosine monophosphate (or inosinic acid); NDK, nucleoside diphosphate kinase; NMK, nucleoside monophosphate kinase; PPi, inorganic pyrophosphate; PRPP, phosphoribosyl pyrophosphate; PRS, PRPP synthetase; RR, ribonucleotide reductase; SAICAR, succinyl-aminoimidazolecarboxamide ribotide; S-AMP, succinyl-AMP or adenylosuccinate; XMP, xanthine monophosphate or xanthylic acid; XOR, xanthine oxidoreductase.

high, and therefore ATP consumption is large [3, 4]. In addition, many different G-protein-coupled receptors regulate synaptic communication, and the antioxidant uric acid may be relevant in brain damage. But in addition to these more common functions, purines play also very specific roles in the nervous system, as adenine nucleotides and nucleosides mediate intercellular signaling [5]. As such, ATP has been identified as a co-neurotransmitter in both sympathetic and parasympathetic nerves. Moreover, multiple purinergic receptor subtypes are widely distributed throughout the central nervous system, both in neurons and glia. Four G-protein-coupled receptors for adenosine have been recognized, as well as multiple ATP receptors that include both classic cationic ligand-operated channels for Na^+, K^+, and Ca^{2+} and G-protein-coupled receptors. Over the last decades, it has become clear that these purinergic signaling pathways are involved in many functional aspects of the nervous system, including the interaction between neuronal and glial networks, neural development and plasticity, regeneration, as well as specialized sensory mechanisms in the retina, inner ear, olfactory and taste system, and in pain transmission [5]. Consequently, purinergic pathways have been associated with multiple aspects of behavior, including feeding, locomotion, sleep, mood, and motivation.

Neurological Phenotypes in Disorders of Purine Metabolism

Enzyme defects in purine metabolism are known to be associated with clinical disorders that often involve neurological dysfunction. However, there does not appear to be a general neurological phenotype associated with purine disorders, as – depending on the specific enzyme that is deficient, and sometimes also on residual enzyme activity – both central and peripheral nervous systems may be involved, or muscle function, to a variable degree. Perhaps the most particular clinical phenotype associated with a purine disorder is Lesch–Nyhan disease (LND). LND patients suffer from a movement disorder dominated by dystonia, specific cognitive deficits, and behavioral abnormalities including self-injury. LND is caused by a deficiency of the purine salvage enzyme HGPRT due to a mutation in the *HPRT1* gene. *HPRT1* was among the first genes to be cloned for any human disease, and it is one of the most intensively studied loci in human genetics. Over the last decades, it has become apparent that the characteristic motor and behavioral abnormalities in LND are due to dysfunction of specific brain circuitry, associated with abnormal development of the brain's dopamine system. The resultant complex clinical phenotype of LND often imposes a challenge on clinical management.

Table 27.1 Monogenetic disorders of purine metabolism with neurological involvement.

Primary defect	Key metabolic effects	Key neurological symptoms	Other symptoms
PRPP synthetase (PRS) deficiency	Uric acid ↓ Hypoxanthine ↓	Progressive hearing impairment in X-linked deafness 1 (DFNX1) Peripheral neuropathy and sensorineural hearing loss in X-linked Charcot–Marie–Tooth inherited neuropathy 5 (CMTX5) Developmental delay/intellectual disability, hypotonia, ataxia, hearing impairment, and optic atrophy in Arts syndrome	Recurrent respiratory infections in Arts syndrome
PRPP synthetase (PRS) superactivity	Uric acid ↑	Developmental delay/intellectual disability, hypotonia, and sensorineural deafness	Gout, urolithiasis, nephropathy, urinary tract calculi, and gouty arthritis
Adenylosuccinate lyase (ADSL) deficiency	Succinyladenosine ↑ SAICA-riboside ↑	Microcephaly, developmental delay/intellectual disability, epilepsy, autistic features, hypotonia	Secondary feeding problems
AICAR transformylase–IMP cyclohydrolase (ATIC) deficiency	AICAR ↑ AICA-riboside ↑	Psychomotor delay, congenital blindness, epilepsy	Dysmorphic features
Deoxyguanosine kinase (dGK) deficiency		Nystagmus, cerebral atrophy, microcephaly, hypotonia	Liver dysfunction
Myoadenylate deaminase (mAMPD) deficiency	Absent NH_3 production in ischemic forearm exercise test	Myalgia, muscle cramps, exercise intolerance; often asymptomatic	
Adenosine deaminase (ADA) deficiency	Adenosine ↑ Deoxyadenosine ↑	Neurobehavioral difficulties including attention deficits, hyperactivity, aggression and social problems, as well as sensorineural deafness	Severe combined immunodeficiency disease (SCID)
Purine nucleoside phosphorylase (PNP) deficiency	Uric acid ↓ (Deoxy)inosine ↑ (Deoxy)guanosine ↑	Variable phenotype, ranging from severe psychomotor retardation to mild motor or cognitive abnormalities	Severe deficiency of cellular immunity
Hypoxanthine guanine phosphoribosyltransferase (HGPRT) deficiency	Uric acid ↑	Dystonia, cognitive impairments, self-injury	Gout, urolithiasis nephropathy, urinary tract calculi, and gouty arthritis

In this section, the other monogenetic purinergic disorders where neurological manifestations are part of the clinical phenotype, are briefly summarized first (Table 27.1). Several of these disorders have been reviewed more extensively elsewhere [6–8]. In the following sections, the clinical spectrum, current understanding of the pathogenesis, clinical diagnosis and work-up, as well as possible treatment strategies of HGPRT deficiency, are discussed in more detail.

Phosphoribosyl Pyrophosphate Synthase 1 Deficiency and Superactivity

PRS-1 (EC 2.7.6.1), one of three PRPP synthetases in humans, is encoded by the *PRPS1* gene. PRS-1 catalyzes the first step of nucleotide synthesis, i.e. the formation of PRPP from ATP and ribose-5-phosphate.

Deficiency and superactivity of PRS-1 may result in different clinical syndromes that appear to depend on residual enzyme activity, with an X-linked recessive inheritance [9]. Overall, the mutations resulting in the severest symptoms are predicted to have the most impact on the protein structure. Mutations in the *PRPS1* gene that lead to a complete absence of PRS-1 activity have been linked with Arts syndrome, characterized by developmental delay, intellectual disability, early-onset hypotonia, ataxia, hearing impairment, and optic atrophy. In addition, *PRPS1* mutations that cause a partial reduction in PRS-1 activity have been linked with X-linked sensorineural

deafness (DFNX1) and X-linked recessive Charcot–Marie–Tooth disease-5 (CMTX5). DFNX1 patients have mild to moderate hearing impairment, or prelingual-onset hearing loss. CMTX5 patients have peripheral sensorimotor neuropathy, sensorineural hearing loss and optic neuropathy. Finally, mutations in the *PRPS1* gene that *increase* the activity of PRS-1, due to the lack of regulatory control, lead to hyperuricemia and sensorineural hearing loss, with or without intellectual disability to varying degrees.

It has been hypothesized that the clinical features due to *PRPS1* mutations primarily result from reduced levels of GTP and possibly other purine nucleotides including ATP. However, the neurological manifestations linked with PRS may result from, perhaps additional, alterations in non-purine pathways, as PRPP is an important cofactor in pyrimidine and pyridine nucleotide metabolism as well.

Adenylosuccinate Lyase Deficiency

ADSL (EC 4.3.2.2) deficiency, with autosomal-recessive inheritance, is caused by a mutation in the *ADSL* gene that often causes enzyme instability [10]. ADSL catalyzes two steps in the purine biosynthetic pathway, as it converts succinyl-aminoimidazolecarboxamide ribotide (SAICAR) into aminoimidazolecarboxamide ribotide (AICAR), as well as adenylosuccinate (S-AMP) into AMP (Figure 27.1). The metabolic hallmark of ADSL deficiency is the accumulation of the succinyl purines SAICA-riboside and succinyladenosine (S-Ado) in the cerebrospinal fluid and urine, i.e. the dephosphorylated substrates of the enzyme.

The clinical presentations of ADSL deficiency are diverse [7], and their severity tends to correlate with residual activity. Patients may have intrauterine growth impairment, microcephaly, developmental delay, intellectual disability, epilepsy, autistic features, hypotonia, feeding problems, and occasional growth retardation with muscle wasting. Rarely, patients are less intellectually impaired and may display only delayed motor development with hypotonia, high-functioning autism with epilepsy, or a behavioral phenotype resembling Angelman syndrome. The prognosis of ADSL-deficient patients is variable, ranging from early death to satisfactory performance in a protected environment.

The exact mechanism by which ADSL deficiency leads to neurobehavioral dysfunction remains uncertain, although it has been hypothesized that neurotoxic effects of accumulating succinyl purines are an important etiological factor.

Myoadenylate Deaminase Deficiency

In humans, three genes have been identified that encode AMP deaminase (AMPD, EC 3.5.4.6) that catalyzes the irreversible deamination of AMP to IMP, freeing ammonia (NH_3). Deficiency of myoadenylate deaminase (mAMPD) is an inherited autosomal-recessive disorder caused by mutations in the *AMPD1* gene, the isoform predominantly involved in skeletal muscle purine metabolism [11].

The vast majority of individuals with mAMPD deficiency are asymptomatic, but non-progressive exercise intolerance accompanied by myalgia and cramping that begins in late childhood or adulthood may occur [7]. Serum creatine kinase can be increased, sometimes only after exercise. Electromyography may be normal. Mutations in the *AMPD1* gene may coincide with other genetic metabolic deficiencies, having a synergistic effect on myopathic symptoms.

The myopathic symptoms are thought to arise from interruption of the purine nucleotide cycle between AMP and IMP. During exercise, the flux through this metabolic cycle is increased in skeletal muscle. mAMPD deficiency is thought to disturb one or more of the proposed functions of this cycle, including maintaining the myocytic adenylate energy charge, enhancing the glycolysis rate, providing citric acid cycle intermediates, and preserving the IMP pool to replenish ATP during recovery [12].

Deficiency of mAMPD is often diagnosed with a forearm lactate-ammonia blood test, in which skeletal muscle does not accumulate NH_3 as occurs in normal subjects. Additionally, histochemical staining of biopsied skeletal muscle, genotyping, and enzyme assay can also be used for diagnosis or confirmation.

There is currently no reliable effective treatment for symptomatic mAMPD deficiency. Avoidance of triggers such as excessive exercise is generally recommended.

Other Purine Enzyme Deficiencies with Neurological Sequelae

Several other, often very rare, purine enzyme deficiencies have been reported, for which the neurological manifestations are less well characterized (Table 27.1).

First, purine nucleoside phosphorylase (PNP, EC 2.4.2.1) deficiency is a rare autosomal-recessive immunodeficiency disorder, with decreased T-cell function. Approximately half of the patients exhibit neurological features with a broad range of severity,

Table 27.2 Spectrum of disease in HGPRT deficiency, in relation to HGPRT activity*

	HRH	HND	LND
Clinical features:			
Hyperuricemia	Yes	Yes	Yes
Motor disorder	None	Variable degree	Yes
Cognitive problems	None	Variable degree	Yes
Self-injury	None	None	Yes
Mean HGPRT activity	12%	7%	<1%

* Abbreviations: HND, HGPRT-related neurological disease; HRH, HGPRT-related hyperuricemia; LND Lesch–Nyhan disease.

ranging from severe psychomotor retardation to mild motor or cognitive abnormalities.

Second, adenosine deaminase (ADA, EC 3.5.4.4) deficiency most often presents with severe combined immunodeficiency, with lethal infections in infancy or early childhood. Children who survive may develop neurobehavioral difficulties such as attention deficits, hyperactivity, aggression and social problems, as well as bilateral sensorineural hearing loss.

Third, deficiency of the mitochondrial enzyme deoxyguanosine kinase (DGK, EC 2.7.1.113) causes a severe form of mitochondrial DNA depletion. Patients typically present with liver failure, and have severe psychomotor retardation with nystagmus, cerebral atrophy, microcephaly, and hypotonia. Fatal multi-organ system failure is common in the first year of life.

Fourth, AICAR transformylase (EC 2.1.2.3) and IMP cyclohydrolase (EC 3.5.4.10) enzymes are present in one protein (ATIC). ATIC deficiency is associated with intellectual deficiency, epilepsy, dysmorphic features, and congenital blindness. The enzyme's substrate AICAR and its dephosphorylated form, AICA-riboside, are increased in patients' cells and urine, respectively.

Finally, mutations in the gene encoding IMP dehydrogenase (IDH, EC 1.1.1.205) have been linked with retinitis pigmentosa type 10 and some cases of Leber congenital amaurosis.

The Clinical Spectrum of the HGPRT-Deficient Phenotype

HGPRT deficiency is associated with a phenotypic continuum (Table 27.2). Classic LND patients exhibit the full phenotype with uric acid overproduction, neurological, cognitive, and behavioral features. Some patients display a Lesch–Nyhan variant (LNV) phenotype characterized by overproduction of uric acid, with or without neurological dysfunction, but no self-injurious behavior (Table 27.2). Although the eponym Kelley–Seegmiller syndrome has been applied to LNV, this term is probably best avoided as its definition is unclear and it suggests another disease entity, but is merely a variant of LND.

In HGPRT deficiency, the overproduction of uric acid results in hyperuricemia and an increased urinary uric acid excretion [13]. The hyperuricemia may cause subsequent problems, as beyond the limit of solubility, uric acid may precipitate. In the urogenital system, this may result in nephrolithiasis with subsequent urinary obstruction and renal failure. In addition, uric acid crystal deposition in the joints can cause gouty arthritis, and in subcutaneous tissues it forms tophi.

The least severe form of HGPRT deficiency is characterized by the overproduction of uric acid and associated problems only, i.e. without clinically overt neurological or behavioral abnormalities. This mild phenotype is most often designated as HGPRT-related hyperuricemia (HRH, Table 27.2) [14]. It should be noted that these patients often have minor motor clumsiness or mild cognitive difficulties that may go unnoticed without specific neurological or psychometric testing.

Movement Disorder in HGPRT Deficiency

The neurobehavioral phenotype of classic LND includes a characteristic motor syndrome with only minor phenotypic variability. The most prominent feature of the motor syndrome, universally present in all patients, is a generalized action dystonia (Figure 27.2) [15, 16]. Dystonia of the upper limbs usually prevents their functional use for activities of daily living, and patients use wheelchairs because lower limb dysfunction prohibits

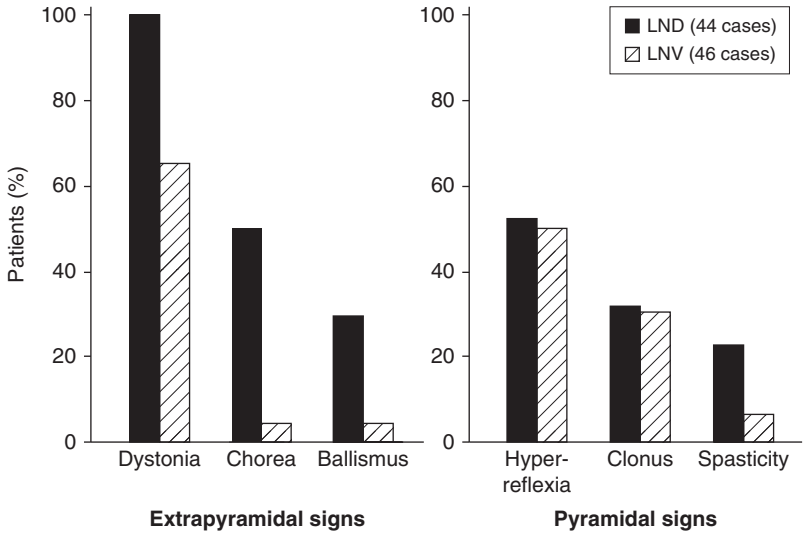

Figure 27.2 The movement disorder associated with HGPRT deficiency. The prevalence of both extrapyramidal and pyramidal signs in patients with classic LND and those with partial enzyme defects (LNV) are expressed as a percentage of the patient population studied. Data from Jinnah HA, Ceballos-Picot I, Torres RJ, Visser JE, Schretlen DJ, Verdu A, et al. Attenuated variants of Lesch-Nyhan disease. Brain. 2010;133(Pt 3):671–89; and from Jinnah HA, Visser JE, Harris JC, Verdu A, Larovere L, Ceballos-Picot I, et al. Delineation of the motor disorder of Lesch–Nyhan disease. Brain. 2006;129(Pt 5):1201–17.

walking or standing unassisted. Some patients have severe opisthotonus or truncal arching. Although dystonia is universal and always the most severe extrapyramidal disorder in LND, many patients also have other extrapyramidal movement disorders, including choreoathetosis or ballismus (Figure 27.2). In virtually all patients, these motor features are superimposed on hypotonia when fully relaxed [15]. Corticospinal signs may sometimes occur, such as pathological reflexes or spasticity, but they are typically mild and often limited to the legs.

If hyperuricemia exists along with some degree of neurological dysfunction and/or cognitive deficits, hence without self-injury, patients are described as having HGPRT-related neurological disease (HND, Table 27.2) [14]. The motor features of HND can vary among these partial phenotypes, from mild clumsiness to severe handicap similar to classic LND.

Non-Motor Features in HGPRT Deficiency

Most LND patients also have a mild or moderate intellectual disability. Reliable cognitive testing is challenging in this population, due to the motor handicap, behavioral disorder with variable cooperation, and usually limited education. With these challenges in mind, IQ scores have been estimated to fall in the 60–80 range. The most affected domains are attention and mental flexibility [17, 18]. Significant generalized cognitive impairment is not an invariable characteristic of LND, and severe intellectual deficiency is uncommon.

In HND patients, some cognitive impairment may be present that is usually less severe than in classic LND patients. The majority of HND patients have some type of learning impairment, and difficulties with attention – similar to LND – is usually the most prominent problem.

The neurobehavioral phenotype of LND includes recurrent severe self-injurious behavior, such as self-biting, self-hitting, eye poking, and others [19, 20]. This behavior is universal in LND, and considered a hallmark of the disease (Figure 27.3). Self-injurious behavior usually emerges before 4 years of age, but may not be present before the second decade of life. In addition to self-injury, patients may exhibit other difficult behaviors, such as spitting at or hitting others, use of foul language, or oppositional defiant behavior. The nature of these disinhibited behaviors is enigmatic, but appears different from purposeful aggression, as patients often apologize afterwards.

By definition, HND patients do not exhibit self-injurious behavior. However, they may have impulsivity and other undesirable behaviors.

Pathogenesis of LND

Genetic Background

LND was the first neurogenetic disorder for which the responsible gene, *HPRT1,* located in the q26-27 region on the X chromosome, was identified [21]. Since then, many different *HPRT1* mutations causing disease have been reported, and these may appear throughout

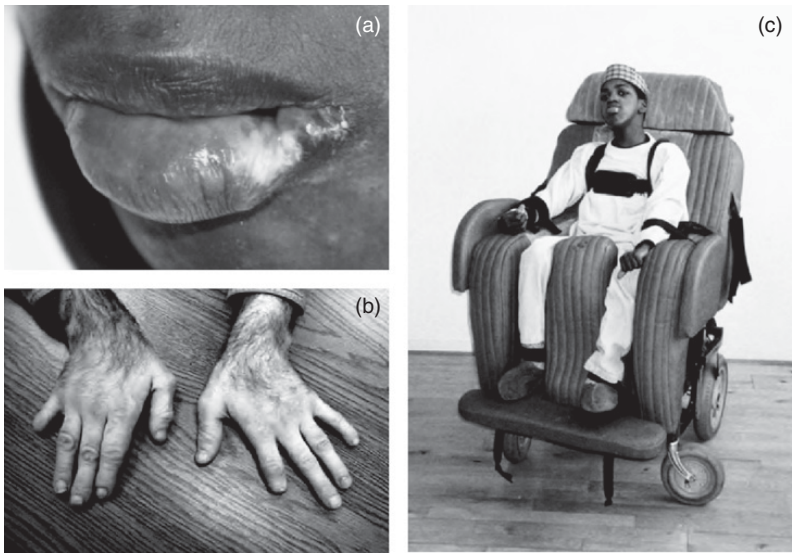

Figure 27.3 Self-injury in LND. Characteristic self-inflicted tissue damage to the lip (a) and the fingers (b) in LND patients. The challenging management of self-injury in LND requires covering any hard surfaces or sharp parts of the wheelchair with soft padding, in combination with protective restraints to prevent hitting or biting. (c) Reproduced with permission from Visser JE, Bar PR, Jinnah HA. Lesch–Nyhan disease and the basal ganglia. Brain Res Brain Res Rev. 2000;32(2–3):449–75.

the gene. The mutations are heterogeneous, including missense, nonsense and splicing mutations, deletions, insertions, partial duplications, non-coding regulatory mutations, and more complex changes [22]. The list of known mutations in the *HPRT1* gene is maintained at www.lesch-nyhan.org. It is generally believed that the majority of mutations occur de novo, since classic LND males do not reproduce.

Several comprehensive studies of genotype–phenotype correlations suggest that the most relevant factor for disease severity is the effect of the *HPRT1* mutation on the residual HGPRT enzyme activity, rather than specific mutation types or sites [22, 23]. As such, less severe clinical manifestations result from mutations predicted to allow some degree of residual enzyme function. These less severely affected patients with HGPRT deficiency typically have the LNV (i.e. HRH or HND) phenotype, rather than the more severe classic LND phenotype.

Biochemical Background

HGPRT drives the recycling of hypoxanthine and guanine into their respective nucleotide pools (Figure 27.1), using the high-energy phosphate bonds of PRPP to catalyze the reaction. HGPRT pyrophosphorylates hypoxanthine into IMP, the central precursor for both adenine and guanine nucleotides, and also guanine directly into GMP. In the absence of HGPRT, hypoxanthine and guanine are degraded to uric acid. The reduced purine salvage, together with an accompanying activation of de novo purine synthesis, causes the uric acid overproduction. The subsequent hyperuricemia, if untreated, is the cause of the nephrolithiasis, gouty arthritis and tophi that is seen in HGPRT deficiency, as explained above.

Neuropathological Findings

Overall, the most frequent abnormality among imaging and autopsy studies that has been reported is a relatively small reduction in brain volume, that may escape notice in routine studies. Quantitative MRI studies showed a 17% reduction of total cerebral volume and 12–34% reduction in volumes of the basal ganglia [24]. In another cross-sectional voxel-based morphometric MRI study, LND patients showed a 17% volume reduction in gray matter compared to controls, particularly in the basal ganglia, frontotemporal, and limbic regions [25]. Moreover, the white matter volume was reduced in LND by 26%, particularly frontal white matter adjoining limbic and temporal regions and the motor cortex [26].

Autopsy studies have not revealed any signs suggestive of a degenerative process or other consistent abnormalities in any brain region. However, neurons of the substantia nigra from the LND cases showed reduced melanization and reduced immunoreactivity for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis [27]. These findings suggest an important relationship between purine recycling

pathways and the neurochemical integrity of the dopamine neurons.

HGPRT and Dopamine

Biochemical and positron emission tomography (PET) studies have provided further evidence for the association between HGPRT deficiency and abnormalities of basal ganglia dopamine systems. First, postmortem biochemical studies of five LND brains have documented a 60–90% reduction of dopamine and its metabolites in the basal ganglia [28, 29]. Dopamine was not significantly reduced in the midbrain, consistent with the preservation of midbrain dopamine neurons but with abnormal axonal projections to the basal ganglia. In addition, PET imaging studies confirmed aberrant dopaminergic fibers in the basal ganglia, showing a 60–70% reduction of the accumulation of ^{18}F-fluorodopa into monoaminergic axons in the striatum and a similar decrease in binding of ^{11}C-WIN-35428 to dopamine uptake sites on dopamine axons [30, 31]. Further evidence for a HGPRT–dopamine connection has been obtained from experimental models. Dopamine content is decreased by ~50% in the striatum of HGPRT-deficient knockout mice, without apparent morphological abnormalities in midbrain dopamine neurons [32].

Microarray techniques applied to HGPRT-deficient immortalized cell lines shed new light on a possible HGPRT–dopamine connection, by showing a disturbed expression of transcription factors involved in dopaminergic neuronal development and differentiation [33–35]. The expression of both upstream regulators of dopaminergic specification (Lmx1a, Msx1, Lmx1b) and transcription factors that allow survival (Engrailed 1/2) and maturation (Pitx3, Nurr1) of dopamine neurons were affected. These transcriptional changes were accompanied by the dysregulation of genes encoding dopamine biosynthetic enzymes and an abnormal neurite outgrowth. Such an early developmental disturbance caused by HGPRT deficiency, where midbrain dopamine neurons do not fully develop their typical phenotype, may explain the decreased dopaminergic dysfunction, in the absence of any obvious histopathology.

The exact mechanisms by which HGPRT deficiency would cause such a dopamine-specific developmental defect remain currently enigmatic, as HGPRT functions have no known relationship with dopamine metabolism. Several proposed theories to explain this HGPRT–dopamine connection have been rejected in the past [36–38]. For example, HGPRT is not concentrated only in the basal ganglia but is ubiquitously expressed in the brain. There is no evidence for metabolic toxicity due to an accumulation of uric acid, oxypurines, PRPP, or Z-nucleotides, nor is oxidative stress the explanation for the dopamine loss. A general GTP deficiency, leading to the dysfunction of widespread postsynaptic GTP-dependent G-protein second messenger systems, would not account for the demonstrated selective presynaptic dopaminergic deficit. Also, a reduced synthesis of tetrahydrobiopterin (for which GTP is essential in the first and rate-limiting step), a cofactor for dopamine synthesis, is not responsible for the dopamine loss.

It has been speculated that the effects of HGPRT-mediated hypoxanthine recycling on adenine nucleotide metabolism, e.g. the deficiency of adenosine, contributes to the dopamine dysfunction. Adenine has important signaling properties, as mentioned before, and adenosine A2A receptors are highly enriched in the basal ganglia, important for normal neural development, and they modulate glutamate and dopamine release. Also, depletion of ATP might cause brain dysfunction by loss of its neurotransmitter properties or by interfering with specific energy-dependent processes – including those during brain development. However, these hypotheses need further investigation in order to determine whether or not these mechanisms are indeed an important factor in abnormal brain development due to HGPRT deficiency. Thus, despite considerable efforts during the last decades, the specific role of HGPRT in dopamine neurons remains currently uncertain.

Pathogenesis of Neurobehavioral Features in LND

Despite the current enigmatic nature of the HGPRT–dopamine connection, the profound dopaminergic dysfunction in LND in basal ganglia pathways in combination with the current knowledge about the functional organization of the basal ganglia, may provide further hints towards the functional anatomy of the characteristic combination of motor, cognitive, and behavioral disturbances in LND.

The basal ganglia nuclei contribute to multiple, parallel, semi-segregated functional circuits that are important for motor and cognitive aspects of behavior [39]. It appears that in LND, much – if not all – of this circuitry is severely affected (Figure 27.4) [37]. More specifically, the movement disorder dominated by

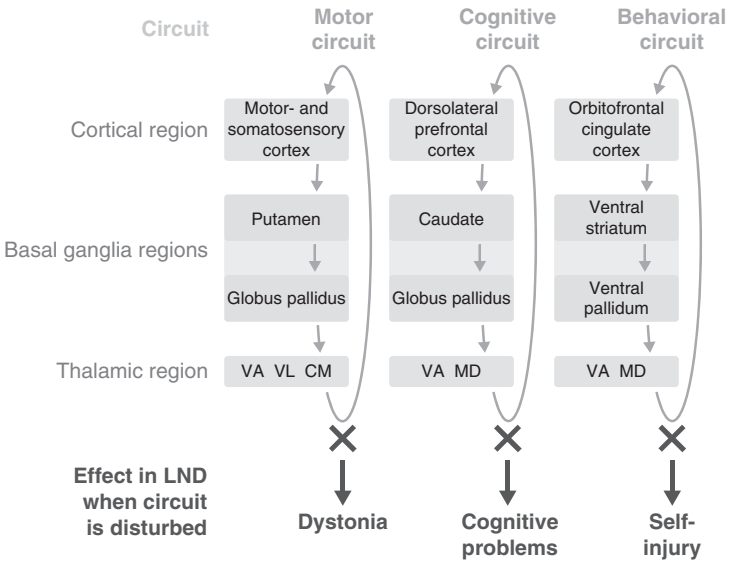

Figure 27.4 Basal ganglia dysfunction in LND. The basal ganglia (i.e. caudate, putamen, ventral striatum, globus pallidus) contribute to multiple, parallel organized functional circuits connected to circuit-specific cortical areas, serving motor, cognitive, and behavioral functions. In LND, dysfunction of each of these networks is considered the underlying mechanism for the motor disorder dominated by severe dystonia, attentional and executive deficits and abnormal behavioral including self-injurious behavior. Abbreviations: CM, central medial nucleus; MD, medial dorsal nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus.

dystonia in LND has been associated with dysfunction of the basal ganglia *motor circuits*, connecting motor and somatosensory cortices with the putamen. The attentional and executive impairments have been attributed to the dysfunction of the *cognitive circuits*, encompassing the dorsolateral prefrontal cortex and caudate. Finally, the aberrant (including self-injurious) behaviors have been ascribed to the dysfunction of the *behavioral circuits* connecting the orbitofrontal cortex and ventral striatum.

Another important determinant of the clinical phenotype in LND appears to be the timing of the dopamine deficiency. It has been known for a long time that dopamine depletion at different ages can result in distinctive movement disorders. As such, a profound loss of striatal dopamine most often causes parkinsonism in adults, but usually causes dystonia in children [40]. For example, early dopamine loss associated with an inherited deficiency of GTP cyclohydrolase or tyrosine hydroxylase is more often associated with dystonia rather than parkinsonism [41, 42]. In experimental studies in rodents, a similar influence on the age at which striatal dopamine depletion causes motor function. For example, in adult rats, the destruction of 95% of nigrostriatal dopamine neurons results in a motor syndrome resembling parkinsonism, but a similar lesion in neonatal animals results in spontaneous hyperactivity and aggressiveness without signs of parkinsonism [43]. It has been proposed that differences in adaptive neuroplasticity – referring to receptor function, post-receptor signaling pathways, electrophysiological function, and synaptic changes – may account for these phenotypic differences caused by dopaminergic lesions at young compared to adult ages.

In that respect, the etiology of dystonia and levodopa-induced exacerbations of the motor disorder in LND may be similar to that of levodopa-induced dyskinesias in advanced Parkinson disease, for which similar neuroplastic changes are thought to be responsible. Of note, also the impulse-control disorders in Parkinson disease, which have been regarded as the behavioral counterpart of levodopa-induced dyskinesias, might share intrinsic properties with the impulsive behaviors in LND, including the self-injury.

It must be acknowledged that an isolated dysfunction of striatal dopamine systems does not easily account for the corticospinal signs that appear in some cases. It is, however, possible that HGPRT deficiency causes additional dysfunction in corticospinal motor systems – perhaps related to the decrease in white and gray matter in volumetric MRI studies [25, 26]. Another possibility is that corticospinal tract signs reflect an indirect, acquired process, secondary to degenerative changes of the cervical spine caused by cervical dystonia with retrocollis. The possibility of a cervical myelopathy is suggested by the frequent observations that the corticospinal tract signs are asymmetrical and limited to the legs. In fact, cervical instability leading to myelopathy has been documented in LND, as well as violent retrocollis causing atlantoaxial dislocation and non-traumatic fractures

of the high cervical spine [16]. Similar cervical myelopathy resulting from involuntary neck movements has also been described in several other hyperkinetic conditions, including cervical dystonia, generalized dystonia, paroxysmal dystonia, dyskinetic cerebral palsy, and Tourette syndrome. Nevertheless, further studies are needed to clarify the source of the pyramidal signs in LND.

Clinical Diagnosis and Work-Up

The prevalence of LND is estimated at 1 case per 235,000 to 380,000 live births [44, 45]. LND has been reported in most ethnic groups, with approximately equal rates. Because of the X-linked recessive mode of inheritance, virtually all patients are male. LND may occur in females as a result of exceptional genetic aberrations. The prevalence of partial HGPRT deficiency is currently unknown.

Most patients with HGPRT deficiency come to medical attention early in life, usually before 4 years of age. Classic LND patients usually present before the age of 1 year, but LNV might be first seen at a later age, usually depending on the age of onset of uric acid-related problems. A history of LND or LNV in other family members might also point toward the diagnosis.

A history of progressive motor delay during the first year of life, as evident from a failure to reach motor milestones, is among the most frequent presenting symptoms in classic LND. Sometimes previously achieved motor milestones are lost. In addition, involuntary movements are often reported at first presentation, although they may become more obvious later in the course of the disease. Typically, self-injurious behavior in LND starts at age 2–5 years, but cases have been described in which it did not start before the age of 18 years.

If not reported spontaneously, the presence of orange "sand" or crystals in the diaper should be checked or asked about. The "sand" and orange color is caused by uric acid crystals and microhematuria.

HGPRT deficiency should be *considered* when delayed development is accompanied by a hyperkinetic movement disorder, particularly when routine brain MRI is normal. HGPRT deficiency should be *suspected* if a delayed development is accompanied by evidence of an excessive production of uric acid or self-injurious behavior. Also, macrocytic anemia could add to the clinical suspicion when blood and chemistry tests are otherwise normal.

Clinical Examination

In individuals with LND, somatic growth may be behind disproportionately compared to head circumference or bone age. In boys, testicular atrophy is common and undescended testes occur. Puberty may be delayed or absent.

On neurological examination, a generalized action dystonia is present in LND, characterized by frequent extraneous movements with sustained muscle contractions in the face, neck, and limbs, which become most obvious with stress, excitement, anticipation, or voluntary movement [14, 15]. Oromandibular and lingual dystonia, with excessive activation of pharyngeal, lingual, and perioral muscles, cause usually a severe dysarthria. Blepharospasm may be present as well.

Other extrapyramidal features that are often present include choreoathetosis and ballism. Ballism is often triggered by excitement or agitation – as well as the presence of an object near enough to strike, raising the question of whether this may also represent impulsive acts.

When fully relaxed, a generalized hypotonia is frequently noted. Hyperreflexia and spasticity, implying the involvement of corticospinal pathways, may be present – often most prominent in the legs, sometimes asymmetrically.

In LNV patients, motor abnormalities are often present (91%), but the functional severity may vary from a motor syndrome dominated by severe dystonia, indistinguishable from classic LND, to mild dystonic overflow, or even only subtle but clear clumsiness (Figure 27.2). In addition, pyramidal signs are seen in ~50% of LNV patients.

Cognitive function is impaired in most LND patients, with average intelligence quotient values of approximately 60–80. However, normal intelligence has been described in LND. It must be noted that patients do not have global intellectual disability, but rather have impairments in specific cognitive domains involving attention and mental flexibility. In LNV patients, cognitive skills may be variably impaired, but are usually less affected than in LND.

LND patients often show signs of impaired impulse control, e.g. using foul language or other defiant behavior. At the same time, they are usually notably engaging when in a safe environment. If self-injury is present, finger and lip biting is frequently seen. Subsequent partial amputations of the fingers, lips, tongue, and oral mucosa are common (Figure 27.3). Such topographic preference is uncommon in other

diseases with self-injury. LNV patients do not perform self-injury, by definition. However, impulsivity or oppositional behaviors have been reported.

Auxiliary Testing

Blood and Urine

LND and LNV patients have increased uric acid production due to the lack of purine recycling in the absence of HGPRT. Uric acid levels in the serum and urine are frequently evaluated as part of the metabolic work-up of developmental delay or hypotonia. The serum uric acid level is elevated in most patients, but efficient renal clearance in children typically limits the average serum uric acid levels to less than two-fold, and serum uric acid levels may be normal at the time of testing. Uric acid excretion in urine is best evaluated by 24-hour urinary uric acid to creatinine ratio, or a total 24-hour uric acid excretion. The total renal uric acid excretion in classic LND is typically about four times that of controls. Although high uric acid levels in the serum and urine may provide important clues to the diagnosis, they lack sufficient sensitivity and specificity for a definitive diagnosis.

In addition to hyperuricemia, macrocytic anemia may be found in LND patients. The cause is unknown, as serum vitamin B12, folate, iron, and thyroid function tests are typically normal.

HPRT1 Gene Analysis

HPRT1 gene analysis is confirmatory of the diagnosis and may be the first test ordered in cases of high clinical suspicion, or a known *HPRT1* mutation in the family. The reported mutations in the *HPRT1* gene are heterogeneous, including point mutations and other substitutions, deletions, and insertions. Mutations that predict large aberrations in the resulting protein and therefore virtually no residual enzyme activity – such as large deletions or early nonsense mutations – are good predictors of high disease severity. Point mutations may cause either classic LND or milder LNV, depending on the ultimate effect on the enzyme activity. To assist in the estimation of the disease severity based on the clinical phenotype reported for prior mutations, a list of mutations is maintained at www.lesch-nyhan.org. In case a newly found sequence does not match a previously reported pathological mutation, enzyme testing can be done to confirm pathogenicity.

HGPRT Enzyme Activity

Measurement of HGPRT activity is not mandatory for the diagnoses if a pathological *HPRT1* gene mutation has been discovered. However, enzyme testing can give additional information about the expected disease severity. As explained before, the clinical phenotype is a continuum and near complete absence of HGPRT activity causes the full phenotype of classic LND. A residual activity of ≥1.5% usually prevents self-injury and most other behavioral disturbances, while residual activity above 8% rarely causes obvious neurological impairment. Of note, HGPRT enzyme activities determined in cultured intact cells, such as fibroblasts, are considered more accurate than those in cell lysates, because of possible kinetic and stability properties of a mutant HGPRT enzyme.

Brain Imaging

Brain imaging is not normally necessary for the diagnosis and management of LND, but may be helpful to rule out other diagnoses in case of suspicion. Generally, neither routine CT scanning nor MRI reveal any obvious structural malformations or signal changes, although a mild loss of brain volume may be noted.

Clinical Course

Classic LND patients do not usually develop the ability to walk or sit unsupported, and need help with activities of daily living – including eating, drinking, and personal hygiene. The movement disorder is usually considered stable after a few years of age, but signs might increase during life. Contractures might further decrease functional abilities if not fully prevented. The limitations in activities of daily living in LNV patients vary, and depend on the severity of the motor disorder and whether or not cognitive deficits are present.

Few people with LND live beyond 40 years of age, though some patients – particularly mildly affected individuals – may have a normal lifespan. Often, despite the use of allopurinol to control hyperuricemia, persistent nephrolithiasis may cause renal failure or urosepsis. Some patients experience progressive dysphagia, and may die after pneumonia caused by aspiration. Sudden unexpected death is relatively common in LND patients, possibly due to respiratory failure from cervical pathology or laryngospasms.

Treatment Strategies

Currently, there are no curative treatments for HGPRT deficiency. Supportive treatments aim at the overproduction of uric acid and – depending on the phenotype – the motor disorder and the behavioral abnormalities including self-injurious behavior. For the macrocytic anemia that may be found in LND patients, supplements are usually not effective.

Prevention

Because there are currently no effective therapies for LND, primary prevention may be considered the most important medical intervention, including genetic counseling for families with LND patients. In addition, carrier testing of women who previously gave birth to a child with LND (or LNV) should be offered, to determine the risk of having more affected children. These mothers are not necessarily obligate carriers because of possible de novo mutations during gametogenesis or early development. Even after a negative screening result, subsequent pregnancies should be monitored because of the risk of gonadal mosaicism. Other female family members may also be screened to determine their risk.

All pregnancies of a carrier should be monitored if the termination of affected pregnancies is being considered. Genetic testing for a mutation in the *HPRT1* gene in the amniotic fluid or chorionic villus samples provides the earliest opportunity and most accurate method.

Treatment for Hyperuricemia and Renal Stones

Almost all patients with HGPRT deficiency have hyperuricemia that may lead to urological and articular complications. Serum acid levels can be effectively reduced by allopurinol, which inhibits the conversion of xanthine and hypoxanthine to uric acid. Doses are titrated to maintain uric acid levels within the high–normal range. In addition, generous hydration at all times – particularly in warm weather and during febrile periods – is absolutely essential to wash out the oxypurines hypoxanthine and xanthine, as well as the allopurinol metabolite oxypurinol, all of which may also cause renal stones.

Renal stones in patients with HGPRT deficiency may become evident by renal colic, urinary obstruction, or routine ultrasound surveillance. They require appropriate treatment in order to decrease the risk of long-term renal complications and premature death. Kidney stones in LND and LNV patients may contain uric acid, xanthine, and hypoxanthine – and, in allopurinol-treated patients, also oxypurinol. As these stones are radiolucent, renal ultrasound is the preferred modality for diagnosis. Small urate stones can usually be managed by increasing fluid intake and by urine alkalinization with potassium citrate. Large stones and oxypurine stones may require lithotripsy or surgery.

Treatment for the Movement Disorder

The movement disorder of LND, particularly dystonia, is mostly resistant to pharmacotherapy. Dopaminergic drugs (e.g. the dopamine precursor levodopa) have inconsistent effects on the motor disorder in anecdotal reports. In an open-label prospective dose-escalation study that enrolled five LND patients of 3–27 years of age, all participants discontinued levodopa/carbidopa early because of worsening of motor function. In contrast, very early treatment with levodopa/carbidopa (e.g. starting within 1 year after the onset of symptoms) has been reported to improve the movement disorder, but confirmative studies are warranted. In addition, the chorea and ballistic movements do not consistently respond to either a dopamine-receptor antagonist (e.g. fluphenazine, pimozide) or drugs that deplete dopamine stores (tetrabenazine). There are no detailed reports on the use of trihexyphenidyl in LND.

In order to improve hand function or prevent contractures, botulinum toxin injections can be performed in selected muscles as symptomatic treatment of severe dystonia.

To manage the spasticity that is seen in some patients, muscle relaxants (e.g. baclofen or dantrolene) can be used. Alternatively, benzodiazepines (e.g. diazepam) may help to reduce muscle tone, with the added benefit of reducing anxiety that is known to exacerbate the movement disorder and abnormal behavior including self-injury. Many patients use a muscle relaxant and a benzodiazepine concurrently.

Finally, physical therapy is important to prevent contractures and preserve overall condition.

Treatment for the Behavioral Disorder

No pharmacological treatment has consistently demonstrated effectiveness in managing the behavioral disturbances in LND, including self-injurious behaviors. Medications that have been tried include those that influence dopamine and serotonin

metabolism, as well as S-adenosylmethionine. The abnormal behavior in LND does not respond consistently to formal psychological treatment either. It is important to realize that negative reinforcement usually increases unwanted behaviors.

Instead, the most effective method of dealing with difficult behaviors is to acknowledge the fact that they are beyond the patient's control, engage the patient in an active environment, provide positive reinforcement for desired behaviors, and actively ignore undesirable behaviors. For many patients, it is of utmost importance that they feel understood.

To prevent self-injury, most LND patients need some form of physical restraint, such as arm splints, limb straps, or protective gloves. In patients that bite their lips or cheeks, teeth extraction may be needed when conservative measures fail [46, 47]. Hard objects within reach, including wheelchairs and tables, need soft padding in order not to trigger self-injurious hitting (Figure 27.3). It is important to note that patients do request these physical measures to prevent self-injury, and they become upset when these methods fail, e.g. when arm straps become too loose.

Because of the self-injurious behavior, inpatient admissions should be limited to those that are absolutely necessary. During these admissions, restraints should be applied at all times to prevent self-injury, including during sleep. This disease is exempted from the regulations of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) against continuous and long-term restraints.

Key Points and Clinical Pearls

- Purine metabolites are involved in many essential cellular processes, including high-energy transfer, oxidative phosphorylation, synthesis of DNA and RNA, and signal transduction.
- Although there is no common neurological phenotype among purine disorders, purinergic metabolic derangements are often associated with variable degrees of psychomotor impairment, movement disorders, epilepsy, neuropathy, and behavioral disorders. Perhaps the most specific neurological phenotype of purine metabolism is that of Lesch–Nyhan disease (LND).
- LND is caused by a mutation in the *HPRT1* gene, leading to a deficiency of the purine salvage enzyme hypoxanthine–guanine phosphoribosyltransferase (HGPRT).
- HGPRT deficiency is associated with a phenotypic continuum. Classic LND patients exhibit the full phenotype with a movement disorder dominated by dystonia, attentional deficits, and behavioral abnormalities including self-injury. Patients with a Lesch–Nyhan variant (LNV) partial phenotype display overproduction of uric acid and a variable degree of neurological dysfunction, but without self-injurious behavior.
- Clinical, neuroimaging, and experimental studies suggest that the neurobehavioral features of LND may result from abnormal brain development, causing dysfunction of dopamine neurons that are involved in distinct ganglia circuits for motor, cognitive, or behavioral function.
- HGPRT deficiency should be *considered* when delayed development is accompanied by a hyperkinetic movement disorder, particularly when routine brain MRI is normal. HGPRT deficiency should be *suspected* if a delayed development is accompanied by evidence of excessive production of uric acid or self-injurious behavior.
- *HPRT1* gene analysis is confirmatory of the diagnosis. Together with HGPRT enzyme activity, results might provide predictive clues regarding disease severity.
- There are currently no effective therapies for LND. Primary prevention may be considered the most important medical intervention. Supportive measures include muscle relaxants for the movement disorder, and physical restraints or teeth extraction to prevent self-injury.

Directions for Future Research

- Future research should focus on the HGPRT–purine–dopamine connection during development, e.g. in HGPRT-deficient pluripotent cell models, as well as the timing of

events during embryonic development, e.g. in the HGPRT-deficient mouse model. This information can then be used for identifying new treatment targets, as well as to define optimal timing of interventions – that might also include gene therapy approaches.

- To date, a number of LND patients who have received deep brain stimulation (DBS) aimed at the globus pallidus pars interna have been reported in the literature. Some showed remarkable improvements in motor dysfunction, and even self-injurious behaviors. However, these effects may not last and complications have been noted frequently. More studies are needed to optimize this technique before DBS can be considered effective and safe in LND.
- A trial of the selective dopamine D1/D5 receptor antagonist ecopipam in LND patients was terminated early due to unanticipated side effects. However, the drug appeared to reduce self-injury in most of the limited number of patients enrolled. Therefore, further studies are warranted to establish whether or not ecopipam – or related compounds – could be a safe and useful treatment for self-injurious behavior in LND.

References

1. Stryer L. Biochemistry. New York: W. H. Freeman and Company; 1988.
2. Gacasan SB, Baker DL, Parrill AL. G protein-coupled receptors: The evolution of structural insight. AIMS Biophys. 2017;**4**(3):491–527.
3. Harris JJ, Attwell D. The energetics of CNS white matter. J Neurosci. 2012;**32**(1):356–71.
4. Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. J Cereb Blood Flow Metab. 2001;**21**(10):1133–45.
5. Abbracchio MP, Burnstock G, Verkhratsky A, Zimmermann H. Purinergic signalling in the nervous system: An overview. Trends Neurosci. 2009;**32**(1):19–29.
6. Camici M, Micheli V, Ipata PL, Tozzi MG. Pediatric neurological syndromes and inborn errors of purine metabolism. Neurochem Int. 2010;**56**(3):367–78.
7. Kamatani N, Jinnah HA, Hennekam FA, Van Kuilenburg ABP. Purine and pyrimidine metabolism. In Rimoin DL, Pyeritz RE, Korf BR, editors. Principles and Practice of Medical Genetics. San Diego, CA: Academic Press; 2013, pp. 1–38.
8. Jinnah HA, Sabina RL, Van Den Berghe G. Metabolic disorders of purine metabolism affecting the nervous system. Handb Clin Neurol. 2013;**113**:1827–36.
9. de Brouwer AP, van Bokhoven H, Nabuurs SB, et al. *PRPS1* mutations: Four distinct syndromes and potential treatment. Am J Hum Genet. 2010;**86**(4):506–18.
10. Baresova V, Skopova V, Sikora J, et al. Mutations of *ATIC* and *ADSL* affect purinosome assembly in cultured skin fibroblasts from patients with AICA-ribosiduria and ADSL deficiency. Hum Mol Genet. 2012;**21**(7):1534–43.
11. Morisaki T, Gross M, Morisaki H, et al. Molecular basis of AMP deaminase deficiency in skeletal muscle. Proc Natl Acad Sci USA. 1992;**89**(14):6457–61.
12. Sabine RL, Holmes EW. Myoadenylate deaminase deficiency. In Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Basis of Inherited Disease. II. New York, NY: McGraw-Hill; 2001, pp. 2627–38.
13. Torres RJ, Puig JG, Jinnah HA. Update on the phenotypic spectrum of Lesch–Nyhan disease and its attenuated variants. Curr Rheumatol Rep. 2012;**14**(2):189–94.
14. Jinnah HA, Ceballos-Picot I, Torres RJ, et al. Attenuated variants of Lesch–Nyhan disease. Brain. 2010;**133**(Pt 3):671–89.
15. Jinnah HA, Visser JE, Harris JC, et al. Delineation of the motor disorder of Lesch–Nyhan disease. Brain. 2006;**129**(Pt 5):1201–17.
16. Watts RW, Spellacy E, Gibbs DA, et al. Clinical, post-mortem, biochemical and therapeutic observations on the Lesch–Nyhan syndrome with particular reference to the neurological manifestations. Q J Med. 1982;**51**(201):43–78.
17. Matthews WS, Solan A, Barabas G. Cognitive functioning in Lesch–Nyhan syndrome. Dev Med Child Neurol. 1995;**37**(8):715–22.
18. Schretlen DJ, Harris JC, Park KS, Jinnah HA, del Pozo NO. Neurocognitive functioning in Lesch–Nyhan disease and partial hypoxanthine–guanine phosphoribosyltransferase deficiency. J Int Neuropsychol Soc. 2001;**7**(7):805–12.
19. Anderson LT, Ernst M. Self-injury in Lesch–Nyhan disease. J Autism Dev Disord. 1994;**24**(1):67–81.
20. Nyhan WL. Behavior in the Lesch–Nyhan syndrome. J Autism Child Schizophr. 1976;**6**(3):235–52.

21. Jolly DJ, Okayama H, Berg P, et al. Isolation and characterization of a full-length expressible cDNA for human hypoxanthine phosphoribosyl transferase. Proc Natl Acad Sci USA. 1983;**80**(2):477–81.
22. Fu R, Ceballos-Picot I, Torres RJ, et al. Genotype–phenotype correlations in neurogenetics: Lesch–Nyhan disease as a model disorder. Brain. 2014;**137** (Pt 5):1282–303.
23. Jinnah HA, De Gregorio L, Harris JC, Nyhan WL, O'Neill JP. The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. Mutat Res. 2000;**463** (3):309–26.
24. Harris JC, Lee RR, Jinnah HA, et al. Craniocerebral magnetic resonance imaging measurement and findings in Lesch–Nyhan syndrome. Arch Neurol. 1998;**55**(4):547–53.
25. Schretlen DJ, Varvaris M, Ho TE, et al. Regional brain volume abnormalities in Lesch–Nyhan disease and its variants: A cross-sectional study. Lancet Neurol. 2013;**12**(12):1151–8.
26. Schretlen DJ, Varvaris M, Vannorsdall TD, et al. Brain white matter volume abnormalities in Lesch–Nyhan disease and its variants. Neurology. 2015;**84** (2):190–6.
27. Gottle M, Prudente CN, Fu R, et al. Loss of dopamine phenotype among midbrain neurons in Lesch–Nyhan disease. Ann Neurol. 2014;**76**(1):95–107.
28. Lloyd KG, Hornykiewicz O, Davidson L, et al. Biochemical evidence of dysfunction of brain neurotransmitters in the Lesch–Nyhan syndrome. N Engl J Med. 1981;**305**(19):1106–11.
29. Saito Y, Ito M, Hanaoka S, et al. Dopamine receptor upregulation in Lesch–Nyhan syndrome: A postmortem study. Neuropediatrics. 1999;**30**(2): 66–71.
30. Ernst M, Zametkin AJ, Matochik JA, et al. Presynaptic dopaminergic deficits in Lesch–Nyhan disease. N Engl J Med. 1996;**334**(24):1568–72.
31. Wong DF, Harris JC, Naidu S, et al. Dopamine transporters are markedly reduced in Lesch–Nyhan disease in vivo. Proc Natl Acad Sci USA. 1996;**93** (11):5539–43.
32. Jinnah HA, Wojcik BE, Hunt M, et al. Dopamine deficiency in a genetic mouse model of Lesch–Nyhan disease. J Neurosci. 1994; **14** (3 Pt 1): 1164–75.
33. Ceballos-Picot I, Mockel L, Potier MC, et al. Hypoxanthine–guanine phosphoribosyl transferase regulates early developmental programming of dopamine neurons: Implications for Lesch–Nyhan disease pathogenesis. Hum Mol Genet. 2009;**18** (13):2317–27.
34. Guibinga GH, Hsu S, Friedmann T. Deficiency of the housekeeping gene hypoxanthine–guanine phosphoribosyltransferase (*HPRT*) dysregulates neurogenesis. Mol Ther. 2010;**18**(1):54–62.
35. Kang TH, Guibinga GH, Jinnah HA, Friedmann T. HPRT deficiency coordinately dysregulates canonical Wnt and presenilin-1 signaling: A neuro-developmental regulatory role for a housekeeping gene? PLoS One. 2011;**6**(1):e16572.
36. Hyland K, Kasim S, Egami K, Arnold LA, Jinnah HA. Tetrahydrobiopterin deficiency and dopamine loss in a genetic mouse model of Lesch–Nyhan disease. J Inherit Metab Dis. 2004;**27**(2):165–78.
37. Visser JE, Bar PR, Jinnah HA. Lesch–Nyhan disease and the basal ganglia. Brain Res Brain Res Rev. 2000; **32** (2–3): 449–75.
38. Visser JE, Smith DW, Moy SS, et al. Oxidative stress and dopamine deficiency in a genetic mouse model of Lesch–Nyhan disease. Brain Res Dev Brain Res. 2002;**133**(2):127–39.
39. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia–thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res. 1990;**85**:119–46.
40. Muller U. The monogenic primary dystonias. Brain. 2009;**132**(Pt 8):2005–25.
41. Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders: Clinical advances and future perspectives. Nat Rev Neurol. 2015;**11**(10):567–84.
42. Wijemanne S, Jankovic J. Dopa-responsive dystonia: Clinical and genetic heterogeneity. Nat Rev Neurol. 2015;**11**(7):414–24.
43. Moy SS, Criswell HE, Breese GR. Differential effects of bilateral dopamine depletion in neonatal and adult rats. Neurosci Biobehav Rev. 1997;**21** (4):425–35.
44. Crawhall JC, Henderson JF, Kelley WN. Diagnosis and treatment of the Lesch–Nyhan syndrome. Pediatr Res. 1972;**6**(5):504–13.
45. Torres RJ, Puig JG. Hypoxanthine–guanine phosophoribosyltransferase (HPRT) deficiency: Lesch–Nyhan syndrome. Orphanet J Rare Dis. 2007;**2**:48.
46. Cotton AC, Bell RB, Jinnah HA. Expert opinion vs patient perspective in treatment of rare disorders: Tooth removal in Lesch–Nyhan disease as an example. JIMD Rep. 2018;**41**:25–7.
47. Goodman EM, Torres RJ, Puig JG, Jinnah HA. Consequences of delayed dental extraction in Lesch–Nyhan disease. Mov Disord Clin Pract. 2014;**1**(3):225–9.

Chapter 28

Disorders of Creatine Metabolism: Creatine Deficiency Syndromes and Movement Disorders

Saadet Mercimek-Andrews

Introduction

Creatine is synthetized from two amino acids, arginine and glycine, in the kidney, liver, and pancreas. Two enzymes that are involved in the synthesis of creatine are L-arginine: glycine amidinotransferase (AGAT) (EC 2.1.4.1), highly expressed in the kidney, and guanidinoacetate N-methyltransferase (GAMT) (EC 2.1.1.2), which is highly expressed in the liver. S-adenosylmethionine (SAM) is the methyl donor in creatine synthesis (Figure 28.1). After synthesis, creatine is taken up by high energy requiring organs such as brain, muscle and retina using the sodium chloride-dependent creatine transporter (CRTR). About 50% of creatine is derived from high-protein-content food in the diet and about 50% is synthetized in the body. Creatine deficiency disorders are inborn errors of metabolism involving creatine synthesis and transport. These disorders include GAMT deficiency (OMIM 612736), AGAT deficiency (OMIM 612718), and CRTR deficiency (OMIM 300352). GAMT is encoded by *GAMT* (OMIM 601240), AGAT is encoded by *GATM* (OMIM 602360), and CRTR is encoded by *SLC6A8* (OMIM 300036). GAMT and AGAT deficiencies are inherited in an autosomal-recessive manner and CRTR deficiency is X-linked. There are <120 patients with GAMT deficiency, <20 patients with AGAT deficiency and <200 patients with CRTR deficiency reported in the literature [1]. The estimated carrier frequency of GAMT deficiency is 0.123% in the general population [2], that of AGAT deficiency is 1 in 929 in the general population [3], and the estimated carrier frequency of CRTR deficiency in females is 1 in 4,060 [4].

The clinical features include global developmental delay, cognitive dysfunction, and behavioral problems in all three creatine deficiency disorders, and seizures and movement disorders in GAMT and CRTR deficiencies. Females with CRTR deficiency can be asymptomatic carriers or can present with a phenotype similar to males. Cerebral creatine deficiency on brain ^{1}H-MRS is the biochemical hallmark of the three creatine deficiency disorders. Urine, plasma, and cerebrospinal fluid (CSF) guanidinoacetate and creatine measurements differentiate the three creatine deficiency disorders. The diagnosis is confirmed by molecular analysis of *GAMT*, *GATM*, or *SLC6A8* [1].

All creatine deficiency disorders are treated with creatine supplementation. GAMT deficiency is treated with ornithine supplementation and a protein- or arginine-restricted diet in addition to creatine. CRTR deficiency is treated with arginine and glycine supplementation in addition to creatine [1].

In this chapter, a general overview for creatine deficiency disorders with emphasis on GAMT and CRTR deficiencies and movement disorders as well as treatment outcomes is provided. Clinical features, diagnostic investigations, and treatment of all three creatine deficiency disorders are summarized in Table 28.1.

Creatine Deficiency Disorders

GAMT Deficiency

GAMT deficiency was first described in 1994 [5]. In three large case series of 97 patients, movement disorders were reported in 36% of those with GAMT deficiency [6–9]. The first of these studies (2006) reported movement disorders in 52% of the patients (14 of 27) with GAMT deficiency [6]. Half of those patients had complex neurological syndromes including extrapyramidal and pyramidal movement disorders. In 43% of those patients (6 of 14), an abnormal signal intensity in the bilateral globus pallidus was present on brain MRI. Treatment improved the movement disorder in 64% of the patients on either creatine supplementation or on the combined creatine and ornithine supplementation and protein- or arginine-restricted diet treatments.

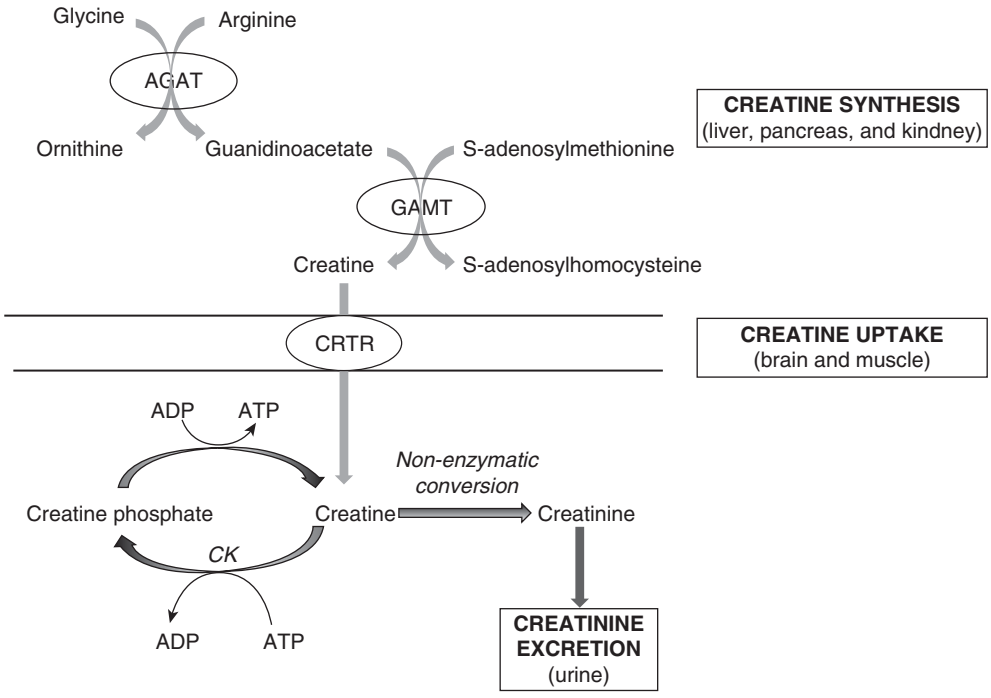

Figure 28.1 Overview of creatine synthesis and transport. Abbreviations: ADP, adenosine diphosphate; AGAT, L-arginine:glycine amidinotransferase; ATP, adenosine triphosphate; CK, creatine kinase; CRTR, creatine transporter; GAMT, guanidinoacetate N-methyltransferase.

A second study reported movement disorders in 27% of the patients (13 of 48) with GAMT deficiency [7]. The authors defined the movement disorder as dystonia, chorea, hemiballism, ataxia, and spasticity. The frequency of each movement disorder or the most common type was not reported in that study. Interestingly, one patient had paroxysmal episodes of ataxia associated with an acute illness; the episodes lasted for several days, followed by a slow but full recovery. The movement disorder was ameliorated in 54% (7 of 13) of the patients on treatment. In some of those patients, creatine supplementation was the only treatment, whereas the majority of the patients were treated with combined creatine and ornithine supplementation and a protein- or arginine-restricted diet.

A more recent study reported movement disorders in 37% of the patients (8 of 22) [9]. The youngest age of onset of a movement disorder was 3 months. The most common movement disorders were dystonia and ataxia. Three patients had one type of movement disorder, either ataxia or choreoathetosis, whereas five patients had more than one type of movement disorder in combination, such as ataxia and tremor; choreoathetosis and dystonia; dystonia, chorea and ataxia; myoclonus and bradykinesia; or ballismus and dystonia. Brain MRI was normal in four patients with movement disorders, whereas two patients with movement disorders had bilateral globus pallidus changes on brain MRI. Additionally, one patient with bilateral globus pallidus changes had no movement disorder. The movement disorder resolved in four patients (all on the combined creatine, ornithine, and a protein- or arginine-restricted diet plus or minus sodium benzoate). Three patients had no improvement in their movement disorder (two patients on the combined creatine, ornithine, and protein- or arginine-restricted diet and one patient on creatine monotherapy).

A late-onset movement disorder was reported in a teenager who presented with global developmental delay and seizures within the second year of life. At the age of 17 years, generalized dystonia affecting the face, neck, and limbs, bradykinesia, and ballistic movements were reported. Brain MRI showed bilateral increased signal intensities in the globus pallidus. In contrast, a 13-year-old younger sibling with GAMT

Table 28.1 Clinical features, diagnostic investigations and treatment of GAMT, AGAT, and CRTR deficiencies.

Disorder	GAMT deficiency	CRTR deficiency	AGAT deficiency
Clinical features	Global developmental delay and intellectual disability (100% of patients) (severe to mild) Epilepsy (86% of patients) Movement disorder (37.5% of patients) Behavioral problems No muscle weakness or myopathy	Global developmental delay and intellectual disability (100% of patients) (severe to mild) Epilepsy (59% of patients) Movement disorder (40% of patients) Behavioral problems (85% of patients) No muscle weakness or myopathy	Global developmental delay and intellectual disability (100% of patients) (severe to mild) Seizures (12.5% of patients) No movement disorder No behavioral problems Muscle weakness or myopathy (53% of patients)
Diagnostic investigations	Elevated guanidinoacetate in urine, plasma, and CSF Creatine deficiency on ^{1}H-MRS in males and females Sequencing of *GAMT*	Elevated creatine to creatinine ratio in urine in males Creatine deficiency on ^{1}H-MRS in males Sequencing of *SLC6A8* (in males and females)	Low guanidinoacetate in either urine or plasma and CSF Creatine deficiency on ^{1}H-MRS in males and females Sequencing of *GATM*
Treatment	Creatine (400–800 mg/kg per day) Ornithine (400–800 mg/kg per day) Protein- or arginine-restricted diet	Creatine (100–200 mg/kg per day) Arginine (400 mg/kg per day) Glycine (150 mg/kg per day)	Creatine (400–800 mg/kg per day)

deficiency did not have any movement disorder at the time of diagnosis [10].

In a cohort of eight patients, ataxia was reported in 50% of cases. All patients with ataxia were older than 6 years of age at the time of diagnosis of GAMT deficiency [11]. In a patient with early-onset global developmental delay, seizures and choreoathetosis developed in the second year of life [12]. Bilateral increased signal intensities in the globus pallidus in brain MRI caused suspicion of mitochondrial encephalopathy, leading to a muscle biopsy which showed deficient complex I activity. However, persistently low plasma and urine creatinine levels led to the diagnosis of GAMT deficiency at the age of 21 months [12].

Globus pallidus changes in brain MRI may or may not be associated with the movement disorder or its severity in patients with GAMT deficiency.

AGAT Deficiency

AGAT deficiency was first described in 2001 [13]. Sixteen patients from eight families have been reported as of 2015 [14]. Only one patient, diagnosed asymptomatically due to a positive family history, had normal neurocognitive function. The remaining 15 patients had various degrees of developmental delay or intellectual disability. About 50% of the patients had either muscle weakness or myopathy. None of them had any type of movement disorder reported to date.

CRTR Deficiency

CRTR deficiency was first described in 2001 [15]. In an international study of 101 males with CRTR deficiency, motor dysfunction such as a wide-based gait, dysarthria, ataxia, and clumsiness was reported in 29% of the males [16, 17]. Dystonia or athetosis including abnormal athetoid hand movements, intermittent dystonic posturing of the hands or wrists during walking, choreoathetoid movements, or dystonia of the face and upper limbs was reported in 11% of the males with CRTR deficiency [16]. A male diagnosed with dystonia at the age of 3 months who was investigated for mitochondrial disorders was diagnosed with CRTR deficiency following an absent creatine peak on brain ^{1}H-MRS and an elevated urine creatine to creatinine ratio [18].

Diagnosis of Creatine Deficiency Disorders

Creatine deficiency on brain ^{1}H-MRS is the biochemical hallmark of GAMT and AGAT deficiencies in males and females and of CRTR deficiency in males. Creatine on ^{1}H-MRS can be partially deficient or normal in females with CRTR deficiency. Urine, plasma, and CSF guanidinoacetate levels are elevated in GAMT deficiency, low (below the reference range or at the lowest level of the reference range) in AGAT deficiency, and normal in CRTR deficiency. The urine creatine to creatinine ratio is elevated in males with CRTR deficiency, whereas females can have mildly elevated or normal urine creatine to creatinine ratio [1]. The diagnosis is confirmed by direct sequencing of *GAMT*, *GATM*, or *SLC6A8*. Many next-generation sequencing panels for epilepsy and intellectual disability cover the creatine deficiency disorders, as does whole-exome sequencing. Homozygous or compound heterozygous variants in *GAMT* and *GATM* and a hemizygous or heterozygous variant in *SLC6A8* confirm the genetic diagnosis. It should be noted that biochemical confirmation using brain ^{1}H-MRS and urine guanidinoacetate and creatine to creatinine ratio are essential to confirm the pathogenicity of variants [1]. GAMT and AGAT enzyme activity or creatine uptake can be measured in cultured skin fibroblasts and can further support a diagnosis. Two variants in *GAMT* are commonly reported in the literature: c.327G>A, a panethnic variant, and c.59G>C, a Mediterranean variant (Portugal, Spain, and Turkey) [1] .

Differential Diagnosis of Creatine Deficiency Disorders

Partial secondary creatine deficiencies on brain ^{1}H-MRS have been reported in a few inherited metabolic disorders including argininosuccinate lyase and argininosuccinate synthetase deficiencies [19], ornithine aminotransferase deficiency (gyrate atrophy of the choroid and retina) [20], and pyrroline-5-carboxylate synthetase (P5CS) deficiency [21]. In these disorders, the urine, plasma, and CSF guanidinoacetate levels and urine creatine to creatinine ratio are normal.

Treatment Outcome of Creatine Deficiency Disorders

Long- or short-term treatment outcomes of GAMT deficiency were reported in three studies with less than 100 symptomatic patients [6, 7, 9]. In the most recent study, neurocognitive function was improved in 23% of the patients, epilepsy was improved in 67%, and the movement disorder was improved in 50% of cases [9]. To date, only two symptomatic patients were reported with normal neurocognitive function on treatment, including one patient with a mild phenotype on creatine and high-dose ornithine therapy, started at the age of 44 months, and another patient with a moderate phenotype on creatine, ornithine, arginine-restricted diet, and sodium benzoate treatment, started at the age of 1 year [7, 9]. Normal neurodevelopmental outcomes have been reported in three asymptomatic individuals with GAMT deficiency, who were diagnosed based on a positive family history in the newborn period [22–24].

Treatment outcomes of 15 symptomatic patients with AGAT deficiency were reported in 2015 [14]; myopathy was improved in 50% of cases. High-dose creatine therapy resulted in a normal neurodevelopmental outcome in one symptomatic patient [25]. Normal neurodevelopment was reported in an asymptomatic individual identified by a positive family history, who was treated from 4 months of age [26].

An unfavourable treatment outcome of CRTR deficiency was reported in less than 30 patients, who were treated either with arginine supplementation or arginine and glycine supplementations [27–30]. Recently, the treatment outcomes of 17 patients with CRTR deficiency were reported [31]. On combined treatment with creatine, arginine, and glycine, none of the males showed either deterioration or improvement in their clinical severity score, whereas two females showed improvement in the clinical severity score. Creatine monotherapy resulted in the deterioration of the clinical severity score in one male [31].

Conclusions

Creatine deficiency disorders are important to recognize in patients with global developmental delay, intellectual disability, epilepsy, movement disorders, and behavioral problems. They are complex neurodevelopmental disorders. The identification of these disorders in infancy is crucial due to disease-specific treatments that improve symptoms as well as the neurodevelopmental outcomes. Brain ^{1}H-MRS and urine guanidinoacetate and creatine measurements are important tests that help to recognize creatine deficiency disorders in patients with global developmental delay. Whole-exome sequencing or targeted gene panels can also identify individuals with creatine deficiency disorders.

Key Points and Clinical Pearls

- Guanidinoacetate N-methyltransferase (GAMT) and L-arginine:glycine amidinotransferase (AGAT) deficiencies are treatable disorders and their early identification can result in normal neurodevelopmental outcomes.
- Movement disorders are common in GAMT and CRTR deficiencies.
- Current treatment of CRTR deficiency halts disease progression and partially improves existing disease symptoms.
- Urinary guanidinoacetate, creatine, and creatinine measurements are useful screening tests for creatine deficiency disorders, particularly in patients with global developmental delay, intellectual disability, epilepsy, and movement disorders.

Directions for Future Research

- Universal newborn screening for GAMT deficiency is essential to treat individuals at the asymptomatic stage of the disease.
- CRTR deficiency is the least treatable creatine deficiency disorder, and developing new treatments is essential to improve neurodevelopmental outcomes.
- Preclinical models for high throughput drug screening or gene editing technologies to restore GAMT, AGAT, and CRTR function are needed

References

1. Mercimek-Mahmutoglu S, Salomons GS. Creatine deficiency syndromes. GeneReviews®. 2009;Jan 15 (updated Dec 10, 2015).
2. Desroches CL, Patel J, Wang P, et al. Carrier frequency of guanidinoacetate methyltransferase deficiency in the general population by functional characterization of missense variants in the *GAMT* gene. Mol Genet Genomics. 2015;**290**(6):2163–71.
3. DesRoches CL, Bruun T, Wang P, Marshall CR, Mercimek-Mahmutoglu S. Arginine–glycine amidinotransferase deficiency and functional characterization of missense variants in *GATM*. Hum Mutat. 2016;**37**(9):926–32.
4. DesRoches CL, Patel J, Wang P, et al. Estimated carrier frequency of creatine transporter deficiency in females in the general population using functional characterization of novel missense variants in the *SLC6A8* gene. Gene. 2015;**565**(2):187–91.
5. Stockler S, Holzbach U, Hanefeld F, et al. Creatine deficiency in the brain: A new, treatable inborn error of metabolism. Pediatr Res. 1994;**36**(3):409–13.
6. Mercimek-Mahmutoglu S, Stoeckler-Ipsiroglu S, Adami A, et al. GAMT deficiency: Features, treatment, and outcome in an inborn error of creatine synthesis. Neurology. 2006;**67**(3):480–4.
7. Stockler-Ipsiroglu S, van Karnebeek C, Longo N, et al. Guanidinoacetate methyltransferase (GAMT) deficiency: Outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring. Mol Genet Metab. 2014;**111**(1):16–25.
8. Mercimek-Mahmutoglu S, Ndika J, Kanhai W, et al. Thirteen new patients with guanidinoacetate methyltransferase deficiency and functional characterization of nineteen novel missense variants in the *GAMT* gene. Hum Mutat. 2014;**35**(4):462–9.
9. Khaikin Y, Sidky S, Abdenur J, et al. Treatment outcome of twenty-two patients with guanidinoacetate methyltransferase deficiency: An international retrospective cohort study. Eur J Paediatr Neurol. 2018;**22**(3):369–79.
10. O'Rourke DJ, Ryan S, Salomons G, et al. Guanidinoacetate methyltransferase (GAMT) deficiency: Late onset of movement disorder and preserved expressive language. Dev Med Child Neurol. 2009;**51**(5):404–7.
11. Dhar SU, Scaglia F, Li FY, et al. Expanded clinical and molecular spectrum of guanidinoacetate methyltransferase (GAMT) deficiency. Mol Genet Metab. 2009;**96**(1):38–43.
12. Morris AA, Appleton RE, Power B, et al. Guanidinoacetate methyltransferase deficiency masquerading as a mitochondrial encephalopathy. J Inherit Metab Dis. 2007;**30**(1):100.
13. Item CB, Stockler-Ipsiroglu S, Stromberger C, et al. Arginine:glycineamidinotransferase deficiency: The third inborn error of creatine metabolism in humans. Am J Hum Genet. 2001;**69**(5):1127–33.
14. Stockler-Ipsiroglu S, Apatean D, Battini R, et al. Arginine:glycineamidinotransferase (AGAT) deficiency: Clinical features and long term outcomes in 16 patients diagnosed worldwide. Mol Genet Metab. 2015;**116**(4):252–9.
15. Salomons GS, van Dooren SJ, Verhoeven NM, et al. X-linked creatine-transporter gene (*SLC6A8*) defect: A new creatine-deficiency syndrome. Am J Hum Genet. 2001;**68**(6):1497–500.

16. van de Kamp JM, Betsalel OT, Mercimek-Mahmutoglu S, et al. Phenotype and genotype in 101 males with X-linked creatine transporter deficiency. J Med Genet. 2013;**50**(7):463–72.

17. van de Kamp JM, Mancini GM, Salomons GS. X-linked creatine transporter deficiency: Clinical aspects and pathophysiology. J Inherit Metab Dis. 2014;**37**(5):715–33.

18. Anselm IA, Alkuraya FS, Salomons GS, et al. X-linked creatine transporter defect: A report on two unrelated boys with a severe clinical phenotype. J Inherit Metab Dis. 2006;**29**(1):214–9.

19. van Spronsen FJ, Reijngoud DJ, Verhoeven NM, et al. High cerebral guanidinoacetate and variable creatine concentrations in argininosuccinate synthetase and lyase deficiency: Implications for treatment? Mol Genet Metab. 2006;**89**(3):274–6.

20. Nanto-Salonen K, Komu M, Lundbom N, et al. Reduced brain creatine in gyrate atrophy of the choroid and retina with hyperornithinemia. Neurology. 1999;**53**(2):303–7.

21. Martinelli D, Haberle J, Rubio V, et al. Understanding pyrroline-5-carboxylate synthetase deficiency: Clinical, molecular, functional, and expression studies, structure-based analysis, and novel therapy with arginine. J Inherit Metab Dis. 2012;**35**(5):761–76.

22. Schulze A, Hoffmann GF, Bachert P, et al. Presymptomatic treatment of neonatal guanidinoacetate methyltransferase deficiency. Neurology. 2006;**67**(4):719–21.

23. El-Gharbawy AH, Goldstein JL, Millington DS, et al. Elevation of guanidinoacetate in newborn dried blood spots and impact of early treatment in GAMT deficiency. Mol Genet Metab. 2013;**109**(2):215–7.

24. Viau KS, Ernst SL, Pasquali M, et al. Evidence-based treatment of guanidinoacetate methyltransferase (GAMT) deficiency. Mol Genet Metab. 2013;**110**(3):255–62.

25. Ndika JD, Johnston K, Barkovich JA, et al. Developmental progress and creatine restoration upon long-term creatine supplementation of a patient with arginine: glycineamidinotransferase deficiency. Mol Genet Metab. 2012;**106**(1):48–54.

26. Battini R, Alessandri MG, Leuzzi V, et al. Arginine: glycineamidinotransferase (AGAT) deficiency in a newborn: Early treatment can prevent phenotypic expression of the disease. J Pediatr. 2006;**148**(6):828–30.

27. Valayannopoulos V, Boddaert N, Chabli A, et al. Treatment by oral creatine, L-arginine and L-glycine in six severely affected patients with creatine transporter defect. J Inherit Metab Dis. 2012;**35**(1):151–7.

28. van de Kamp JM, Pouwels PJ, Aarsen FK, et al. Long-term follow-up and treatment in nine boys with X-linked creatine transporter defect. J Inherit Metab Dis. 2012;**35**(1):141–9.

29. Chilosi A, Leuzzi V, Battini R, et al. Treatment with L-arginine improves neuropsychological disorders in a child with creatine transporter defect. Neurocase. 2008;**14**(2):151–61.

30. Fons C, Sempere A, Arias A, et al. Arginine supplementation in four patients with X-linked creatine transporter defect. J Inherit Metab Dis. 2008;**31**(6):724–8.

31. Bruun TUJ, Sidky S, Bandeira AO, et al. Treatment outcome of creatine transporter deficiency: International retrospective cohort study. Metab Brain Dis. 2018;**33**(3):875–84.

Chapter 29

Hereditary Spastic Paraplegia-Related Inborn Errors of Metabolism

Henry Houlden, Sarah Wiethoff, and Thomas Bourinaris

Introduction

Hereditary spastic paraplegias (HSPs) represent a large and heterogeneous group of inherited disorders, presenting with a phenotype that is predominated by lower limb spasticity and weakness, often accompanied by pyramidal-tract signs and neurogenic bladder dysfunction. This phenotype is typically associated with the degeneration of the corticospinal tract that leads to the hallmark manifestations of the condition. The HSPs have been traditionally divided into pure and complicated forms. Patients with pure HSP present isolated pyramidal signs and mild sensory symptoms with predominantly diminished vibration sensation, while patients with complicated HSP have other accompanying neurological or systemic signs, such as cognitive impairment, epilepsy, ataxia, extrapyramidal movement disorders, dysmorphic features, and peripheral neuropathy among others [1, 2].

The genetic and molecular background of HSPs is complex. More than 70 associated loci and more than 60 different genes have been identified to date, including all types of Mendelian inheritance, such as autosomal-dominant (AD), autosomal-recessive (AR), and X-linked forms [3, 4]. Several molecular pathways are involved in the pathogenesis of HSPs: membrane trafficking, mitochondrial function, myelination, cytoskeleton stability, autophagy, and protein or RNA metabolism [5, 6].

The same syndromic phenotype of predominantly lower limb spasticity and weakness can be caused by other inherited or acquired neurological conditions, including motor neuron disorders, spinocerebellar ataxia, various forms of myelopathies, neurodegenerative disorders, as well as inherited leukodystrophies and other inborn errors of metabolism (IEMs) [7, 8].

The IEMs are a continuously expanding group of monogenic inherited metabolic disorders, today representing more than 750 different conditions, most of which are rare but together have an estimated prevalence of more than 1 in 1,000 live births. IEMs are generally caused by specific defects in various enzymes, cofactors, and transporters involved in specific cellular pathways. The presenting symptoms may result from enzyme deficiencies, from the accumulation of metabolic products that have toxic effects on tissues and organs, or from both. Inheritance of IEMs usually follows an autosomal-recessive pattern, but some conditions are inherited in an autosomal-dominant or X-linked fashion, and sporadic cases exist as well [9, 10].

Neurological symptoms are not uncommon in IEMs and range from severe encephalopathy, accompanied by hypotonia and seizures in neonates, to clinical heterogeneous and sometimes attenuated forms that present with a later onset during childhood, adolescence, or adulthood. The presenting symptoms and signs encountered may vary significantly and include spasticity, cognitive decline, cerebellar ataxia, extrapyramidal syndromes, seizures, psychiatric manifestations, or peripheral neuropathy [9, 10].

Motor neurons represent a significant target of the metabolic defects caused by IEMs. Therefore pyramidal symptoms and signs, including lower limb spasticity and weakness, are often present and occasionally produce a phenotype that resembles pure or complicated HSPs. The particular vulnerability of pyramidal cells might be explained by their long axons with high energy and transport demand [11].

Since most of the associated clinical syndromes have an onset during infancy and childhood, IEMs deserve a significant consideration in the differential diagnosis of childhood-onset HSPs [12]. It is not rare, though, that even adult cases with an HSP phenotype can be caused by various IEMs, either due to later onset of disease, or a milder phenotype that may result in diagnostic delay [11, 13].

Here, we summarize and review the most common IEMs that are associated with prominent lower limb spasticity and weakness and various pyramidal signs (Table 29.1). The classification of IEMs is done

Table 29.1 Classification and main characteristics of IEMs presenting with phenotypes that resemble HSPs

	Gene	Pattern of inheritance*	Age of onset	Common additional clinical features
Cofactor-related disorders				
Homocysteine remethylation defects	*MTHFR* *MMACHC*	AR AR	Childhood to adulthood Childhood to adulthood	Cognitive decline, psychiatric symptoms, epilepsy, peripheral neuropathy, thrombotic episodes Cognitive decline, psychiatric symptoms, cerebellar ataxia, hematological complications/ thromboembolic episodes
Biotinidase deficiency	*BTD*	AR	Childhood to adulthood	Optic atrophy, ataxia, hearing defects, respiratory problems, skin manifestations
Urea cycle disorders				
Arginase deficiency	*ARG1*	AR	Infancy to early childhood (rarely adolescence/ adulthood)	Cognitive decline, epilepsy, cerebellar ataxia, dystonia, extrapyramidal signs
HHH syndrome	*SLC25A1S*	AR	Infancy to adulthood	Learning disabilities, ataxia, epileptic seizures, episodes of confusion
Disorders of phenylalanine metabolism				
Phenylketonuria	*PAH*	AR	Infancy to childhood	Cognitive decline, visual disturbances, cerebellar ataxia, parkinsonism
Dopamine synthesis defects				
Atypical dopa-responsive dystonia (DRD-plus)	*GCH1* *TH* *SPR* *PTPS*	AD or AR AR AR AR	Childhood to adulthood	Dystonia, axial hypotonia, oculogyric crises, cerebellar ataxia, cognitive decline
Organic acidurias				
3-Methylglutaconic aciduria type 3	*OPA3*	AR	Infancy to early childhood	Optic atrophy, choreoathetosis, ataxia, mild cognitive deficits
Peroxisomal disorders				
Adrenomyeloneuropathy	*ABCD1*	X-linked	Adulthood	Peripheral neuropathy
Lysosomal disorders				
Metachromatic leukodystrophy	*ARSA*	AR	Late infancy to adulthood	Cognitive decline, psychiatric symptoms, ataxia, peripheral neuropathy
Krabbe disease	*GALC*	AR	Childhood to adulthood (rarely)	Cognitive decline, ataxia, optic atrophy, peripheral neuropathy
Disorders of lipid and lipoprotein metabolism				
Sjögren–Larsson syndrome	*ALDH3A2*	AR	Childhood	Cognitive impairment, reduced visual acuity/photophobia, congenital ichthyosis
Disorders of bile acid biosynthesis				
Cerebrotendinous xanthomatosis	*CYP27A1*	AR	Childhood to adulthood	Cognitive decline, cerebellar ataxia, dystonia/parkinsonism, seizures, peripheral neuropathy, tendon xanthomas, early-onset cataracts
Congenital disorders of glycosylation				
Adult polyglucosan body disease	*GBE1*	AR	Late adulthood	Peripheral neuropathy

* AD, autosomal-dominant; AR, autosomal-recessive.

Table 29.2 SPG-designated disorders with identified metabolic defects

	Gene	Pattern of inheritance*	Metabolic defect	Phenotype
SPG5A	*CYP7B1*	AR	Defect in the degradation of cholesterol to primary bile acids	Pure HSP, or complicated HSP with presence of cerebellar signs, extrapyramidal signs, and peripheral neuropathy
SPG9	*ALDH18A1*	AD or AR	Defect in the biosynthesis of ornithine and proline	Complicated HSP with cataracts, motor neuronopathy, ataxia, and cognitive impairment
SPG11	*SPG11*	AR	Defect of autophagy	Complicated HSP with cognitive impairment, peripheral neuropathy, ataxia, parkinsonism
SPG15	*ZFYVE26*	AR	Defect of autophagy	Complicated HSP with cognitive impairment, peripheral neuropathy, ataxia
SPG26	*B4GALNT1*	AR	Defect in the biosynthesis of complex gangliosides	Complicated HSP with peripheral neuropathy, mild cognitive impairment, cerebellar and extrapyramidal signs
SPG28	*DDHD1*	AR	Defect in phospholipid metabolism	Pure HSP
SPG35	*FA2H*	AR	Impaired hydroxylation of sphingolipid fatty acids	Complicated HSP with dystonia, dysarthria, seizures, and mild cognitive decline
SPG47, SPG50, SPG51, SPG52	*AP4B1, AP4M1, AP4S1, AP4E1*	AR	Deficiency in adaptor protein-4 complex leading to defect of autophagy	Complicated HSP with developmental delay, microcephaly
SPG49	*TECPR2*	AR	Defect of autophagy	Complicated HSP with developmental delay
SPG54	*DDHD2*	AR	Defect in phospholipid metabolism	Complicated HSP with cognitive impairment, optic atrophy
SPG56	*CYP2U1*	AR	Defect in hydroxylation of long-chain fatty acids	Complicated HSP with severe cognitive impairment, dystonia, and peripheral neuropathy

* AD, autosomal-dominant; AR, autosomal-recessive.

according to the latest proposed scheme by the Society for the Study of Inborn Errors of Metabolism, and includes disorders of intermediary metabolism, such as cofactor- and amino acid-related disorders, and disorders of complex molecule metabolism, such as peroxisomal and lysosomal storage disorders that cause various types of leukodystrophies [9, 10]. Many of these conditions are covered in detail in other chapters.

It is important to note that several of spastic paraplegia (SPG)-designated genes have an important association with metabolic defects, including impaired amino acid metabolism, defective fatty acid and phospholipid metabolism, and congenital defects of autophagy, representing an emerging subclass of inherited errors of metabolism. It is beyond the scope of this chapter to present them in detail, but the relevant genes and conditions are summarized in Table 29.2.

Disorders of Intermediary Metabolism

Disorders in the Metabolism of Vitamins and Cofactors

Homocysteine Remethylation Defects (*MTHFR, MMACHC*)

This category includes inherited conditions that are caused by defects in the pathway that involves the remethylation of homocysteine to methionine, associated with reduced activity of methionine

synthase. These include defects in the synthesis of methylcobalamin, which is a cofactor for methionine synthase, and deficiencies in the supply of the substrate 5-methyltetrahydrofolate. The latter is caused by mutations in the *MTHFR* gene that encodes methylenetetrahydrofolate reductase (MTHFR), which is involved in the production of 5-methyltetrahydrofolate, while defects in the synthesis of methylcobalamin are part of the more complex genetic disorders of intracellular cobalamin (Cbl) metabolism (Figure 29.1a). One of the most common inherited errors of cobalamin (vitamin B12) metabolism is caused by mutations in the *MMACHC* gene, which leads to combined methylmalonic acidemia and homocystinuria, cblC type [14, 15].

Both conditions are inherited in an autosomal-recessive pattern. More than 100 mutations have been associated with MTHFR deficiency. No genotype–phenotype correlations have been established, although cases with later onset seem to be associated with residual enzymatic activity [16]. More than 50 mutations in *MMACHC* have been linked with cblC disease and the genotype seems to correlate with the phenotypic classification to early- and late-onset forms [17].

There is incomplete understanding of the underlying pathophysiology, and possible theories include an accumulation of toxic metabolites, oxidative stress, and impaired enzymatic or non-enzymatic protein functions [18]. Although the clinical manifestations of homocysteine remethylation defects can be severe and life-threatening in infantile-onset forms, later-onset cases in childhood, adolescence, or even adulthood have also been reported and are characterized by a complex phenotype, consisting of neurological and hematological manifestations. Neurological symptoms seem to arise due to progressive demyelination affecting the long tracts and causing a clinical presentation that resembles a complex form of HSP [19].

Most cases of MTHFR deficiency present in infancy or childhood. The condition is often characterized by severe encephalopathy, hypotonia, failure to thrive, microcephaly, seizures, and coma, frequently leading to early demise. When the condition manifests after the first year of life the presentation is more insidious with hematological manifestations, usually thrombotic events, and neurological manifestations, including developmental delay and later regression, epilepsy, peripheral neuropathy, and spastic paresis. Cases with onset in adolescence or adulthood have also been identified. Here, the presentation is quite heterogeneous and the phenotype often resembles a complicated slowly progressive HSP, which is commonly preceded or accompanied by cognitive, psychiatric, or behavioral symptoms. Cognitive and psychiatric features may present in episodic fashion as psychotic episodes and relapsing encephalopathy. Epileptic seizures have also been reported [16, 18, 20].

The phenotype of cblC disease is characterized by a wide range of manifestations and age at onset of disease. The earlier onset form of cblC deficiency is associated with intrauterine growth retardation, microcephaly, and dysmorphic features. The infantile-onset form of the disease is the most recognized and is typically associated with hypotonia, failure to thrive, difficulties in feeding, and progressive neurological deterioration. Later-childhood- and adult-onset cases have also been reported and occur after the age of 4 years, and may present in any decade of life. Here, manifestations include cognitive decline, psychiatric symptoms, ataxia, and myelopathy with lower limb weakness and a spastic gait. Additionally, these patients often show hematological complications and thromboembolic events [17, 21].

Brain MRI is usually significant for non-specific white matter abnormalities, usually affecting the posterior areas of the brain. Patients with cblC disease do not have specific radiological findings, but brain atrophy and white matter changes have been reported, particularly in later-onset cases [22].

Homocysteine remethylation defects can be diagnosed by specific changes of laboratory markers. The hallmark feature is hyperhomocysteinemia with levels of >50 μmol/L, and usually >100 μmol/L. In MTHFR deficiency, additional markers include homocystinuria and increased plasma cystathionine with low or normal plasma methionine. Enzymatic activity can also be measured with a direct assay, although this is difficult to perform. Additionally, MTHFR deficiency is characterized by the absence of methylmalonic aciduria, which is commonly present in complex cobalamin metabolism disorders, including cblC deficiency, along with increased plasma methylmalonic acid, homocysteine, and cystathionine. Final confirmation of the diagnosis is made by the identification of pathogenic mutations in the associated genes. Prenatal molecular testing is possible [17, 18].

MTHFR deficiency can be well managed with combined supplementation strategies. This includes the administration of vitamins B12 and B9, in order to increase methionine synthesis, combined with a

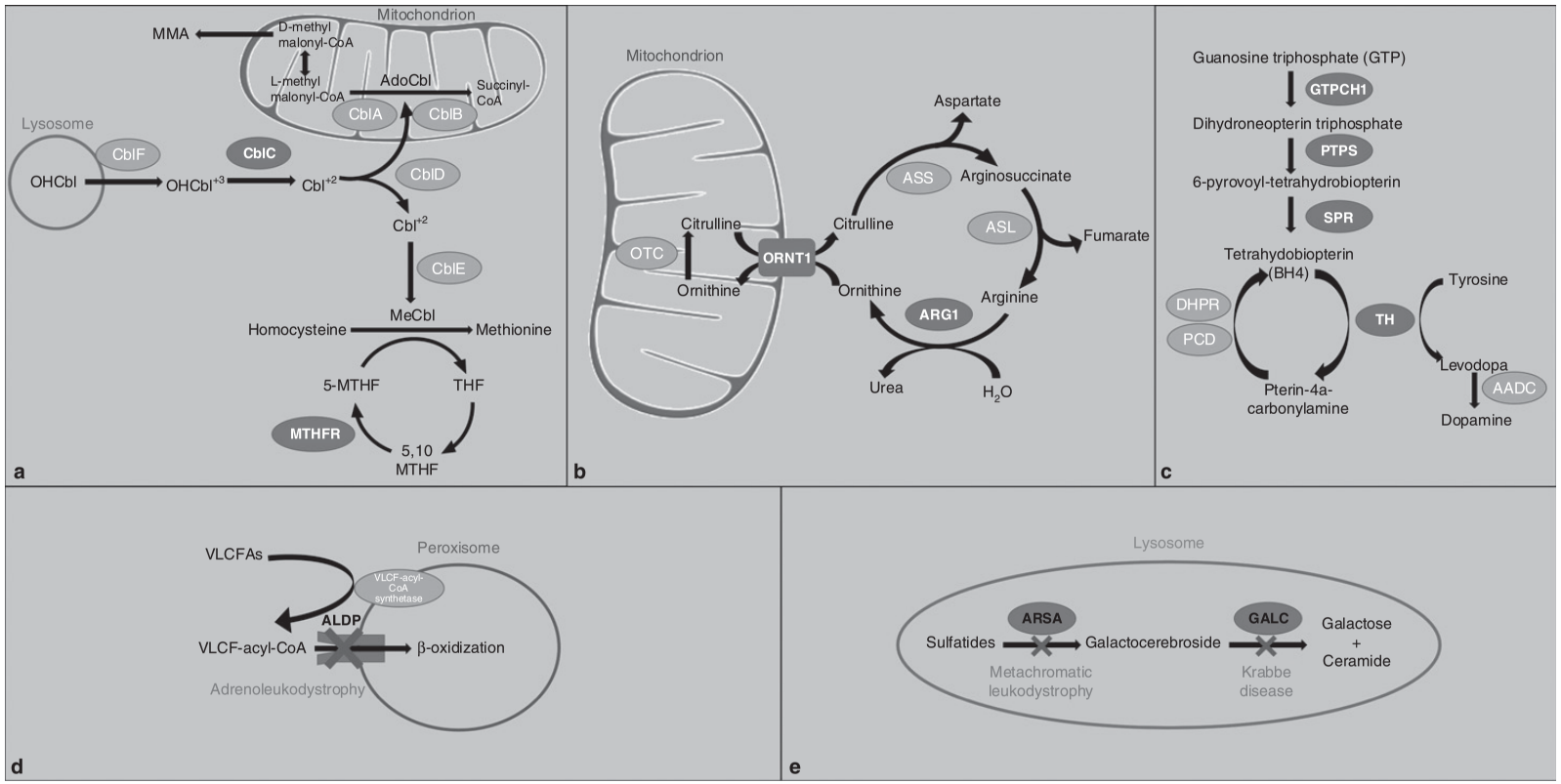

Figure 29.1 Metabolic pathways involved in the most common HSP-related IEMs. (a) Homocysteine remethylation defects include a deficiency of methylenetetrahydrofolate reductase (MTHFR), which is involved in the production of the substrate 5-methyltetrahydrofolate (5-MTHF). This is necessary for the remethylation of homocysteine to methionine, and complex defects of intracellular cobalamin (Cbl) that lead to impaired production of MeCbl, which acts as a cofactor for the remethylation. MTHFR deficiency leads to increased levels of homocysteine, while complex defects, including cblc deficiency, lead to the combined elevation of homocysteine and methylmalonic acid levels. (b) Urea cycle disorders include arginase deficiency (*ARG1*) and ornithine translocase 1 (*ORNT1*) deficiency that causes HHH syndrome. The reaction catalyzed by arginase is the last step in the urea cycle and its deficiency leads to increased levels of arginine and, rarely, to hyperammonemia, while ORNT1 is a mitochondrial transporter and its deficiency causes the typical combination of hyperornithinemia, hyperammonemia, and homocitrullinuria. (c) Dopamine synthesis defects include deficiency of tyrosine hydroxylase (TH), which is the rate-limiting enzyme of catecholamine biosynthesis, or deficiency of the enzymes involved in the biosynthesis of tetrahydrobiopterin (BH4), which is a necessary cofactor for TH, and include GCH1, SPR, and PTPS. (d) Peroxisomal disorders include adrenoleukodystrophy, caused by deficiency of the peroxisomal transporter protein ATP binding cassette subfamily D member 1 (ALDP), leading to the accumulation of very long chain fatty acids (VLCFAs) (e) Lysosomal disorders include metachromatic leukodystrophy caused by a deficiency of arylsulfatase A (ARSA), and Krabbe disease caused by a deficiency of galactosylceramidase (GALC). Both are lysosomal enzymes and they are involved in the metabolism of sulfatides and galactocerebroside. Additional abbreviations: AdoCbl, adenosylcobalamin; ASL, argininosuccinic acid lyase ; ASS, argininosuccinic acid synthetase; DHPR, dihydropteridine reductase; GCH1, GTP cyclohydrolase 1; OHCbl, hydroxycobalamin; OTC, ornithine transcarbamylase; PCD, pterin-4a-carbinolamine dehydratase; PTPS, 6-pyruvoyltetrahydrobiopterin synthase; SPR, sepiapterin reductase; TH, tyrosine hydroxylase; THF, tetrahydrofolate; VLCFA, very long chain fatty acid.

supplementation of methionine and betaine, which is a substrate for an alternative pathway of homocysteine remethylation to methionine. These therapeutic strategies seem to be effective in children and adults, resulting in an inhibition of the progression, or even sometimes improvement of existing neurological symptoms [18, 19]. Patients with cblC disease respond well to parenteral hydroxycobalamin (OHCbl), showing a significant improvement in biological markers, and an improvement of neurological and hematological manifestations [21].

Biotinidase Deficiency (*BTD*)

Biotinidase deficiency represents an inherited defect in the metabolism of biotin, resulting in multiple carboxylase deficiencies. It is inherited in an autosomal-recessive manner and the prevalence is 1 in 60,000 births [23]. The condition causes an abnormal endogenous recycling of biotin, which is an important cofactor for four carboxylases involved in gluconeogenesis, the synthesis of fatty acids, and the catabolism of branched-chain amino acids. Defects in these metabolic pathways have been shown to cause delayed myelination, resulting in several neurological sequelae [24, 25]. There are no clear genotype–phenotype correlations, although a later onset of the disease may be related to the genotype of the condition, especially with missense mutations that allow residual enzyme activity [26].

Biotinidase deficiency usually manifests during infancy or early childhood. Presenting symptoms include a neurocutaneous syndrome with eczematous skin rash, seizures, hypotonia, ataxia, optic atrophy, hearing defects, and developmental delay, as well as respiratory problems. Skin manifestations include alopecia, skin rash due to seborrhea, atopic dermatitis and glossitis. If the condition is left untreated it can lead to coma and death. Some delayed-onset cases have also been reported, occurring in children or even in young adults. In these cases the condition presents mainly with an acute or subacute onset of myelopathy, causing spastic paraparesis, or optic neuropathy, sometimes leading to the misdiagnosis of neuromyelitis optica spectrum disorder. Later-onset cases are associated with residual enzymatic activity and symptoms may be triggered by stress or infections [24, 25, 27].

The diagnosis of biotinidase deficiency is usually made with a direct enzyme assay, showing low or undetectable biotinidase activity (<10% in most severe cases and 10–30% in later-onset cases with partial deficiency) [28]. Additional biochemical markers include elevated blood and CSF lactate and pyruvate levels, as well as elevated urinary excretion of 3-hydroxyisovaleric acid, 3-hydroxypropionate, and 3-methylcrotonyl glycine. MRI can be helpful, particularly in the later-onset presentations, showing diffuse white matter abnormalities suggestive of dysmyelination, brain atrophy, and signs of myelopathy [23]. The confirmation of the diagnosis is based on molecular testing.

The condition is successfully managed with biotin and pyridoxine supplementation, which can result in the prevention of disease progression when administrated early. Unfortunately, replacement therapy does not seem to be equally effective in cases that have already developed severe neurological symptoms due to impaired myelination, resulting in irreversible neurological damage.

Disorders of Amino Acid Metabolism

Urea Cycle Disorders (*ARG1*, *SLC25A1S*)

The urea cycle disorders (UCDs) are a group of IEMs, caused by defects in genes encoding the enzymes and transporters that are involved in the ammonia detoxification pathways. This group of disorders is characterized by the accumulation of ammonia and other intermediate metabolic by-products, causing dysfunction in several organs and systems, including the central nervous system. Among the UCDs, some conditions have been reportedly associated with neurological presentations that in some cases may resemble a slowly progressive complicated form of HSP. Two of these conditions are arginase 1 deficiency, caused by mutations in the *ARG1* gene, and hyperornithinemia–hyperammonemia–homocitrullinuria (HHH) syndrome, caused by mutations in the *SLC25A1S* or *ORNT1* gene that encodes the mitochondrial ornithine translocase 1 (Figure 29.1b). Both conditions follow an autosomal-recessive mode of inheritance and may present with significant phenotypic variability [29].

Hyperargininemia due to arginase 1 deficiency is distinctive among the UCDs for the relatively rare occurrence of hyperammonemia and infrequent hyperammonemic crises. Arginase 1 deficiency is a very rare condition with an estimated prevalence of 1 in 300,000–2,000,000 live births, but it is nevertheless considered one of the most common reversible causes of spastic paraplegia in children. More than

100 mutations in *ARG1* have been associated with hyperarginemia, but no clear genotype–phenotype correlation has been established. Patients with nonsense mutations tend to have more severe disease [30]. The disease onset usually happens during infancy and two distinct forms of presentation have been described so far. The first has an acute onset and episodic presentation with nausea, vomiting, and confusion, usually triggered by high protein intake, similar to other UCDs. Most patients, however, present with a slowly progressive neurological phenotype that consists of spastic paraplegia, cognitive decline, and seizures. Additional clinical features, such as ataxia, dystonia, and extrapyramidal signs, may also be present. Onset can be delayed and many cases are diagnosed during childhood, while rare cases with later initial presentation during adolescence or early adulthood have been reported [31–33]. Given that hyperammonemia is not a prominent feature of the disease, the exact pathogenic mechanism is not yet completely understood, although a neurotoxic role of arginine and its metabolites has been suggested by some studies [34, 35].

HHH syndrome has an estimated prevalence of 1 in 35,000 live births and is also characterized by a variable phenotypic presentation that ranges from mild neurological dysfunction to a severe form with encephalopathy, lethargy, hepatic dysfunction, and seizures. In a systematic review of patients diagnosed with HHH syndrome, four different forms, according to age of onset, were recognized: neonatal (22%), infantile (24%), childhood (44%), and adolescence/adulthood onset (9%). In some cases the diagnosis may be significantly delayed [36]. The clinical presentation can also be separated into acute and chronic forms. The acute presentation is characterized by hyperammonemia that is triggered by a large protein intake. Symptoms consist of nausea and vomiting, ataxia, seizures, confusion, lethargy, or even coma. The chronic presentation is characterized by slowly progressive neurological dysfunction that includes pyramidal signs and lower limb spasticity, learning disabilities, cerebellar signs, and seizures. Episodes of confusion and lethargy may also occur. Many of these patients show a chronic aversion to protein intake that seems to act in a protective fashion [36–38].

On laboratory testing, arginase 1 deficiency is characterized by hyperargininemia, while *SLC25A1S* mutations result in the typical combination of hyperornithinemia, hyperammonemia, and homocitrullinuria. Increased plasma ammonia may be associated with abnormal liver function tests in HHH syndrome, especially during attacks, while they are usually normal in arginase 1 deficiency. Brain MRI may reveal diffuse white matter abnormalities or atrophy in some patients. The diagnosis can be assisted by enzymatic assays and confirmation is made by genetic testing [29].

Both conditions are well managed with a restriction of protein intake and supplementation of essential amino acids. Patients with arginase 1 deficiency who are diagnosed and treated early generally remain asymptomatic. Patients with HHH syndrome are additionally treated with citrulline and arginine supplementation, both in acute crises, as well as for long-term therapy [29].

Phenylketonuria (*PAH*)

Phenylketonuria (PKU) is an autosomal-recessive inborn error of metabolism, caused by the deficiency of the enzyme hepatic phenylalanine hydroxylase (PAH), which is responsible for converting phenylalanine to tyrosine. The resulting accumulation of phenylalanine and its metabolites affects the development of the central nervous system. The prevalence of PKU is one of the highest among the various IEMs, and its incidence is estimated to be around 1:10,000 in Caucasians, although this varies in different populations [39]. Almost 1,000 different mutations in the *PAH* gene have been associated with the condition, the majority being missense mutations. A correlation between the genotype, the residual activity of the enzyme, and the clinical presentation has been confirmed by several studies [40].

PKU usually presents during infancy or early childhood and is characterized by a severe phenotype that includes developmental delay, cognitive decline, and seizures. Neurological damage tends to be irreversible if the condition is left untreated and such cases may present in childhood with intellectual disability, epilepsy, and pyramidal and extrapyramidal signs. In rare cases, PKU presents as a later-onset progressive spastic paraparesis with or without cognitive decline, visual disturbances, ataxia, and parkinsonism. In many instances deterioration has been reported to occur in an acute or subacute manner. Cases of reversible but progressive spastic paraparesis in adult PKU patients have been identified, especially after discontinuing or relaxing the low phenylalanine diet. Finally, many

treated cases can still show attenuated neurological signs, such as tremor, brisk tendon reflexes, poor motor coordination, or epilepsy [40, 41].

Brain MRI can be characteristic in untreated cases, showing typically diffuse white matter abnormalities, predominantly in posterior periventricular regions, and extending to subcortical and frontal regions in more severe cases. The diagnosis is established by the demonstration of elevated serum phenylalanine levels. Additional diagnostic markers include low serum tyrosine levels, and the presence of phenylacetate in the urine. Systematic newborn screening for PKU, established since the second half of the twentieth century in many countries, has significantly reduced the occurrence of undiagnosed and untreated cases, although false negatives in the initial screening may still occur [39].

A low phenylalanine diet is the standard treatment for PKU, while an alternative treatment is the administration of tetrahydrobiopterin (BH4), which is a required cofactor for PAH. Additional potential therapeutic strategies include using benzylhydantoin instead of BH4 and a drug called phenylalanine ammonia lyase (PAL) that is useful in reducing the levels of phenylalanine in the plasma. Many of the patients who present with a later onset of the disease respond well to treatment and usually show significant improvement of the neurological symptoms [42].

Dopamine Synthesis Defects (*GCH1*, *TH*, *SPR*, *PTPS*)

Mutations in genes related to dopamine synthesis are typically associated with dopa-responsive dystonia (DRD). This group of disorders includes defects in the biosynthesis of BH4 or in rate-limiting enzymes of catecholamine biosynthesis: (i) GTP cyclohydrolase 1 (GTPCH1) deficiency, (ii) tyrosine hydroxylase (TH) deficiency, (iii) sepiapterin reductase (SPR) deficiency, and (iv) 6-pyruvoyltetrahydrobiopterin synthase (PTPS) deficiency (Figure 29.1c). Autosomal-dominant *GCH1* mutations were first identified in cases with DRD, also known as Segawa disease or DYT5a dystonia. Subsequently, autosomal-recessive mutations in *GCH1*, as well as in *TH*, *SPR*, and *PTPS* genes have been associated with a similar phenotype, as well as with a wider and more complex range of neurological symptoms. In the latter cases, spasticity is a prominent clinical feature. The term DRD-plus has been proposed to describe these atypical presentations [43–45].

Classic DRD is characterized by childhood or adolescent onset of dystonia with diurnal fluctuations and mild parkinsonism, that responds well to levodopa. Dystonia initially often affects the lower limbs, presenting with toe walking and frequent falls, while brisk tendon reflexes are not uncommon. Atypical DRD, or DRD-plus syndromes, include cases of juvenile parkinsonism, ataxia, and spastic paraplegia [46]. Later-adulthood-onset cases have also been reported, presenting with parkinsonism, focal dystonia, or, occasionally, with no dystonia at all [45].

The most common cause of DRD is autosomal-dominant *GCH1* mutations and patients usually show an excellent and sustained response to levodopa. Autosomal-recessive *GCH1* patients may present with more complex phenotypes, usually in infancy, that include limb spasticity, axial hypotonia, oculogyric crises, and delay in motor and cognitive development. Some of these patients show only a partial response to levodopa. TH deficiency has a wide clinical spectrum ranging from severe progressive encephalopathy to typical DRD. Complex DRD-plus syndromes have also been reported with a few cases resembling spastic paraplegia. SPR deficiency may present as typical DRD or a more complex DRD-plus with spasticity, axial hypotonia, ataxia, oculogyric crises, developmental delay, and cognitive decline. Finally, patients with PTPS deficiency usually have earlier-onset and severe and complex presentations with axial hypotonia, limb spasticity, seizures, psychiatric symptoms, and cognitive defects. These patients may have poor motor outcomes [45, 47–49].

The diagnosis of dopamine synthesis defects is supported by specific changes in the blood and CSF levels of neopterin, biopterin, homovanillic acid, and 5-hyroxyindolacetic acid. Hyperphenylalaninemia may be found in cases with autosomal-recessive *GCH1*, *TH* and *PTPS* mutations. A helpful diagnostic tool in selected cases is the oral phenylalanine loading test, with an increase in the phenylalanine:tyrosine ratios and biopterin concentrations in plasma being diagnostic. Brain MRI usually shows no significant abnormalities.

Treatment is based on the administration of levodopa or dopamine agonists with a good response and long-term benefit in most cases. The response to levodopa varies though and seems to correlate with the associated genotype. Patients that harbor autosomal-dominant *GCH1* and *SPR* mutations overall have the best motor outcomes. A dopamine trial should be offered in all patients with symptoms suggestive of dopamine synthesis defects, even if the presentation might seem atypical [50].

Organic Acidurias

3-Methylglutaconic Aciduria Type 3 (*OPA3*)

Bi-allelic mutations in *OPA3* gene have been associated with a rare neuro-ophthalmological syndrome, known as Costeff syndrome. The disorder is caused by secondary 3-methylglutaconic aciduria (type 3), due to a mitochondrial membrane-associated defect. The exact function of the gene product remains unknown, although a possible role in the regulation of mitochondrial morphology, fusion, and fission has been suggested. More than 250 mutations have been reported to date [51, 52].

Bilateral optic atrophy along with a progressive complex motor disorder, including mainly spasticity, choreoathetosis and ataxia are the hallmark features of the disease. Mild cognitive deficits may be present. Most patients eventually develop spastic paraparesis and cases with early-onset pyramidal signs and marked lower limb spasticity and dystonia have also been reported [52].

Brain MRI usually reveals cerebellar atrophy. The diagnosis is suspected based on the detection of elevated levels of urinary 3-methylglutaconic acid and 3-methylglutaric acid and is confirmed by the presence of mutations in *OPA3* [52].

No effective treatment is available to date. Patients are managed symptomatically for visual impairment, spasticity and movement disorders.

Disorders of Complex Molecule Metabolism

Peroxisomal Disorders

Adrenoleukodystrophy (*ABCD1*)

Adrenoleukodystrophy is an X-linked leukodystrophy that is caused by impaired oxidation of very long chain fatty acids (VLCFAs) leading to their accumulation in the central nervous system, adrenal glands, and other tissues. The responsible gene is *ABCD1*, which encodes the peroxisomal transporter protein ATP-binding cassette subfamily D member 1 (ALDP) (Figure 29.1d). The accumulation of VLFCAs in the central nervous system is thought to have a toxic effect on neurons, causing demyelination and eventually leading to a slowly progressive dying-back axonopathy, affecting ascending and descending spinal pathways [53, 54].

The condition typically presents in males and is characterized by a range of associated phenotypes that are specific to the age of onset. These phenotypes include: (1) classic Addison's disease due to adrenal insufficiency; (2) X-linked adrenoleukodystrophy, a childhood-onset rapidly progressive cerebral form with cognitive and behavioral symptoms, hearing and visual defects, and adrenocortical insufficiency; and (3) adult-onset adrenomyeloneuropathy (AMN). AMN is defined by the presence of progressive myelopathy and peripheral neuropathy and is characterized by progressive spastic paraparesis, bladder dysfunction, and distal sensory impairment. Female carriers can also present signs of the condition, resembling a milder AMN phenotype usually with later age of onset [53, 55].

MRI of the brain usually reveals characteristic findings in patients with adrenoleukodystrophy. These include diffuse white matter lesions in the parieto-occipital regions, often involving the splenium of the corpus callosum in the childhood-onset form, while in patients with AMN the internal capsule and brainstem are often involved.

The detection of increased plasma VLFCA levels is typical for adrenoleukodystrophy and adrenomyeloneuropathy. The diagnosis is confirmed by the presence of a pathogenic variant in *ABCD1*. No phenotype–genotype correlation has been established so far.

In terms of management, it is generally accepted that allogeneic hematopoietic cell transplantation is the only effective treatment for the cerebral forms of the disease and when it is performed early it can prevent disease progression. *Ex vi*vo gene therapy may be a safe and effective alternative to allogeneic stem-cell transplantation in patients with early-stage cerebral adrenoleukodystrophy. Unfortunately there is no effective treatment for AMN. The effectiveness of Lorenzo's oil, suggested by earlier studies, has not been confirmed in large placebo-controlled trials [53].

Lysosomal Disorders

Metachromatic Leukodystrophy (*ARSA*)

Metachromatic leukodystrophy is an autosomal-recessive lysosomal disorder, caused by a deficiency of arylsulfatase A (Figure 29.1e), which results in the accumulation of sulfatides in the central and peripheral nervous systems. The condition is caused by bi-allelic mutations in the *ARSA* gene and the estimated prevalence is at 1.4–1.8 in 100,000 live births. More

than 160 disease-causing mutations have been recognized, and many of them produce null alleles, while others result in pseudoefficient alleles with 10–15% residual enzyme activity. A more rare cause of the condition is saposin B deficiency due to mutations in the *PSAP* gene [56–58].

The disorder is classified into three clinical subtypes: late-infantile, juvenile, and adult forms. The phenotype seems to correlate with the residual enzyme activity. The late-infantile form has an onset of before 30 months of age and is characterized by rapid neurocognitive and motor decline, with ataxia, epileptic seizures, and early hypotonia that can evolve to spasticity. The mortality rate is high. Juvenile and adult forms have more variable phenotypic presentations, with either more prominent cerebellar and pyramidal signs, or mainly cognitive and behavioral problems. Peripheral neuropathy is common.

Brain MRI typically shows large symmetrical confluent supratentorial periventricular white matter lesions, usually demonstrating a characteristic pattern with tigroid stripes. The corpus callosum is typically involved early, while subcortical fibers can also be affected with disease progression. Some later-onset cases present a predominantly frontal distribution of the white matter lesions [57, 59, 60].

The diagnosis is based on enzymatic assays showing low arylsulfatase A activity in leukocytes and can be assisted by the detection of sulfatides in the urine and a nerve biopsy showing the characteristic staining. Laboratory diagnosis can be hindered by pitfalls related to residual enzymatic activity of arysulfatase A, or when saposin B deficiency is the cause. Therefore, confirmation of the diagnosis with molecular genetic techniques is often necessary [57, 59].

There is no effective treatment for metachromatic leukodystrophy. The only treatment available today is hematopoietic stem-cell transplantation, which may halt or slow down disease progression, when performed early. The results are not satisfactory though in patients with the late-infantile form, as well as in many adult patients that have already developed significant neurological deficits. Other potential therapeutic strategies include enzyme-replacement therapy and gene therapy, with several animal and clinical studies performed to date, showing promising results [57, 59, 61].

Krabbe Disease (*GALC*)

Krabbe disease is inherited in an autosomal-recessive manner and is caused by a deficiency of the lysosomal enzyme galactosylceramidase (GALC), which is responsible for the degradation of galactocerebroside to ceramide and galactose (Figure 29.1e). Defects in the enzyme, caused by mutations in the *GALC* gene, lead to the accumulation of galactosylsphingosine, a by-product of the alternative catabolic pathway of galactocerebroside. More than 130 pathogenic mutations in *GALC* have been reported and the estimated prevalence of the disease is 1 in 100,000 live births [58, 62]. No specific phenotype–genotype correlations have been established [63].

The most common presentation of Krabbe disease is an infantile form of leukodystrophy with a severe phenotype, consisting of severe psychomotor regression, irritability, seizures, and progressive spasticity. This infantile form usually progresses rapidly, and is almost universally fatal before the age of 3 years. There is a later-onset form with a variable phenotype and disease progression [60, 62, 64]. Most of these cases have an onset within the first 10 years of life, and usually have a complex phenotype consisting of cognitive decline, spasticity, ataxia, and optic atrophy. Some rare adult-onset cases may present with spastic paraparesis with or without additional symptoms, such as ataxia, vision impairment due to optic atrophy, and peripheral neuropathy [65–67].

Neuroimaging usually shows symmetrical cerebral and cerebellar white matter abnormalities due to demyelination. There seems to be a posterior predominance and midbrain atrophy seems to correlate with the disease progression [68].

The diagnosis of Krabbe disease is suspected upon detection of low galactocerebrosidase levels in leukocytes and confirmed by the detection of bi-allelic variants in *GALC*.

No effective treatment has been established so far. Hematopoietic stem-cell transplantation seems to show some benefit when used early. Symptomatic management of spasticity, seizures, and prevention of infections is important [69]. Recent studies have suggested the use of chaperones as a potential therapeutic strategy to restore enzymatic activity of GALC [70].

Disorders of Lipid and Lipoprotein Metabolism

Sjögren–Larsson Syndrome (*ALDH3A2*)

Sjögren–Larsson syndrome (SLS) is an autosomal-recessive disease caused by mutations in *ALDH3A2* that result in deficiency of fatty aldehyde dehydrogenase (FALDH), which catalyzes the oxidation of long-

chain aliphatic aldehydes and alcohols to corresponding fatty acids. This leads to an accumulation of fatty aldehydes or fatty alcohol in tissues, such as the skin and brain. The condition is ultra-rare with an incidence of 0.4 in 100,000 live births [71, 72].

The phenotype of SLS is defined by a childhood-onset neurocutaneous syndrome consisting of congenital ichthyosis, spastic paresis evolving to quadriplegia, and cognitive impairment. Common additional features include dysarthria and reduced visual acuity with photophobia. Brain MRI usually shows diffuse white matter abnormalities, indicating delayed myelination [71, 72]. When the diagnosis is suspected, testing should include FALDH activity in patient-derived fibroblasts, which is usually low. Additional laboratory tests include the detection of increased levels of fatty alcohols and leukotriene B4 in the blood and urine, although these tests are difficult to perform. The diagnosis is confirmed when bi-allelic mutations in *ALDH3A2* are found. Treatment is symptomatic [71, 72].

Disorders of Bile Acid Biosynthesis

Cerebrotendinous Xanthomatosis (*CYP27A1*)

Cerebrotendinous xanthomatosis (CTX) is caused by bi-allelic mutations in *CYP27A1* gene, which encodes the mitochondrial enzyme sterol 27-hydroxylase that is involved in the bile synthesis pathway by converting cholesterol to cholic acid and chenodeoxycholic acid (CDCA). Decreased synthesis of bile acid, inadequate feedback inhibition of cholesterol production, and subsequently abnormal deposition of cholestanol and cholesterol in tissues and organs are the hallmark features of CTX. The estimated worldwide prevalence lies at 3–5 in 100,000. No genotype–phenotype correlations have been established so far [73, 74].

The phenotypic presentation of CTX can be insidious but progressive with a combination of neurological and non-neurological manifestations. Typical clinical features include the presence of tendon xanthomas (although these might occur late in the disease course), bilateral childhood-onset cataracts, and various neurological manifestations, including progressive spastic paraparesis, cognitive decline, cerebellar ataxia, dystonia/parkinsonism, psychiatric symptoms, seizures, and peripheral neuropathy. Common early features of the disease include gastrointestinal symptoms, with neonatal cholestatic jaundice and childhood-onset intractable diarrhea, long before neurological symptoms present in adolescence or adulthood. A classification of patients into two distinct groups, according to their clinical presentation, has been suggested and lists a classic form with predominantly cerebellar and other supratentorial symptoms, and a less common spinal form, characterized by the presence of chronic myelopathy. Occasionally, neurological symptoms may be the first presentation of the disease, for example developmental delay and learning disabilities. Additional systematic clinical features may also include early arteriosclerosis and osteoporosis in adults [73–76].

MRI often shows cerebellar and cerebral atrophy, white matter abnormalities in the brain and spinal cord, and T2 hyperintensities of the deep gray matter, including the dentate nucleus, which is a characteristic feature of the disease [73, 74].

The diagnosis of CTX may be challenging due to the slowly progressive course of the disease and the wide range of presenting symptoms. A thorough clinical examination is therefore essential. A combination of at least two out of the following four clinical hallmarks are suggestive of CTX: tendon xanthomas, early-onset cataracts, intractable diarrhea, and progressive neurological manifestations. Laboratory evaluation requires screening for plasma cholestanol levels that is usually increased more than five-fold times than normal. Additional biochemical biomarkers include increased levels of bile alcohols in the urine and plasma, and decreased levels of CDCA in bile. Confirmation of the diagnosis is made with genetic testing [73, 74].

The treatment of CTX is based on supplementation with CDCA, which is effective both in normalizing the biochemical markers and improving the neurological symptoms. Patients with an earlier diagnosis and early initiation of treatment, before irreversible neurological damage occurs, show better outcomes [73, 74].

Congenital Disorders of Glycosylation

Adult-Onset Polyglucosan Body Disease (*GBE1*)

Adult-onset polyglucosan body disease (APBD) is a rare autosomal-recessive, adulthood-onset error of glycosylation, associated with the deficiency of glycogen branching enzyme (GBE) that leads to the accumulation of polyglucosan bodies in the central and peripheral nervous system. It is caused by bi-allelic mutations in *GBE1* and it is allelic to glycogen storage disease, type IV. To date, around 20 different mutations in *GBE1* have been associated with APBD and are more commonly found in the Ashkenazi Jewish population [77, 78].

The condition usually presents in the fifth or sixth decade of life and is characterized by progressive spastic paraparesis, accompanied by neurogenic bladder and distal axonal peripheral neuropathy. Various atypical presentations have also been reported and include parkinsonian syndromes, motor neuron disease, episodic vomiting, plexopathy, and cognitive decline resembling frontotemporal dementia [77, 78].

Imaging findings include atrophy of medulla and cervical spinal cord, and periventricular white matter lesions. Nerve biopsies may show characteristic deposition of polyglucosan bodies. The diagnosis is made with assays showing a reduced activity of the enzyme in fibroblasts and molecular genetic testing. No effective treatment is available [77, 78].

Conclusions

IEMs represent a rare but important cause of an HSP phenotype that should be considered in previously undiagnosed cases. Most of the associated metabolic defects result in the dysfunction of myelin, leading to dys- or demyelination and loss of neurons. The underlying pathophysiological mechanisms include impaired enzymatic function, the accumulation of toxic metabolites, and increased oxidative stress.

Various neurological symptoms may be present but spastic paraparesis is often a dominant feature. Additional manifestations include cognitive dysfunction, cerebellar ataxia, optic atrophy, and peripheral neuropathy, while others such as seizures or psychiatric symptoms may also be present. Non-neurological manifestations are common in specific IEMs, and the recognition of their presence in combination with a constellation of neurological symptoms can assist the clinical diagnosis.

The severity of phenotypes usually depends on the age of onset. Many of the disorders reviewed here present with severe infantile forms. In other cases, later onset during childhood, adolescence or even adulthood results in milder phenotypes that often resemble pure or complicated HSP. Clear genotype–phenotype correlations are often missing.

Brain MRI frequently demonstrates white matter abnormalities suggestive of dysmyelination or demyelination and additional tests, such as nerve conduction studies to identify peripheral neuropathy, can assist a diagnosis. For all metabolic disorders, specific laboratory tests that support the diagnosis are available and can guide differential diagnosis (Table 29.3). The final confirmation of the diagnosis is made with genetic testing.

Finally, it is important to stress that some IEMs with an HSP phenotype can be well managed with replacement therapies or dietary restrictions. Some cases show minimal clinical features when the diagnosis is made promptly and treatment is instituted early, and other cases may have reversible symptoms with targeted management.

Key Points and Clinical Pearls

- Inborn errors of metabolism (IEMs) represent a rare but important cause of hereditary spastic paraplegia (HSP) phenotypes both in children and adults.
- Childhood-onset IEMs tend to resemble complex HSP whereas late-onset IEMs often present with an ameliorated phenotype that may mimic pure HSP.
- Specific non-neurological manifestations can act as a diagnostic clue to some IEMs that resemble HSP.
- In IEMs that mimic HSP, brain MRI often demonstrates white matter abnormalities suggestive of dysmyelination or demyelination. Specific laboratory test and - where available - next-generation sequencing based molecular testing can establish a diagnosis.

Directions for Future Research

- The use of molecular analysis techniques will increase the detection of rare genetic conditions in previously undiagnosed patients.
- The use of bioinformatics allows an advanced multiomics analysis approach for future studies, including studies on genetic variability, clinicogenetic heterogeneity and possible genotype–phenotype correlations, as well as large-scale metabolomics and transcriptomics.
- The use of induced pluripotent stem cells allows the development of disease-specific models, which represent a useful and more targeted research approach in ultra-rare conditions, such as most of the IEMs.
- New therapy strategies could potentially include enzyme-replacement therapies, cellular therapies, and gene replacement and gene editing approaches.

Table 29.3 Laboratory investigations useful in diagnostic approach of suspected IEMs

Laboratory tests and diagnostic procedures	Findings in associated conditions	Additional diagnostic tests
Plasma homocysteine levels	Increased in MTHFR deficiency and cblC disease (>50–100 μmol/L)	Low plasma methionine, increased plasma cystathionine
Plasma and urine methylmalonic acid	Increased in cblC disease	
Biotinidase enzyme panel	Reduced activity (<10%) in BTD	Elevated urine levels of 3-hydroxyisovaleric acid, 3-hydroxypropionate, and 3-methylcrotonyl glycine
Plasma ammonia levels, plasma and urine amino acid analysis	Argininemia (arginase 1 deficiency), hyperornithinemia, hyperammonemia, and homocitrullinuria (HHH syndrome)	Elevated plasma ammonia and liver function tests during attacks in arginase 1 deficiency
Plasma phenylalanine levels	Increased in phenylketonuria	Low tyrosine levels in plasma, presence of phenylacetate in urine
Dopamine trial	Positive response in dopa-responsive dystonia	Low/normal CSF levels of biopterins, neopterins, homovanillic acid, and 5-hyroxyindolacetic acid, hyperphenylalaninemia (autosomal-recessive *GCH1*, *TH*, and *PTPS*), positive phenylalanine loading test
Urine 3-methylglutaconic acid and 3-methylglutaric acid levels	Elevated in 3-methylglutaconic aciduria type 3	
Plasma VLCFA levels	Increased in adrenoleukodystrophy	Brain MRI findings suggestive of leukodystrophy
Arylsulfatase-A enzyme panel	Reduced activity (<10%) in metachromatic leukodystrophy	Brain MRI findings suggestive of leukodystrophy, nerve biopsy showing metachromatic staining, detection of sulfatides in urine
Galactocerebrosidase activity in leukocytes	Reduced in Krabbe disease	Brain MRI findings suggestive of leukodystrophy, increased CSF protein levels
FALDH enzyme panel (in cultured skin fibroblasts)	Reduced activity in Sjögren–Larsson syndrome	Detection of abnormal metabolites of leukotriene B4 in urine
Plasma cholestanol levels	Increased in cerebrotendinous xanthomatosis	Normal/low plasma cholesterol levels, decreased CDCA in bile, increased levels of bile alcohols in urine and plasma, increased CSF levels of cholestanol and apolipoprotein B
GBE enzyme panel (in cultured skin fibroblasts)	Reduced activity in adult-onset polyglucosan body disease	Brain and spine MRI showing typical findings, sural nerve biopsy showing deposition of polyglucosan bodies

References

1. Parodi L, Fenu S, Stevanin G, Durr A. Hereditary spastic paraplegia: More than an upper motor neuron disease. Rev Neurol (Paris). 2017;**173**(5):352–60.
2. Finsterer J, Loscher W, Quasthoff S, et al. Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance. J Neurol Sci. 2012; **318** (1-2): 1-18.
3. Renvoise B, Blackstone C. Hereditary spastic paraplegias: Genetics and clinical features. In LeDoux MS, editor. Movement Disorders: Genetics and Models. 2nd edn. Academic Press; 2015, pp. 1063–71.
4. Schule R, Schols L. Genetics of hereditary spastic paraplegias. Semin Neurol. 2011;**31**(5): 484–93.
5. Blackstone C. Hereditary spastic paraplegia. Handb Clin Neurol. 2018;**148**:633–52.
6. Lo Giudice T, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A. Hereditary spastic paraplegia: Clinical–genetic characteristics and evolving molecular mechanisms. Exp Neurol. 2014;**261**:518–39.
7. Hedera P. Hereditary and metabolic myelopathies. Handb Clin Neurol. 2016;**136**:769–85.
8. de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, Bortholin T, Oliveira ASB. Hereditary

spastic paraplegia: Clinical and genetic hallmarks. Cerebellum. 2017;**16**(2):525–51.

9. Ezgu F. Inborn errors of metabolism. Adv Clin Chem. 2016;**73**:195–250.
10. Saudubray JM, Garcia-Cazorla A. Inborn errors of metabolism overview: Pathophysiology, manifestations, evaluation, and management. Pediatr Clin North Am. 2018;**65**(2):179–208.
11. Sedel F, Fontaine B, Saudubray JM, Lyon-Caen O. Hereditary spastic paraparesis in adults associated with inborn errors of metabolism: A diagnostic approach. J Inherit Metab Dis. 2007;**30**(6):855–64.
12. de Bot ST, van de Warrenburg BP, Kremer HP, Willemsen MA. Child neurology: Hereditary spastic paraplegia in children. Neurology. 2010;**75**(19):e75–9.
13. Mochel F, Sedel F. Inborn errors of metabolism in adults: A diagnostic approach to neurological and psychiatric presentations. In Saudubray JM, Baumgartner M, Walter J, editors. Inborn Metabolic Diseases. Berlin: Springer-Verlag; 2016, pp. 71–89.
14. Fowler B. Homocysteine: Overview of biochemistry, molecular biology, and role in disease processes. Semin Vasc Med. 2005;**5**(2):77–86.
15. Watkins D, Rosenblatt DS. Inborn errors of cobalamin absorption and metabolism. Am J Med Genet C Semin Med Genet. 2011;**157C**(1):33–44.
16. Froese DS, Huemer M, Suormala T, et al. Mutation update and review of severe methylenetetrahydrofolate reductase deficiency. Hum Mutat. 2016;**37**(5):427–38.
17. Carrillo-Carrasco N, Chandler RJ, Venditti CP. Combined methylmalonic acidemia and homocystinuria, cblC type. I. Clinical presentations, diagnosis and management. J Inherit Metab Dis. 2012;**35**(1):91–102.
18. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis. 2017;**40**(1):21–48.
19. Schiff M, Benoist JF, Tilea B, et al. Isolated remethylation disorders: Do our treatments benefit patients? J Inherit Metab Dis. 2011;**34**(1):137–45.
20. Gales A, Masingue M, Millecamps S, et al. Adolescence/adult onset MTHFR deficiency may manifest as isolated and treatable distinct neuro-psychiatric syndromes. Orphanet J Rare Dis. 2018;**13**:29.
21. Liu YR, Ji YF, Wang YL, et al. Clinical analysis of late-onset methylmalonic acidaemia and homocystinuria, cblC type with a neuropsychiatric presentation. J Neurol Neurosurg Psychiatry. 2015;**86**(4):472–5.
22. Wang SJ, Yan CZ, Liu YM, Zhao YY. Late-onset cobalamin C deficiency Chinese sibling patients with neuropsychiatric presentations. Metab Brain Dis. 2018;**33**(3):829–35.
23. Desai S, Ganesan K, Hegde A. Biotinidase deficiency: A reversible metabolic encephalopathy. Neuroimaging and MR spectroscopic findings in a series of four patients. Pediatr Radiol. 2008;**38**(8):848–56.
24. Wolf B. Clinical issues and frequent questions about biotinidase deficiency. Mol Genet Metab. 2010;**100**(1):6–13.
25. Raha S, Udani V. Biotinidase deficiency presenting as recurrent myelopathy in a 7-year-old boy and a review of the literature. Pediatr Neurol. 2011;**45**(4):261–4.
26. Sivri HS, Genc GA, Tokatli A, et al. Hearing loss in biotinidase deficiency: Genotype–phenotype correlation. J Pediatr. 2007;**150**(4):439–42.
27. Yilmaz S, Serin M, Canda E, et al. A treatable cause of myelopathy and vision loss mimicking neuromyelitis optica spectrum disorder: Late-onset biotinidase deficiency. Metab Brain Dis. 2017;**32**(3):675–8.
28. Strovel ET, Cowan TM, Scott AI, Wolf B. Laboratory diagnosis of biotinidase deficiency, 2017 update: A technical standard and guideline of the American College of Medical Genetics and Genomics (Published erratum: Genet Med 2018 Feb; **20**(2):282). Genet Med. 2017;**19**(10);doi:10.1038/gim.2017.84.
29. Haberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012;**7**:32.
30. Sin YY, Baron G, Schulze A, Funk CD. Arginase-1 deficiency. J Mol Med (Berl). 2015;**93**(12):1287–96.
31. Scaglia F, Lee B. Clinical, biochemical, and molecular spectrum of hyperargininemia due to arginase I deficiency. Am J Med Genet C Semin Med Genet. 2006;**142C**(2):113–20.
32. Baranello G, Alfei E, Martinelli D, et al. Hyperargininemia: 7-Month follow-up under sodium benzoate therapy in an Italian child presenting progressive spastic paraparesis, cognitive decline, and novel mutation in *ARG1* gene. Pediatr Neurol. 2014;**51**(3):430–3.
33. Carvalho DR, Brum JM, Speck-Martins CE, et al. Clinical features and neurologic progression of hyperargininemia. Pediatr Neurol. 2012;**46**(6):369–74.
34. Deignan JL, Marescau B, Livesay JC, et al. Increased plasma and tissue guanidino compounds in a mouse model of hyperargininemia. Mol Genet Metab. 2008;**93**(2):172–8.
35. Deignan JL, De Deyn PP, Cederbaum SD, et al. Guanidino compound levels in blood, cerebrospinal fluid, and post-mortem brain material of patients

with argininemia. Mol Genet Metab. 2010;**100** Suppl 1:S31–6.

36. Martinelli D, Diodato D, Ponzi E, et al. The hyperornithinemia–hyperammonemia–homocitrullinuria syndrome. Orphanet J Rare Dis. 2015;**10**:29.
37. Kim SZ, Song WJ, Nyhan WL, et al. Long-term follow-up of four patients affected by HHH syndrome. Clin Chim Acta. 2012; **413** (13-14): 1151–5.
38. Qadri SK, Ting TW, Lim JS, Jamuar SS. Milder form of urea cycle defect revisited: Report and review of hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome diagnosed in a teenage girl presenting with recurrent encephalopathy. Ann Acad Med Singapore. 2016;**45**(12):563–6.
39. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010;**376**(9750):1417–27.
40. Blau N. Genetics of phenylketonuria: Then and now. Hum Mutat. 2016;**37**(6):508–15.
41. Trefz F, Maillot F, Motzfeldt K, Schwarz M. Adult phenylketonuria outcome and management. Mol Genet Metab. 2011;**104** Suppl:S26–30.
42. van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: Diagnosis and treatment. Orphanet J Rare Dis. 2017;**12**:162.
43. Hyland K. Inherited disorders affecting dopamine and serotonin: Critical neurotransmitters derived from aromatic amino acids. J Nutr. 2007;**137**(6 Suppl 1):1568S–72S; discussion 73S–75S.
44. Wijemanne S, Jankovic J. Dopa-responsive dystonia: Clinical and genetic heterogeneity. Nat Rev Neurol. 2015;**11**(7):414–24.
45. Lee WW, Jeon BS. Clinical spectrum of dopa-responsive dystonia and related disorders. Curr Neurol Neurosci Rep. 2014;**14**(7):461.
46. Lee WW, Jeon B, Kim R. Expanding the spectrum of dopa-responsive dystonia (DRD) and proposal for new definition: DRD, DRD-plus, and DRD look-alike. J Korean Med Sci. 2018;**33**(28):e184.
47. Friedman JR. What is not in the name? Dopa-responsive dystonia may respond to more than L-dopa. Pediatr Neurol. 2016;**59**:76–80.
48. Leuzzi V, Carducci CA, Carducci CL, et al. Phenotypic variability, neurological outcome and genetics background of 6-pyruvoyl-tetrahydropterin synthase deficiency. Clin Genet. 2010;**77**(3):249–57.
49. Giovanniello T, Leuzzi V, Carducci C, et al. Tyrosine hydroxylase deficiency presenting with a biphasic clinical course. Neuropediatrics. 2007;**38**(4):213–5.
50. Kim R, Jeon B, Lee WW. A systematic review of treatment outcome in patients with dopa-responsive dystonia (DRD) and DRD-plus. Mov Disord Clin Pract. 2016;**3**(5):435–42.
51. Wortmann SB, Duran M, Anikster Y, et al. Inborn errors of metabolism with 3-methylglutaconic aciduria as discriminative feature: Proper classification and nomenclature. J Inherit Metab Dis. 2013;**36**(6):923–8.
52. Yahalom G, Anikster Y, Huna-Baron R, et al. Costeff syndrome: Clinical features and natural history. J Neurol. 2014;**261**(12):2275–82.
53. Engelen M, Kemp S, Poll-The BT. X-linked adrenoleukodystrophy: Pathogenesis and treatment. Curr Neurol Neurosci Rep. 2014;**14**(10):486.
54. Berger J, Forss-Petter S, Eichler FS. Pathophysiology of X-linked adrenoleukodystrophy. Biochimie. 2014;**98**:135–42.
55. Kemp S, Pujol A, Waterham HR, et al. *ABCD1* mutations and the X-linked adrenoleukodystrophy mutation database: Role in diagnosis and clinical correlations. Hum Mutat. 2001;**18**(6):499–515.
56. Rauschka H, Colsch B, Baumann N, et al. Late-onset metachromatic leukodystrophy: Genotype strongly influences phenotype. Neurology. 2006;**67**(5):859–63.
57. van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: Disease spectrum and approaches for treatment. Best Pract Res Clin Endocrinol Metab. 2015;**29**(2):261–73.
58. Ferreira CR, Gahl WA. Lysosomal storage diseases. Transl Sci Rare Dis. 2017; **2** (1–2): 1–71.
59. Gieselmann V, Krageloh-Mann I. Metachromatic leukodystrophy: An update. Neuropediatrics. 2010;**41**(1):1–6.
60. Kohlschutter A. Lysosomal leukodystrophies: Krabbe disease and metachromatic leukodystrophy. Handb Clin Neurol. 2013;**113**:1611-8.
61. Rosenberg JB, Kaminsky SM, Aubourg P, Crystal RG, Sondhi D. Gene therapy for metachromatic leukodystrophy. J Neurosci Res. 2016;**94**(11):1169–79.
62. Wenger DA, Rafi MA, Luzi P. Krabbe disease: One hundred years from the bedside to the bench to the bedside. J Neurosci Res. 2016;**94**(11):982–9.
63. Tappino B, Biancheri R, Mort M, et al. Identification and characterization of 15 novel *GALC* gene mutations causing Krabbe disease. Hum Mutat. 2010;**31**(12):E1894–914.
64. Suzuki K. Globoid cell leukodystrophy (Krabbe's disease): Update. J Child Neurol. 2003;**18**(9):595–603.
65. Tokushige S, Sonoo T, Maekawa R, et al. Isolated pyramidal tract impairment in the central nervous

system of adult-onset Krabbe disease with novel mutations in the *GALC* gene. Brain Dev. 2013;**35**(6):579–81.

66. Debs R, Froissart R, Aubourg P, et al. Krabbe disease in adults: Phenotypic and genotypic update from a series of 11 cases and a review. J Inherit Metab Dis. 2013;**36**(5):859–68.
67. Shao YH, Choquet K, La Piana R, et al. Mutations in *GALC* cause late-onset Krabbe disease with predominant cerebellar ataxia. Neurogenetics. 2016;**17**(2):137–41.
68. Zuccoli G, Narayanan S, Panigrahy A, Poe MD, Escolar ML. Midbrain morphology reflects extent of brain damage in Krabbe disease. Neuroradiology. 2015;**57**(7):739–45.
69. Escolar ML, West T, Dallavecchia A, Poe MD, LaPoint K. Clinical management of Krabbe disease. J Neurosci Res. 2016;**94**(11):1118–25.
70. Graziano AC, Pannuzzo G, Avola R, Cardile V. Chaperones as potential therapeutics for Krabbe disease. J Neurosci Res. 2016;**94**(11):1220–30.
71. Fuijkschot J, Theelen T, Seyger MM, et al. Sjögren–Larsson syndrome in clinical practice. J Inherit Metab Dis. 2012;**35**(6):955–62.
72. Cho KH, Shim SH, Kim M. Clinical, biochemical, and genetic aspects of Sjögren–Larsson syndrome. Clin Genet. 2018;**93**(4):721–30.–
73. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: A comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;**9**:179.
74. Salen G, Steiner RD. Epidemiology, diagnosis, and treatment of cerebrotendinous xanthomatosis (CTX). J Inherit Metab Dis. 2017;**40**(6):771–81.
75. Sekijima Y, Koyama S, Yoshinaga T, Koinuma M, Inaba Y. Nationwide survey on cerebrotendinous xanthomatosis in Japan. J Hum Genet. 2018;**63**(3):271–80.
76. Pilo-de-la-Fuente B, Jimenez-Escrig A, Lorenzo JR, et al. Cerebrotendinous xanthomatosis in Spain: Clinical, prognostic, and genetic survey. Eur J Neurol. 2011;**18**(10):1203-11.
77. Hellmann MA, Kakhlon O, Landau EH, et al. Frequent misdiagnosis of adult polyglucosan body disease. J Neurol. 2015;**262**(10):2346–51.
78. Harigaya Y, Matsukawa T, Fujita Y, et al. Novel *GBE1* mutation in a Japanese family with adult polyglucosan body disease. Neurol Genet. 2017;**3**(2):e138.

Chapter 30

Metabolic Movement Disorders in the Era of Next-Generation Sequencing

Fatima Y. Ismail, Mohammed Almuqbil, and Ali Fatemi

Introduction

Considering a genetic etiology for movement disorders of childhood often requires a high index of suspicion due to the heterogenous phenotypic expression, variable penetrance, and the influence of epigenetic modifiers that are largely unknown. It is, therefore, important to emphasize that neither a period of normality (normal development prior to onset of symptoms) or an association with infectious processes or single static insults, for example, exclude a genetic disorder. Molecular genetic testing has emerged as a powerful approach to identify molecular causes for previously "idiopathic" conditions such as cerebral palsy, dystonia, and parkinsonism. Molecular genetic testing can be done on any DNA-containing specimen (e.g. saliva, skin, or other organ biopsy) and its reliability is less influenced by sampling procedures, storage conditions, and transferring media of the sample under investigation compared to metabolic/biochemical testing of urine, plasma, or cerebrospinal fluid (CSF). In many cases, molecular testing can provide a more accurate diagnosis than biochemical testing. For example, in glucose transporter type 1 deficiency syndrome, a normal plasma to CSF glucose ratio should not preclude molecular testing in the appropriate phenotypic setting.

First-generation gene sequencing (Sanger sequencing) was among the first molecular techniques to be integrated in clinical practice. In this approach, DNA fragments are tagged with labeled nucleotides that are then separated by gel electrophoresis. Then, a chromatogram with the appropriate nucleotide order is generated via laser-emitted light. Sanger sequencing can identify changes or variants in a single gene. It often requires a-priori knowledge of the gene to target based on the clinical and radiological differential diagnosis. Indication-specific gene panels provide a good sequencing "coverage" of genes of interest. This approach can be cost-effective if the target gene is identified correctly. However, due to variable penetrance and allelic heterogeneity in metabolic movement disorders, the diagnostic yield of Sanger sequencing can be limited and time-consuming.

In contrast to Sanger sequencing, next-generation sequencing (NGS) enables a high-throughput parallel sequencing of the entire exome (whole-exome sequencing) or genome (whole-genome sequencing) and the analysis of large amount of data using bioinformatics [1, 2].

The integration of NGS into clinical practice requires appropriate infrastructure and the expertise to analyze and interpret genomic data and provide results in a timely manner. The workflow of NGS includes library preparation, cluster amplification, sequencing by synthesis, and alignment with data analysis (Illumina NGS). The goal of the first step (library preparation) is adding i5/i7 sequences to DNA, which allow for flow cell interaction. These specific DNA fragments as defined by a DNA library then undergo clonal amplification (cluster amplification). This is followed by multiple repeated cycles of labeled nucleic acid sequencing. The resultant DNA reads/fragments are then aligned to the reference genome [2] (Figure 30.1).

In 2000, massively parallel signature sequencing (MPSS) was launched, the first of the NGS technologies which have the capacity to produce billions of small DNA reads per instrument run, with an ability to deliver quick, economical, and reliable genome information. The technology has since been refined many times, resulting in a dramatic reduction of the cost of genomic sequencing [1]. A recent joint recommendation of the Association for Molecular Pathology and the College of American Pathologists, reporting the standards and guidelines for validating next generation sequencing bioinformatics pipelines, has been published [3].

NGS can be useful in rapidly identifying disease-causing mutations and higher-risk alleles, mapping new mutation sites and providing an insight into pathogenic mechanisms, all of which have expanded

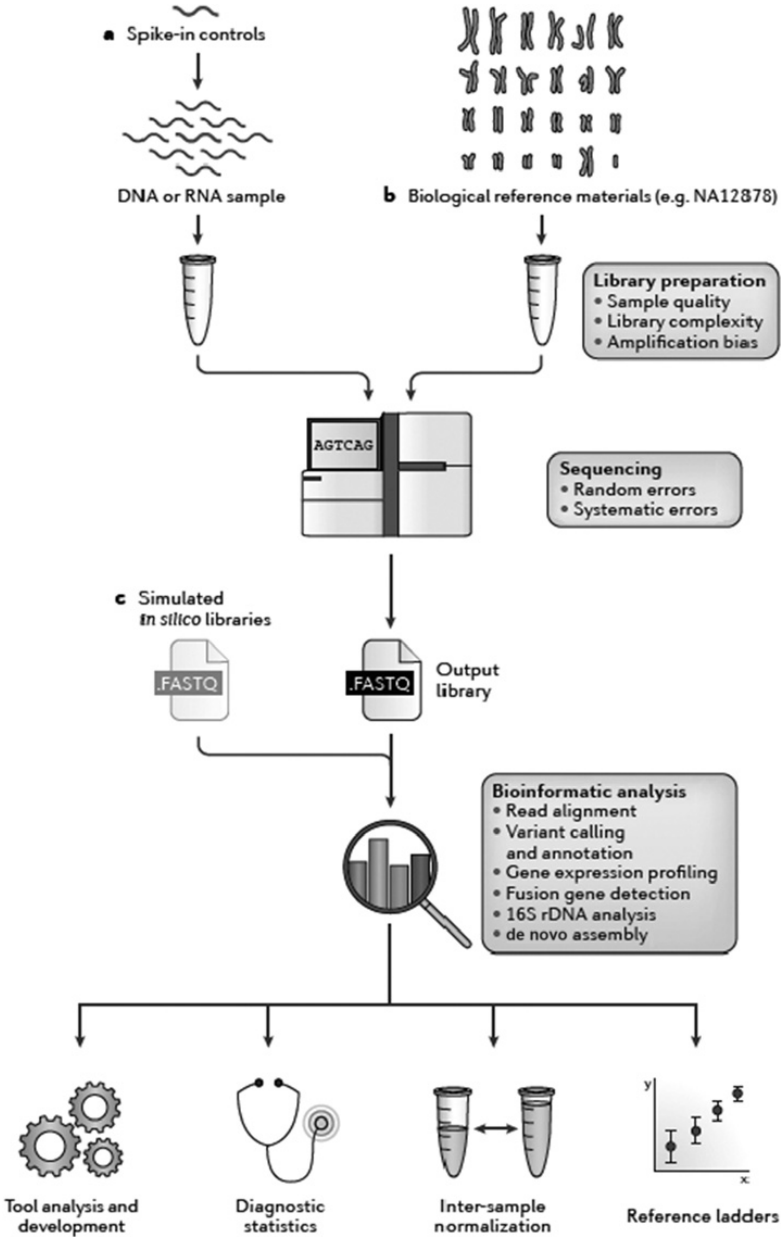

Figure 30.1 Schematic overview of an NGS workflow. Hardwick, S.A., Deveson, I.W. & Mercer, T.R., 2017. Reference standards for next-generation sequencing. Nat Rev Genet, 18(8), pp.473–484. Available at: http://dx.doi.org/10.1038/nrg.2017.44.

the diagnostic sphere of rare Mendelian genetic disorders. NGS can identify disease-causing variants, benign genomic variations, and variants of unknown significance. The latter implies insufficient evidence to support pathogenicity of the detected variants [4]. As a result, NGS refined the classification of some neurological disorders through accurate profiling of their molecular basis.

However, NGS poses new challenges pertaining to the analysis, storage, and interpretation of the massive amount of generated data, raising new legal and ethical concerns [4]. For instance, the identification of epigenetic changes, trinucleotide repeats, or changes in non-coding regions will depend upon the number of DNA reads and the coverage. Technically, complete coverage using NGS may never be reached since

specific genomic regions such as GC-rich areas and repetitive elements are difficult to amplify and large copy number variations are sometimes not detected.

Whole-Genome Sequencing

Whole-genome sequencing (WGS) allows the high throughput sequencing of the whole human genome. It bypasses the need for targeted capture before sequencing (as seen in whole-exome sequencing [WES]), shortening the turnaround time to obtain results [5]. In the right clinical setting, WGS has reduced the number of tests required for a diagnosis to be established.

The limitation of WGS includes the limited access to WGS technology (especially in a non-specialist setting), relatively high costs, and incomplete coverage of candidate genes. The enormous amount of generated data can be difficult to interpret, and thus WGS has not yet been universally integrated into clinical genetics services.

Whole-Exome Sequencing

WES allows the targeted capture and sequencing of all coding parts of the human genome. It is widely used in the clinic and has become a frontline diagnostic tool for gene discovery and diagnosis of rare diseases [6]. The use of WES has advanced our ability to conclusively arrive at a specific genetic diagnosis in monogenic disorders [7]. For example, in overlapping clinical phenotypes of early-onset generalized dystonia, WES is used to establish or confirm the molecular diagnosis, highlighting the heterogenous genetic causes of this condition [8].

Employing WES as a diagnostic tool in the clinic might be limited by the need for the appropriate system infrastructure, including computer tools, pipelines, and filter for data analysis and storage, as well as expertise in data analysis and appropriate genetic counseling [5]. For example, the finding of variants of unknown significance or pathogenic variance in genes not known to be associated with the phenotype of interest is a significant challenge for clinicians and researchers, to correctly interpret the data. Consequently, the cost-effectiveness and validity of exome sequencing for the diagnosis of complicated neurodegenerative disorders is yet to be established [9].

Custom Targeted Design

The custom targeted design approach involves the sequencing of a variable number of known genes, and is also known as targeted re-sequencing (or gene panels). With targeted re-sequencing, a subset of genes or target regions are tested and sequenced [10]. Commercial panels for a specific group of diseases, e.g. a dystonia panel, or design panels including only specific genes of interest (custom panel) are available at a low cost and with a rapid turnaround time [4, 11]. Gene panels allow an increased coverage and depth of the candidate genes compared to WES and WGS [12]. A major limitation of gene panels is the rapid expansion of gene discovery. Most commercial labs are lagging behind in incorporating new genes into their panels. Therefore, negative testing does not necessarily negate a genetic diagnosis, especially if the gene of interest is not included in the panel.

A comparative summary of WGS, WES, and custom targeted design is provided in Table 30.1.

Next-Generation Sequencing in Diagnosing Inborn Errors of Metabolism

Inborn errors of metabolism (IEMs) encompass a complex and heterogenous group of genetic diseases with evolving and overlapping clinical phenotypes of varying severity. More than 600 genes for IEMs have been identified to date. Many IEMs are associated with movement disorders (hyperkinetic and/or hypokinetic) [13]. The prompt and accurate identification of the molecular basis of IEMs is crucial for appropriate treatment and genetic counseling.

The implementation of NGS technologies has changed the diagnostic approach and yield in IEMs of childhood [4]. In a study of 146 patients with either a suspected IEM based on clinical and biochemical evidence (n = 81) or a suspected IEM based on clinical evidence and non-specific biochemical markers (n = 65), a genetic diagnosis was achieved in 50% of patients using a custom targeted genes panel followed by Sanger validation. Not surprisingly, the diagnostic yield was higher in the first group (78%) compared to 15.4% in the second group [14].

The diagnostic utility of NGS has proven beneficial in adults with undiagnosed IEMs as well. The diagnosis of IEMs of complex phenotypes or IEMs with episodic presentation and insidious progression is a clinical challenge. Patients with atypical presentations or atypical age of onset are often misdiagnosed

Table 30.1 A comparative summary of different NGS approaches: WGS, WES, and custom targeted design (gene panels)

Next-generation sequencing	Summary of method	Advantages	Disadvantages
WGS	High throughput sequencing of the whole human genome	Bypasses the need for targeted capture before sequencing Short turnaround time to obtain results	Limited access in clinical practice Relatively high cost Incomplete coverage of candidate genes Requires infrastructure and expertise in data analysis and interpretation
WES	Targeted capture and sequencing of all coding parts of the human genome	Widely used in clinical practice	Requires infrastructure and expertise in data analysis and interpretation Challenge of interpretation of variants of unknown significance
Custom targeted design (gene panels)	Subset of genes or target regions are tested and sequenced	Commercially available platforms Low cost Rapid turnover time Increased coverage and depth of the candidate genes	Due to rapid expansion of gene discovery, newly identified genes are not immediately included in commercially available panels

for years. NGS can improve the diagnostic yield in patients with atypical presentations and shorten the time to diagnosis. Examples include adolescent-onset Krabbe disease masquerading as multiple sclerosis due to episodic presentation and demyelination on MRI and diagnosed by genetic testing at age 40 years [15] or Pompe disease diagnosed at age 59 years in a woman presenting with a cerebral stroke and left ventricular hypertrophy with a long-standing history of gait disturbance [16].

Use of Next-Generation Sequencing for Genomic Newborn Screening

The current standard of newborn screening (NBS) includes testing for enzyme activity (e.g. biotinidase) or specific molecules on a tandem mass spectrometry platform (e.g. some lysosomal storage diseases, urea cycle defects, organic acid disorders, fatty acid oxidation disorders). In many cases, a positive result by first-tier testing is confirmed by molecular analysis as second-tier testing.

Genomic newborn screening (GNS) is a screening for genetic diseases that can cause death, serious lifelong disability, or chronic disease if not treated shortly after birth. The aim of GNS is to identify conditions for which effective therapy is available and to provide this treatment early enough to prevent or ameliorate complications of a disease. Dried blood spots are considered an appropriate material for future newborn screening programs relying on high-throughput sequencing technologies [17].

The use of genome-wide (whole-genome or -exome) sequencing for population-based newborn screening presents an opportunity to detect and treat or prevent many more serious early-onset health conditions. However, some disorders still have no clear natural history, specific treatment, or age of onset and hence are less ideal candidates for GNS.

NGS in the Diagnosis of Specific Inherited Metabolic Movement Disorders

The diagnostic pathway for metabolic movement disorders of childhood is based primarily on detailed clinical phenotyping; metabolic/biochemical profiling in the urine, plasma, or CSF; and neuroimaging findings. While biochemical profiling has a rapid turnover and is readily available, its diagnostic yield is low. Similarly, neuroimaging findings can be non-specific (e.g. hyperintense signal in the basal ganglia). NGS technologies have been increasingly utilized as first-tier testing in different movement disorders [18], including dystonia [19], cerebral palsy [20], ataxia [21], and Parkinson disease [22].

In this section, we will showcase a few examples of how NGS technology is used to diagnose metabolic movement disorders, to identify novel genetic variants, and to expand phenotypic–genotypic associations.

Dopa-Responsive Dystonia

Dopa-responsive dystonia (DRD) refers to a group of neurometabolic movement disorders of

Table 30.2 Summary of five classic DRD syndromes with identified phenotype–genotype associations (adapted from Wijemanne and Jankovic [23])

Molecular basis	Gene	Phenotype
Autosomal-dominant GTP cyclohydrolase 1 enzyme deficiency (Segawa disease)	*GCH1*	Childhood-onset dystonia + parkinsonism + sleep/ mood disturbance Dramatic repose to levodopa
Autosomal-recessive GTP cyclohydrolase 1 enzyme deficiency	*GCH1*	Infantile-onset dystonia + extrapyramidal signs Dramatic response to levodopa at high doses
Autosomal-recessive tyrosine hydroxylase deficiency	*TH*	Infantile-onset dystonia + autonomic disturbance + parkinsonism + hypotonia Partial response to levodopa
Autosomal-recessive sepiapterin reductase enzyme deficiency	*SPR*	Childhood-onset dystonia + hypotonia + autonomic disturbance + developmental delay Partial response to levodopa
Autosomal-recessive 6-pyruvoyltetrahydropterin synthase deficiency	*PTS*	Infantile-onset dystonia + seizures + extrapyramidal + cognitive impairment Dramatic repose to levodopa

tetrahydrobiopterin (BH4) and monoamine neurotransmitter synthesis that share a favorable clinical response to levodopa treatment. These disorders overlap in the clinical phenotype, but vary in the underlying enzymatic defect and genetic etiology [23].

Traditionally, the diagnostic algorithm of DRD is based on a suggestive history of childhood-onset focal or segmental progressive lower limb dystonia with diurnal fluctuation, a positive family history of DRD, and robust clinical improvement following an adequate 3-month trial of levodopa treatment [24]. In cases with an equivocal response to levodopa, a phenylalanine challenge to determine the phenylalanine to tyrosine ratio can support the diagnosis of DRD but does not identify the underlying enzymatic or genetic defect. CSF testing for intermediate metabolites of dopamine and BH4 synthetic pathways (biopterin, neopterin, 5-hydroxyindoleacetic acid, homovanillic acid) and phenylalanine in the blood can provide signature profiles of abnormalities associated with specific subtypes of DRD [23, 24].

There are five classic DRD syndromes with an identified phenotype–genotype association [23] where the heterogeneity of underlying genetic defects influences the clinical phenotype. These include the following syndromes: (1) Autosomal-dominant GTP cyclohydrolase 1 enzyme deficiency or classic DRD (Segawa disease) is associated with more than 200 pathogenic mutations in the *GCH1* gene. This is the most common genetic defect identified in DRD and is associated with a robust response to levodopa treatment. (2) The autosomal-recessive type of GTP cyclohydrolase 1 enzyme deficiency is characterized by neonatal onset of symptoms, hyperphenylalaninemia, and responsiveness to levodopa treatment. (3) Tyrosine hydroxylase deficiency-associated DRD is caused by bi-allelic mutations in the *TH* gene, with more than 100 mutations described, and it is associated with encephalopathy, autonomic dysfunction, and an incomplete response to L-dopa. (4) Sepiapterin reductase enzyme deficiency-associated DRD is caused by bi-allelic mutations in the *SPR* gene and is associated with severe encephalopathy and dysautonomia and suboptimal response to levodopa. (5) 6-Pyruvoyltetrahydropterin synthase deficiency is caused by bi-allelic mutations in the *PTS* gene and is associated with cognitive dysfunction, seizures, and responsiveness to levodopa (Table 30.2).

Specific gene sequencing for *GCH1*, *TH*, *SPR*, and *PTS* is considered an appropriate first-tier testing. However, as the repertoire of novel mutations in these genes is expanding, current commercially available panels might fall short of identifying recently described mutations, yielding a false negative interpretation [23, 25].

In cases with an atypical presentation, inadequate response to levodopa, or negative gene sequencing results, WES might be considered to cover mutations not included in the panel testing or to rule out other genetic disorders, including those that may show some response to levodopa such as ataxia–telangiectasia [26], spastic paraplegia type 11 [27], and spinocerebellar ataxia type 3 [28].

Table 30.3 Summary of some molecular pathways and genetic mutations associated with NBIA syndromes (adapted from Di Meo and Tiranti [31])

Pathways	Molecular targets	Gene
Iron metabolism	Hereditary neuroferritinopathy	*FTL1*
	Aceruloplasminemia	*ACP*
Coenzyme A biosynthesis	Pantothenate kinase-associated neurodegeneration (PKAN)	*PANK2*
	COASY protein-associated neurodegeneration (CoPAN)	*COASY*
Lipid metabolism	Phospholipase-associated neurodegeneration (PLAN)	*PLA2G6*
	Fatty acid hydroxylase-associated neurodegeneration (FAHN)	*FA2H*
	Mitochondrial membrane protein-associated neurodegeneration (MPAN)	*C19orf12*
	Leukoencephalopathy with dystonia and motor neuropathy	*SCP2*
Lysosomal/autophagosome function	Kufor–Rakeb syndrome	*ATP132A*
	Beta-propeller protein-associated neurodegeneration (BPAN)	*WDR45*
Unknown function	Woodhouse–Sakati syndrome	*DCAF17*
	GTPBP2 related neurodegeneration	*CTPBP2*

With the use of NGS the construct of DRD, therefore, has shifted from a single phenotypic–genotypic association (Segawa disease) to include heterogenous genetic disorders of similar clinical phenotype with significant treatment and management implications. With more than 150 genes implicated in IEMs, including mitochondrial disorders and neurodegenerative conditions identified in patients with childhood dystonia, experts support the strategy of prioritizing NGS in a selected subset of patients to reach a definitive diagnosis in a time-efficient and cost-effective manner [29].

Finally, the implication of a molecular diagnosis using NGS extends beyond diagnosis to therapy. While levodopa is considered the standard treatment in DRD, the heterogeneity of the underlying enzymatic and molecular defects often require additional treatments such as 5-hydroxtryptophan and BH4 for 6-pyruvoyltetrahydropterin synthase deficiency [30].

Neurodegeneration with Brain Iron Accumulation Syndromes

Neurodegeneration with **brain iron accumulation (NBIA)** syndromes encompass a clinically heterogenous group of genetic disorders that are associated with iron accumulation and neurodegeneration, primarily in the basal ganglia, leading to progressive pyramidal and extrapyramidal symptoms including dystonia, ataxia and spasticity, neuropsychiatric symptoms, axonal neuropathy, and ocular abnormalities [31]. Brain MRI to evaluate the pattern of iron accumulation is at the root of the diagnostic tree in NBIA syndromes. However, while the pattern of iron deposition in the basal ganglia can be associated with some specific NBIA syndromes, in other NBIA syndromes no iron accumulation is seen. Two pathogenetic mutations directly implicated in iron metabolism (neuroferritinopathy and aceruloplasminemia) and 10 pathogenetic mutations in pathways not associated directly with iron metabolism have been described. These include defects in the coenzyme A biosynthesis pathway (pantothenate kinase-associated neurodegeneration and COASY protein-associated neurodegeneration); lipid metabolism (phospholipase-associated neurodegeneration, fatty acid-2-hydoxylase-associated neurodegeneration, mitochondrial membrane protein-associated neurodegeneration); lysosomes and autophagy (Kufor–Rakeb syndrome, beta-propeller protein-associated neurodegeneration) and other mutations of unknown functions (Woodhouse–Sakati syndrome) (Table 30.3). Consequently, controversies about the spectrum of NBIA disorders, the phenotypic–genotypic associations, the role of iron in pathogenesis, and targeted therapies have been raised [32].

The identification of molecular defects in metabolic pathways not directly linked to iron metabolism in disorders where iron accumulation is the hallmark called into question our understanding of iron homeostasis. A recent study that investigated NBIA-enriched networks using whole-transcriptome gene expression data from normal human brain identified two basal ganglia gene co-expression modules that were significantly enriched for iron-related genes.

These genes were involved in synapse and lipid metabolism and were dysregulated by iron overload. Iron overload was also associated with a disruption of the function of several NBIA genes even in the absence of NBIA mutations [33]. A deeper understanding of how these pathways converge genetically, epigenetically, and metabolically might open opportunities for targeted and unconventional therapeutic interventions.

Copper Metabolism (Wilson Disease)

Given its monogenic profile, specific gene testing for Wilson disease is a sensitive and cost-effective first-tier test and should include the entire *ATP7B* coding region and adjacent splicing sites. More than 500 mutations in the copper-transporting P-type ATPase (*ATP7B*) gene have been identified with population-specific predilections, variable penetrance, and a functional impact on protein expression [34]. Wilson disease has an age-related expression of symptoms spanning infantile-onset liver dysfunction to adult-onset neuropsychiatric symptoms. Genotype–phenotype associations on a population level are modest, which reinforces the impact of epigenetics and possibly environment on the clinical expression of the disease.

Population-wide genetic prevalence studies have implied that *ATP7B* mutations are more common than previously reported in epidemiological studies, which is potentially explained by subclinical phenotypic expression, variable penetrance, and underdiagnosis [35–37]. Novel pathogenic variants and allelic variants as modifiers of the phenotype have also been identified using WES [38].

The need for a prompt diagnosis of Wilson disease stems from the availability of interventions that can alter the natural course of the disease.

Lysosomal Storage Disorders

With more than 50 monogenic disorders of diverse phenotypes and overlapping biochemical profiles, lysosomal storage disorders can be challenging to diagnose in a timely manner. The mean time between disease onset and diagnosis was between 1 year and 40 years in some cohorts [39]. A time-sensitive diagnosis and accurate assessment of the severity of enzymatic derangement is important for choosing therapeutic interventions such as hematopoietic cell transplant or enzyme-replacement therapy. Traditionally, the biochemical assessment of undegraded macromolecules or the level of enzymatic activity are the mainstay of screening. However, this approach often requires an a-priori hypothesis of potential testing targets, which can be challenging in young patients or patients with atypical presentations and it does not inform precise and comprehensive genetic counseling. Moreover, not all lysosomal storage disorders are related to lysosomal enzymatic deficiencies. Therefore, the integration of NGS techniques to establish an accurate diagnosis more rapidly and cost-effectively is important in cases with equivocal clinical and biochemical profiles.

WES is showing promising results in patients with lysosomal storage disorders of unknown etiology. Wang and colleagues investigated the utility of WES in 14 such patients with a suspected diagnosis of lysosomal storage disorders of unknown etiology. More than 2,000 candidate genes associated with lysosomal function were tested. Eight variants in five genes were identified in four individuals as causal mutations [40]. A targeted NGS approach using an 891-gene panel involved in autophagy–lysosomal pathways (Lysoplex) was validated in 14 different types of lysosomal storage disorders and identified pathogenic mutations in 67% of patients with previously unknown etiology [41]. Advanced molecular genetics has implications in genetic counseling, including the settings of prenatal and pre-implantation screening [42].

Mitochondrial Disorders

Mitochondrial disorders are exceptionally challenging to diagnose due to multisystem involvement, varying clinical phenotypes, and the genetic heterogeneity of disease-causing mutations in the nuclear and mitochondrial genomes. Standard clinical assessments are often inconclusive. Concomitant WES and mitochondrial genome sequencing have improved the diagnostic yield for patients with suspected mitochondrial disorders when conventional molecular genetic testing failed to identify causative mutations in Leigh syndrome, coenzyme Q10 deficiency, and mitochondrial complex 1 deficiency [43].

Gene discovery through NGS enabled the accurate molecular classification of Leigh syndrome, for example, to include deficiencies in mitochondrial respiratory chain complexes 1–5, pyruvate dehydrogenase complex deficiency, and thiamine transporter deficiency in addition to other genetic causes such as mutations in succinyl-coenzyme A ligase or *POLG* mutations resulting in mitochondrial DNA depletion [44].

Conclusions

The rapidly evolving and high-throughput character of NGS enables the identification of novel mutations or genes implicated in metabolic movement disorders of overlapping phenotypes. To some degree this has swayed the diagnostic algorithm away from biochemical testing. In disorders where phenotypic–genotypic associations are well understood, biochemical testing is being "repurposed" to serve as a therapeutic monitoring/biomarker tool. For example, in spastic paraplegia due to mutations in *CYP7B1* that encodes cytochrome P450 7α-hydroxylase, involved in bile acid and cholesterol metabolism, plasma oxysterols (25-hydroxycholesterol and 27-hydroxycholesterol and their ratio to total cholesterol) demonstrated 100% sensitivity and specificity as diagnostic biomarkers for spastic paraplegia type 5 [45], with potential therapeutic response to atorvastatin [46].

A trend toward such a strategy regarding rare neurometabolic genetic diseases is on the rise and might be offering promising prospects. It is important, therefore, to remember the challenges ahead. While NGS has dramatically expanded the scope of genetic disorders, with over 8,000 OMIM-cited genetic disorders identified so far, most of these having been discovered within the last 5 years, there is still a great need to further characterize the phenotype of these many new and rare disorders. Understanding the molecular disease mechanisms via cellular analysis and functional studies, and exploration of biomarkers that are specific to the phenotype-genotype of interest are frontiers for future research.

Key Points and Clinical Pearls

- Next-generation sequencing (NGS) has caused a paradigm shift in our diagnostic algorithm for metabolic movement disorders of genetic origin due to its high-throughput, time-efficient and cost-effective profile.
- The choice of whole-genome sequencing (WGS), whole-exome sequencing (WES), or targeted gene panels depends on the clinical phenotype, the candidate genes, and the availability of infrastructure and expertise to analyze and interpret genomic data.
- Data derived from NGS has identified novel metabolic pathways of clinically defined diseases (NBIA syndromes), changed the known prevalence of certain diseases (Wilson disease), shortened the time to diagnosis in diseases with complex phenotypes (lysosomal storage diseases), and refined the classification of diseases to their molecular basis (mitochondrial disorders).
- As the field moves toward genomic diagnosis, careful appraisal of phenotypic–genotypic associations and accurate understanding of molecular mechanisms of diseases is important to inform biomarker discovery and therapeutic interventions.

Directions for Future Research

- Establishing NGS as the first-line test for IEMs associated with movement disorders with improved turnaround times, coverage, and variant interpretation.
- Investigation of NGS-based genetic newborn screening for IEMs.
- Understanding the genotypic and phenotypic spectrum of rare IEMs associated with movement disorders.
- Understanding the molecular disease mechanisms via cellular analysis and functional studies, and exploration of biomarkers that are specific to the phenotype–genotype of interest.

References

1. Goodwin S, McPherson JD, McCombie WR. Coming of age: Ten years of next-generation sequencing technologies. Nat Rev Genet. 2016;**17**(6):333–51.
2. Hardwick SA, Deveson IW, Mercer TR. Reference standards for next-generation sequencing. Nat Rev Genet. 2017;**18**(8):473–84.
3. Roy S, Coldren C, Karunamurthy A, et al. Standards and guidelines for validating next-generation sequencing bioinformatics pipelines: A joint recommendation of the Association for Molecular Pathology and the College of American Pathologists. J Mol Diagn. 2018;**20**(1):4–27.
4. Olgiati S, Quadri M, Bonifati V. Genetics of movement disorders in the next-generation sequencing era. Mov Disord. 2016;**31**(4):458–70.

5. Stranneheim H, Engvall M, Naess K, et al. Rapid pulsed whole genome sequencing for comprehensive acute diagnostics of inborn errors of metabolism. BMC Genomics. 2014;**15**:1090.
6. Ku CS, Naidoo N, Pawitan Y. Revisiting Mendelian disorders through exome sequencing. Hum Genet. 2011;**129**(4):351–70.
7. Retterer K, Juusola J, Cho MT, et al. Clinical application of whole-exome sequencing across clinical indications. Genet Med. 2016;**18**(7):696–704.
8. Zech M, Boesch S, Jochim A, et al. Clinical exome sequencing in early-onset generalized dystonia and large-scale resequencing follow-up. Mov Disord. 2017;**32**(4):549–59.
9. Bettencourt C, Lopez-Sendon JL, Garcia-Caldentey J, et al. Exome sequencing is a useful diagnostic tool for complicated forms of hereditary spastic paraplegia. Clin Genet. 2014;**85**(2):154–8.
10. Sikkema-Raddatz B, Johansson LF, de Boer EN, et al. Targeted next-generation sequencing can replace Sanger sequencing in clinical diagnostics. Hum Mutat. 2013;**34**(7):1035–42.
11. Reale C, Panteghini C, Carecchio M, Garavaglia B. The relevance of gene panels in movement disorders diagnosis: A lab perspective. Eur J Paediatr Neurol. 2018;**22**(2):285–91.
12. Reid ES, Papandreou A, Drury S, et al. Advantages and pitfalls of an extended gene panel for investigating complex neurometabolic phenotypes. Brain. 2016;**139** (11):2844–54.
13. Christensen CK, Walsh L. Movement disorders and neurometabolic diseases. Semin Pediatr Neurol. 2018;**25**:82–91.
14. Yubero D, Brandi N, Ormazabal A, et al. Targeted next generation sequencing in patients with inborn errors of metabolism. PLoS One. 2016;**11**(5):e0156359.
15. Tomas J, Duraes J, Lacerda L, Macario MC. Adolescent-onset Krabbe disease with an initial diagnosis of multiple sclerosis and a novel mutation. BMJ Case Rep. 2015;2015.
16. Vanderver A, Prust M, Tonduti D, et al. Case definition and classification of leukodystrophies and leukoencephalopathies. Mol Genet Metab. 2015;**114** (4):494–500.
17. Boemer F, Fasquelle C, d'Otreppe S, et al. A next-generation newborn screening pilot study: NGS on dried blood spots detects causal mutations in patients with inherited metabolic diseases. Sci Rep. 2017;**7**(1):17641.
18. Krebs CE, Paisan-Ruiz C. The use of next-generation sequencing in movement disorders. Front Genet. 2012;**3**:75.
19. Fuchs T, Ozelius LJ. Genetics in dystonia: An update. Curr Neurol Neurosci Rep. 2013;**13**(12):410.
20. Moreno-De-Luca A, Ledbetter DH, Martin CL. Genetic [corrected] insights into the causes and classification of [corrected] cerebral palsies. Lancet Neurol. 2012;**11**(3):283–92.
21. Filla A, De Michele G. Overview of autosomal recessive ataxias. Handb Clin Neurol. 2012;**103**:265–74.
22. Jansen IE, Ye H, Heetveld S, et al. Discovery and functional prioritization of Parkinson's disease candidate genes from large-scale whole exome sequencing. Genome Biol. 2017;**18**(1):22.
23. Wijemanne S, Jankovic J. Dopa-responsive dystonia: Clinical and genetic heterogeneity. Nature Reviews *Neurology*. 2015;**11**:414.
24. Malek N, Fletcher N, Newman E. Diagnosing dopamine-responsive dystonias. Pract Neurol. 2015;**15** (5):340–5.
25. Jan MM. Misdiagnoses in children with dopa-responsive dystonia. Pediatr Neurol. 2004;**31** (4):298–303.
26. Charlesworth G, Mohire MD, Schneider SA, et al. Ataxia telangiectasia presenting as dopa-responsive cervical dystonia. Neurology. 2013;**81**(13):1148–51.
27. Wijemanne S, Shulman JM, Jimenez-Shahed J, Curry D, Jankovic J. SPG11 mutations associated with a complex phenotype resembling dopa-responsive dystonia. Mov Disord Clin Pract. 2015;**2**(2):149–54.
28. Wilder-Smith E, Tan EK, Law HY, et al. Spinocerebellar ataxia type 3 presenting as an L-dopa responsive dystonia phenotype in a Chinese family. J Neurol Sci. 2003; **213** (1–2): 25–8.
29. van Egmond ME, Kuiper A, Eggink H, et al. Dystonia in children and adolescents: A systematic review and a new diagnostic algorithm. J Neurol Neurosurg Psychiatry. 2015;**86**(7):774–81.
30. Kim R, Jeon B, Lee WW. A systematic review of treatment outcome in patients with dopa-responsive dystonia (DRD) and DRD-plus. Mov Disord Clin Pract. 2016;**3**(5):435–42.
31. Di Meo I, Tiranti V. Classification and molecular pathogenesis of NBIA syndromes. Eur J Paediatr Neurol. 2018;**22**(2):272–84.
32. Keogh MJ, Chinnery PF. Current concepts and controversies in neurodegeneration with brain iron accumulation. Semin Pediatr Neurol. 2012;**19** (2):51–6.
33. Bettencourt C, Forabosco P, Wiethoff S, et al. Gene co-expression networks shed light into diseases of brain iron accumulation. Neurobiol Dis. 2016;**87**:59–68.

34. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol. 2015;**14**(1):103–13.

35. Coffey AJ, Durkie M, Hague S, et al. A genetic study of Wilson's disease in the United Kingdom. Brain. 2013;**136**(Pt 5):1476–87.

36. Collet C, Laplanche JL, Page J, et al. High genetic carrier frequency of Wilson's disease in France: Discrepancies with clinical prevalence. BMC Med Genet. 2018;**19**(1):143.

37. Gao J, Brackley S, Mann JP. The global prevalence of Wilson disease from next-generation sequencing data. Genet Med. 2019; **21**(5):1155–63.

38. Kluska A, Kulecka M, Litwin T, et al. Whole-exome sequencing identifies novel pathogenic variants across the ATP7B gene and some modifiers of Wilson's disease phenotype. Liver Int. 2019;**39**(1):177–86.

39. Komlosi K, Sólyom A, Beck M. The role of next-generation sequencing in the diagnosis of lysosomal storage disorders. J Inborn Error Metab Screen. 2016;**4**:2326409816669376.

40. Wang N, Zhang Y, Gedvilaite E, et al. Using whole-exome sequencing to investigate the genetic bases of lysosomal storage diseases of unknown etiology. Hum Mutat. 2017;**38**(11):1491–9.

41. Di Fruscio G, Schulz A, De Cegli R, et al. Lysoplex: An efficient toolkit to detect DNA sequence variations in the autophagy–lysosomal pathway. Autophagy. 2015;**11**(6):928–38.

42. Giugliani R, Brusius-Facchin AC, Pasqualim G, et al. Current molecular genetics strategies for the diagnosis of lysosomal storage disorders. Expert Rev Mol Diagn. 2016;**16**(1):113–23.

43. Dinwiddie DL, Smith LD, Miller NA, et al. Diagnosis of mitochondrial disorders by concomitant next-generation sequencing of the exome and mitochondrial genome. Genomics. 2013;**102** (3):148–56.

44. Gerards M, Sallevelt SC, Smeets HJ. Leigh syndrome: Resolving the clinical and genetic heterogeneity paves the way for treatment options. Mol Genet Metab. 2016;**117**(3):300–12.

45. Marelli C, Lamari F, Rainteau D, et al. Plasma oxysterols: Biomarkers for diagnosis and treatment in spastic paraplegia type 5. Brain. 2018;**141** (1):72–84.

46. Schols L, Rattay TW, Martus P, et al. Hereditary spastic paraplegia type 5: Natural history, biomarkers and a randomized controlled trial. Brain. 2017;**140** (12):3112–27.

Chapter

31

Deep Brain Stimulation for Metabolic Movement Disorders

Philippe De Vloo, George M. Ibrahim, Scellig S. Stone, and Suneil K. Kalia

Introduction

As pharmacological management is dissatisfying in many metabolic movement disorders, neurosurgical procedures have been attempted to alleviate the most disabling symptoms, which are often severe dystonia, chorea, tremor, and self-mutilating behavior. These neurosurgical procedures include ablative procedures and deep brain stimulation (DBS), typically targeting the basal ganglia. DBS is a neuromodulation technique in which electrodes are precisely implanted in deep brain structures, such as the basal ganglia, by applying methods based on brain imaging and coordinate systems. Electrical pulses are then delivered by an implantable pulse generator, thereby modulating the neural tissue in the vicinity of the electrodes. Although the underlying mechanism is not completely understood, the effect of DBS is usually very similar to that of ablative procedures. However, DBS has the advantage of being adaptable and (at least partially) reversible.

Unlike many other indications for DBS, large randomized blinded crossover trials, directly comparing DBS on vs. off, are not available for metabolic movement disorders. Conducting such trials is difficult for various reasons. First, most metabolic movement disorders are very rare and large trials would face slow recruitment. Moreover, these disorders are often heterogeneous in terms of genotype and phenotype [1]. Next, practical difficulties could arise from long wash-in and wash-out periods as reported in DBS for many forms of dystonia [2, 3]. Further, direct DBS on vs. off comparisons may be deemed unethical, because of the risk of life-threatening rebound effects such as dystonic storms [4] and the psychological issues associated with the cessation of DBS only for scientific purposes [5]. Lastly, many patients are not able to provide consent because they are too young or have intellectual disability and associated communication difficulties. Non-randomized studies including an open control group of patients who were offered but refused to undergo DBS are scientifically less valid, but may represent a more pragmatic alternative [6].

The scientific evidence for DBS in metabolic movement disorders is therefore limited to case reports or small case series, with a high likelihood of publication bias, causing under-reporting of negative outcomes. In the majority of publications, neither patients nor assessors were blinded to the procedure, opening the possibility of the placebo effect or observer bias. Moreover, DBS on vs. off comparisons are almost completely lacking. Consequently, the effect of DBS on the natural course of the disease and vice versa is unclear, and the additional benefit of DBS over the sometimes long-lasting insertional effect has not been demonstrated [7–9].

General Considerations in DBS for Metabolic Movement Disorders

Goals and Outcome Measurement

Any treatment for movement disorders should aim to improve functionality and quality of life by improving movement and posture and relieving any associated disability, pain, and discomfort [10]. Assessing symptom severity with a uniform scale is difficult as metabolic movement disorders vary largely in age at presentation and symptoms. Table 31.1 provides an overview of the frequently used scales in metabolic movement disorders.

As dystonia is the main indication for DBS in metabolic movement disorders, most publications report the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) or Barry–Albright Dystonia Scale (BADS). Chorea/ballism and other involuntary movements are generally rated through the Unified

Table 31.1 Frequently used clinical outcome scales in DBS for metabolic movement disorders

Scale	Abbreviation	Measurement	Patient group	Range
Burke–Fahn–Marsden Dystonia Rating Scale - Motor part	BFMDRS-M	Severity of primary torsion dystonia	Adults	0–120
Burke–Fahn–Marsden Dystonia Rating Scale - Disability part	BFMDRS-D	Disability in activities of daily living caused by dystonia	Adults	0–30
Barry–Albright Dystonia Scale	BADS	Severity of secondary (CP) dystonia	Children and adults	0–32
Unified Huntington Disease Rating Scale	UHDRS	Motor and cognitive function, behavioral abnormalities, and functional capacity	11+ years	0–124 (motor)
Abnormal Involuntary Movement Scale	AIMS	Occurrence and severity of tardive dyskinesia	Adults	0–40

Huntington Disease Rating Scale (UHDRS) or Abnormal Involuntary Movement Scale (AIMS). However, as BFMDRS was originally established for the quantitative assessment of primary torsion dystonia in adults, it is limited to the assessment of a single symptom of a movement disorder and does not discriminate between abnormal postures and movements caused by non-dystonic symptoms. Moreover, scales such as the BFMDRS and AIMS are relatively insensitive to clinically meaningful changes in axial dystonia, vocalization, communication, fine motor skills, hand dexterity, and swallowing [11]. Even the authors of the BFMDRS-D acknowledge that "major changes are required before the change registers on the scale" [12].

Many publications on DBS for metabolic movement disorders emphasize that the reported scales do not fully express the subjective benefit experienced by the patient, the caregiver, or the physician because they are not fine enough or because they do not take into account certain activities which can be highly relevant to the quality of life [13]. In the given context, what may seem a minor functional improvement can be of utmost importance to the patient or caregivers. Although this underscores the need for disease- and age-specific severity scales, the main function of these scales remains to objectively compare symptoms and their impact, within but also between patients. Therefore, over-refinement of scales to perfectly match a small subset of patients is not beneficial per se. Moreover, when seeking approval and reimbursement for DBS in these disorders, a direct comparison with other treatment options, such as medications, requires the continued use of relatively generic scales.

Patient Selection and Timing of Surgery

In metabolic movement disorders in general, patients who have isolated dystonia, chorea/ballism, or tremor (no other combined symptoms), without fixed skeletal deformities or muscle contractures, and who have experienced a short duration of symptoms, are probably the best candidates for DBS [14]. Therefore, discussing the possibility of DBS with the patient and his or her caregivers is justified as soon as the functional capacity and/or quality of life are impaired despite optimal medical management, or when the side effects of medical treatment are intolerable. Brain imaging is paramount to assess the status of the intended target, although surgery is not necessarily precluded if the target is severely compromised (e.g. pallidal stimulation in pantothenate kinase-associated neurodegeneration [PKAN]). Nevertheless, patients with a long-standing disease, who already display skeletal deformities and contractures, can still benefit from DBS, particularly in PKAN. Importantly, DBS is not only intended to improve the quality of life but can also become an emergent last resort in patients presenting with intractable dystonic storm.

The best results can probably be obtained when the patient and caregivers are assessed, counseled, operated, programmed, and followed by an experienced and interdisciplinary movement disorder team, consisting not only of (pediatric) neurologists and neurosurgeons, but also psychiatrists, neuropsychologists, and physiotherapists.

Technical Considerations in Children

Many patients with metabolic movement disorders are children, especially those with PKAN or Lesch–Nyhan disease, and hence special considerations apply.

General anesthesia is usually required in these children with severe movement disorders, not only for the surgery itself, but also for the frame placement and preoperative imaging [14–16]. Electrophysiological measurements to confirm the electrode position are therefore omitted [17] or are performed under anesthetic conditions that make some recordings possible, often under bispectral monitoring [18]. Direct anatomical targeting and accuracy verification using intraoperative brain imaging can be proposed when electrophysiological measurements are impossible [19].

For the neurosurgeon, it is important to take care when adjusting the pressure applied to the frame pins to the softer and thinner skull in children, especially in those with metabolic diseases such as abetalipoproteinemia. In children ≤7 years of age, implantation of the DBS electrode so that its deepest contact is ventral to the target area is reasonable to prevent the loss of effect due to the growth of the brain and the skull [20, 21]. While tunneling, enough slack should be inserted in the extension wires to avoid a hardware fracture because of body growth, and in girls, the breast buds should be avoided [22]. As body weight is often low, especially in dystonic patients and/or those with dysphagia, the implantable pulse generator (IPG) is often implanted in an abdominal wall pocket rather than subclavicularly [23]. Other technical pearls sometimes include staged procedures or the prolonged use of head wraps to prevent cerebrospinal fluid (CSF) leakage along the wires to the IPG pocket, suturing the connector to the nuchal fascia, or burying the connector in a partial skull thickness groove and using two completely separate systems in case of bilateral stimulation (although there is a risk of the IPGs interfering with each other when positioned too closely together, which can be a consideration in the pediatric population) [15, 22]. Proposals to reduce the infection risk of DBS in children have been described [24].

However, despite all these measures, the postoperative risk of infections and hardware complications in children remains substantial, probably because of their immature immune system, limited tissue to cover the devices, and stress induced by growth or physical activities [22, 25, 26].

From a medicolegal point of view, it is noteworthy that commonly used DBS systems are not approved in young children (e.g. the Medtronic Activa system is only approved by the US Food and Drug Administration in children age 7 years and older) [22]. Their use in certain situations and/or jurisdictions may warrant single-use institutional review board approval.

Surgery

The general anesthetic rule in patients suffering metabolic diseases is to avoid perioperative metabolic decompensation, which may be triggered by prolonged preoperative starvation, dehydration, hypoxia, hypotension, hypothermia, stress response during surgery, and certain anesthetic agents. Adequate perioperative analgesia reduces the stress response. In general, patients with metabolic disorders are prone to develop osteoporosis, and therefore special attention to frame placement, surgical positioning, and transfer is required [15, 21]. Anesthetics should be administered by a team familiar with the nuances of agent selection in the context of metabolic disorders.

Typical DBS targets for movement disorders are the posteroventral globus pallidus internus (GPi), the subthalamic nucleus (STN), and the motor thalamus (ventral intermediate [Vim] and ventral oral posterior [Vop] nuclei)). All of these targets are within a neural circuit connecting the motor cortex, basal ganglia, and brainstem. In metabolic movement disorders, thus far only these three targets have been reported, with most patients undergoing bilateral GPi-DBS.

Complications

The most frequent and deleterious complications of DBS in general include stroke, infection, skin erosion, electrode malposition, and hardware failure or breakage. In metabolic movement disorders, it appears that the infection rate is low, even in young children. Nevertheless, in children, there is a relatively high incidence of hardware problems with the electrodes and extension wires [25]. Electrode malposition is an infrequent problem, irrespective of the degree of basal ganglia degeneration [27].

Postoperative Management

It often takes several weeks of stimulation before the tonic component of dystonia starts to improve, and even several months of stimulation before this effect is maximal. Therefore, sufficient patience is paramount. Moreover, maximizing the benefit and reducing the side effects may take many reprogramming sessions,

again taking into account the protracted time to potentially realize benefits. Importantly, DBS should be considered as an addition to ongoing treatment, not as a replacement. Therefore, continuation of medical treatment with necessary adaptations, and follow-up and extensive rehabilitation, are essential for patients who lose functionality in the period immediately preceding DBS surgery. The acute cessation of stimulation, typically because of battery depletion, hardware fracture, or system removal because of infection, has the potential to elicit a life-threatening status dystonicus. When suspected, battery replacement or revision surgery should be performed emergently [28]. In the case of system removal because of infection, radiofrequency ablation through the DBS system preceding removal can be considered.

Ethics

Performing DBS in childhood, in adults with impaired cognition and/or communication, or during a life-threatening dystonic storm in an anesthetized patient, requires careful ethical consideration. Moreover, the parents of these vulnerable patients struggle in the face of uncertainty over the outcome whilst trying to do their best as parents, and therefore require adequate social support [29].

Indications

The largest experience with DBS for metabolic movement disorders exists in PKAN, choreo-acanthocytosis, Lesch–Nyhan disease, kernicterus, and glutaric aciduria type 1. Other metabolic movement disorders, with less than five DBS cases reported in the literature, will be discussed only briefly.

Pantothenate Kinase-Associated Neurodegeneration

Pathophysiology and Clinical Features

PKAN is a rare (prevalence 1–2 in 1,000,000) autosomal-recessive disorder. It is characterized by progressive iron accumulation preferentially affecting the globus pallidus and pars reticularis of the substantia nigra, typically as a result of *PANK2* gene mutations [30, 31]. *PANK2* encodes an enzyme of the same name, which has an important role in coenzyme A synthesis. Coenzyme A plays a central role in fatty acid synthesis and energy metabolism. Coenzyme A deficiency can lead to a high concentration of cysteine in the basal ganglia, and then to iron accumulation. By provoking oxidative stress, the cysteine–iron complex results in tissue damage [32].

PKAN is associated with progressive extrapyramidal findings (generalized dystonia, rigidity, choreoathetosis), corticospinal tract dysfunction, and cognitive deterioration. Typically, there is a so-called "eye of the tiger" sign on T2-weighted MRI, referring to a hypointensity with central hyperintensity in the globus pallidus [33]. The hypointensity corresponds to iron deposits in dense tissue, and the hyperintensity appears pathologically as an area of loose tissue with vacuolization [34]. Many publications have made a distinction between two types of PKAN, based on the age of onset and rate of progression. Classic PKAN is characterized by early-childhood-onset of progressive dystonia, dysarthria, rigidity, and choreoathetosis. Pigmentary retinal degeneration and optic atrophy are common. Atypical PKAN is characterized by later onset (typically >15 years of age), prominent speech defects, psychiatric disturbances, and a more gradual progression of disease [35]. Pharmacological therapy with dopamine, clonazepam, trihexyphenidyl, tetrabenazine, and baclofen is generally unsatisfactory.

Patient Selection, Timing, and Target of Surgery

Medication-refractory cases with severe functional impairment are candidates for neurosurgical treatment. Neurosurgical options include intrathecal baclofen delivery using pumps [36], pallidotomy [37], thalamotomy [38], pallidothalamotomy [39], and DBS targeting the GPi, or alternatively the STN or motor thalamus. Our systematic review of the literature encompasses 99 cases of DBS for PKAN (58 classic type, 15 atypical type, 27 undetermined type), published since 2001 [40]. GPi is the most common target (88%). It is intriguing that, although severely affected by iron accumulation, neuronal degeneration, and gliosis, the GPi still contains viable neurons (as demonstrated during microelectrode recording [MER]) and that these neurons can be stimulated with a clear benefit [41]. Although clearly efficacious for Parkinson dystonia, the benefit of STN-DBS for PKAN dystonia is highly variable, but may be an option for appendicular dystonia [42, 43]. In general, thalamic DBS appears inferior to GPi-DBS for dystonia [44].

The ideal timing of DBS in the course of the disease has not yet been determined. Patients with classic PKAN underwent DBS implantation surgery at the median age of 11 years (range 4–36 years) after

a median disease duration of 7 years. Atypical PKAN cases treated with DBS are operated on at a median age of 31 years (range 17–46 years), after a median disease duration of 15 years. Ideally, the surgical procedure should be performed electively to allow sufficient time for counseling and preparation. However, urgent DBS surgery for medically refractory status dystonicus is not uncommon in classic PKAN, with 10% of published cases operated in status dystonicus [40].

Surgery

Essentially, the surgical technique of DBS for PKAN is the same as in DBS for any type of dystonia. However, there are at least three nuances. First, many classic PKAN cases are operated during childhood (as early as 6 years of age). In these cases, all considerations for pediatric DBS (see above) apply. Second, there are many anesthetic challenges, before and after anesthesia (e.g. articulation difficulties and cognitive impairment limiting communication), during induction (e.g. oromandibular rigidity, dysphagia, aspiration), during anesthesia (e.g. seizures), and postoperatively (e.g. respiratory disability) [45]. Third, whether or not MER should be used, and if so, under local or general anesthesia, remains a matter of debate. Conflicting MER characteristics of GPi neurons have been reported in PKAN patients. Shields *et al.* published quiet areas and areas that show a 37.5-Hz irregular firing pattern in an awake patient [3], McClelland *et al.* found a regular 25-Hz firing rate in eight patients under isoflurane anesthesia [46], similar to Valentin *et al.* who found a discharge rate of 35 Hz under sevo/isoflurane anesthesia in six patients [47], while Justesen *et al.* reported a regular firing rate of 91 Hz in a single patient under light propofol anesthesia [37]. Despite these variable firing rates, MER can certainly be useful to localize the optic tract and hence the ventral GPi border. The MER is, however, not an absolute requirement and there are variable techniques utilized between different specialized centers, with some using purely radiological-based approaches to place the DBS electrodes.

Programming and Follow-Up

Programming is usually initiated between 1 day [48] and several weeks [14] after electrode implantation, although in cases of dystonic storm immediate programming is reasonable. As for other types of dystonia, stimulation settings vary largely, and there is no general agreement on the best combination or programming algorithm [49]. Typically, amplitudes in GPi-DBS increase slowly over time [50] from 1 V to 5 V (median 2.0 V), with a frequency ranging from 120 Hz to 185 Hz (median 130 Hz) in a monopolar or double monopolar configuration. The median programmed pulse width is 140 μs–145 μs, although some groups use much larger pulse widths (450 μs) [40, 50].

Given the risk of a dystonic storm after battery depletion, planning follow-up visits and/or instructing caregivers to assess the battery status are paramount. If the battery depletes unexpectedly, close monitoring and semi-urgent replacement must be considered based on the patient's clinical status.

Outcome, Outcome Predictors, and Complications

DBS for PKAN has been reported to result in a considerable reduction of dystonia severity, similar to [44, 50] or slightly smaller [51] than in primary dystonia (DYT-1). However, the outcome in PKAN is much more heterogeneous. In our review of 99 published cases, the mean BFMDRS-M reduction after 1 year of –26% was more prominent in atypical (–45%) than in classic (–16%) PKAN cases. Patients with atypical PKAN also had a lower mean baseline BFMDRS-M than those with classic PKAN (52 vs. 82) [40]. Many factors may contribute to the better outcome in atypical PKAN cases, including less fixed skeletal deformities and muscle contractures than in classic PKAN (0/15 vs. 8/58) and later disease onset (median of 15 vs. 6 years of age), thereby acquiring a higher level of motor skills and potentially facilitating postoperative rehabilitation.

As dystonic postures and abnormal movements improve substantially, medication doses can often be reduced [23, 52]. Walking capacity improves in the majority of patients, even those who were wheelchair-bound preoperatively [50]. Speech and writing skills improve in ≥50% of cases [50]. Oromandibular dystonia appears to respond less to GPi-DBS [41, 52]. Several publications report a major improvement of pain secondary to hypertonic muscle cramps, often resulting in a complete cessation of analgesics [50, 53]. Similar to dystonia severity, improvement in disability is more prominent in atypical PKAN than in classic PKAN (BFMDRS-D –31% vs. –1%), with a lower mean baseline disability in atypical vs. classic PKAN (BFMDRS-D 17 vs. 25) [40]. Data on the evolution in the quality of life after DBS for PKAN is scarce. In a retrospective assessment on a 0–10 scale

by the caregivers, an 80% improvement was noted 3 months postoperatively and sustained at 1 year. However, these numbers are likely affected by recall bias [6].

It appears that GPi-DBS for PKAN does not only improve dystonic features, pain, and quality of life, but also psychosocial wellbeing [3, 54] and cognitive test scores [52, 54, 55]. Whether the latter is due to reduced pain and hence reduced analgesics [50, 53], improved dystonia and hence reduced anticholinergic medication [23], improved speech [50] and hence easier responding [56], or true improvement in cognition and memory (e.g. via decreased response inhibition [55]) is difficult to determine [54].

The median reported follow-up is 1 year, and publications with a longer follow-up duration are scarce (7/99 ≥ 2 years and 2/99 ≥ 5 years). Conclusions drawn from these few patients are likely to be affected by selection bias, as patients with poor outcomes may not be followed as closely. Nevertheless, even in these selected cases, a gradual decline in efficacy is typically observed, with dystonia severity returning to baseline between 4 years and 7 years post implantation, despite extensive reprogramming and excluding hardware failure. One of the possible explanations for this phenomenon could be progressive pallidal neuronal degeneration, thereby confining the DBS substrate [57]. As long-term DBS on vs. off comparisons are lacking, it is unclear whether DBS continues to improve dystonia in the long term. One year postoperatively, 27/56 (48%) and 17/56 (57%) of the PKAN patients experienced a ≥30% or ≥50% improvement in BFMDRS-M, respectively. Again, patients with atypical PKAN display a higher response rate (73% of atypical PKAN patients demonstrate >30% improvement vs. 35% of classic PKAN patients) [40].

In our analysis of 99 published cases, the preoperative dystonia severity, disease duration, and proportion of life lived with symptoms were not predictive of the relative BFMDRS-M reduction. Interestingly, in classic PKAN cases, there was no difference in outcome (relative BFMDRS-M reduction) between patients with and without fixed skeletal deformities and/or muscle contractures preoperatively. The numbers are, however, small and potentially affected by reporting bias [40].

The exact mechanism of the action of GPi-DBS in PKAN remains unknown. A technetium single-photon emission CT study demonstrated prominent tracer accumulation in the bilateral pallidum, which was completely reversed 9 weeks after successful GPi-DBS, although an artifact induced by insertional edema cannot be ruled out completely [58]. An EEG study demonstrated the correction of electrophysiological responses during response inhibition tasks with GPi-DBS on vs. off [55].

The complication risk is not significantly different in children and adults with PKAN compared with what has been reported in other types of dystonia [59]. In our review, 5/10 patients operated in status dystonicus had a complication, compared to only 1/18 patients who were explicitly reported not to be operated in status dystonicus. In 6/99 cases, an infection was reported, of which led to a brain abscess. Hardware problems were relatively common (three cable fractures causing status dystonicus in one patient; two IPG malfunctions; two lead migrations). In one patient, revision surgery was necessary because of inadequate targeting. Death was reported in nine patients, mostly because of end-stage disease >1 year postoperatively, although two patients died within 3 months. Another patient needed a tracheostomy 1 month postoperatively after an aspiration pneumonia. Status dystonicus resulting from surgery and anesthesia caused a spontaneous femur fracture immediately postoperatively in one patient and a hip subluxation in another. Stimulation-caused side effects included blepharospasm and worsening of gait with GPi-DBS and reduced verbal fluency and worsening of dystonia with STN-DBS. In the case of a hardware infection necessitating system removal, a pallidotomy through the infected electrode lead before removal can be considered to reduce the risk of status dystonicus.

Conclusion

There is Oxford Centre for Evidence-Based Medicine (OCEBM) level 4 evidence that in about half of patients undergoing surgery, GPi-DBS substantially reduces dystonia severity (mean BFMDRS-M reduction of –26%) and improves functionality, pain, cognitive scores, and quality of life at 1 year postoperatively. Patients with atypical PKAN benefit significantly more from DBS than those with classic PKAN. However, in the long term, this benefit is lost, although the relative contribution of disease progression and loss of DBS effect is unknown. The risk of infection and hardware malfunction is in line with other types of dystonia, although two patients died within 3 months and the complication rate was particularly high in patients operated in status dystonicus.

Choreoacanthocytosis

Pathophysiology and Clinical Features

Choreoacanthocytosis (ChAc) is an autosomal-recessive disease with mutations in the *VPS13A* gene, encoding the protein chorein, for which the function is not well understood. ChAC is characterized by progressive cortical and basal ganglia neurodegeneration and abnormal red blood cell morphology (acanthocytes). It manifests generally in the third to fourth decade with a mixed movement disorder, predominantly in the orofacial region. Symptoms include dysarthria, chorea, hypotonia, and truncal spasms which often cause involuntary head banging. These are typically accompanied by cognitive decline, psychiatric manifestations, epilepsy, myopathy, and axonal neuropathy [60–62].

Many of these features resemble Huntington disease (HD) and ChAC symptom severity is often expressed using the UHDRS. However, ChAC patients generally progress more slowly than HD patients, and exhibit tongue- and lip-biting, self-mutilating behavior (SMB), and seizures, and these symptoms are usually not seen in HD [60].

ChAC is characterized by neuronal loss in the striatum, resulting in striatal atrophy and mild ventriculomegaly [63]. The diagnosis can be confirmed by the western blot [64], or by sequencing of the *VPS13A* gene [65]. A blood smear presence of acanthocytes is suggestive but not pathognomonic for ChAC.

The most debilitating symptoms, chorea and dystonia, are often poorly controlled by pharmacological therapy, which includes botulinum toxin injections, tetrabenazine, and atypical neuroleptics.

Patient Selection and Timing of Surgery

So far, DBS has been reported in 22 ChAC patients (17 male). The median age at surgery was 38.5 years (range 30–54 years) after a median disease duration of 7.5 years (range 1–24 years). In a multicenter retrospective case series of 15 patients, the indications for surgery were disabling motor symptoms (chorea, dystonia, trunk spasms, falls, and gait impairment; $n = 11$), SMB ($n = 6$), head banging induced by trunk spasms or head drops ($n = 4$), feeding dystonia ($n = 3$), and recurrent belching ($n = 2$) [60]. None of the patients suffered a dystonic storm.

Surgery

Following a report on a successful pallidotomy in ChAC [9], GPi-DBS for ChAC was first reported in 2001 [66] and the GPi has been targeted bilaterally in all cases, except for one patient treated successfully with bilateral thalamic (Vo) stimulation [61]. Nakano *et al.* also implanted Vo electrodes in addition to GPi electrodes. Interestingly, in these patients, GPi stimulation alone improved falls and oromandibular dystonia but was insufficient to reduce trunk spasm and chorea (19–27% UHDRS reduction 1 year postoperatively). Vo stimulation alone improved UHDRS more than GPi stimulation alone (33–38% UHDRS reduction), but combined GPi and Vo stimulation was superior (40–46% UHDRS reduction) [67].

From an anesthetic perspective, it seems that dexmedetomidine is a useful agent to reduce the orofacial dystonia, which may interfere with stereotactic MRI and/or the surgical procedure [68]. The use of MER was reported in 6/22 patients, but no details about the characteristics of GPi neurons in ChAC patients have been published to date.

Programming and Follow-Up

It usually takes approximately 1 month before improvement in oromandibular dyskinesias and limb chorea is observed, and it takes several months before the maximal benefit is obtained [62, 69, 70]. As in other types of dystonia, there is no consensus on the ideal DBS settings. Typically, the complexity increases when several types of abnormal movements are present simultaneously, such as a combination of chorea and dystonia, which is usually the case in ChAC. In a multicenter retrospective case series of 15 ChAC patients, the majority of patients required high-frequency stimulation (130–185 Hz), while in 4/14 patients, high-frequency stimulation worsened chorea and/or dystonia, and therefore low-frequency stimulation (40–60 Hz) was (initially) applied [60]. Low-frequency stimulation may worsen truncal spasms [8]. Very low-frequency stimulation (10 Hz) had no effect, and very high-frequency stimulation (>500 Hz) worsened the symptoms [66]. Stimulation settings thus need to be highly individualized based on the presence of various symptoms and their relative contribution to global function [71]. With longer follow-up, the amplitude, pulse width, and number of active contacts had to be gradually increased to maintain the stimulation benefit [60].

Outcome

A multicenter retrospective case series of 15 patients reported on outcomes and covariates associated with better results for bilateral GPi-DBS in ChAC [60]. On

average, choreatic movements were substantially reduced early postoperatively, by 50% on the UHDRS-Movement Scale (UHDRS-MS) [60] and 38% on the AIMS [7, 69]). It appears that chorea (within hours), dystonia (within hours to days for the phasic component; within weeks to months for the tonic component), trunk spasms, head drops, orofacial movements, and SMB have a >90% chance of improvement with DBS. Dysarthria rarely improves [72]. Gait improved in patients with chorea and dystonia, but not in patients with parkinsonism. Feeding status improved in 6/9 patients. In two patients severe truncal hypotonia did not respond to DBS [61, 73]. DBS did not influence the Mini-Mental Status Exam [72, 74]. Postoperative weight gain, most likely because of less impaired feeding, has been reported [69]. Although no formal DBS on vs. off comparisons have been published, a rapid loss and resolution of effect after system removal and re-implantation, respectively, has been described [7]. Moreover, EMG registrations have shown a more than threefold decrease in muscle spasms with DBS [61]. The functional status, as measured by the UHDRS independence score (UHDRS-IS) and functional capacity score (UHDRS-FCS), improved shortly after surgery from on average 53 to 73 (+37%) and 4.1 to 7.2 (+76%), respectively. Seventy to 80% of patients had a clinically relevant functional improvement. In the long term, this functional improvement seems more stable than that of the UHDRS-MS [60]. No formal quality of life evaluations before and after DBS have been published in ChAC.

In the long term, the UHDRS-MS reduction is not retained in all patients. At 3 and 5 years postoperatively, only 3/7 and 0/2 patients still had a ≥20% UHDRS-MS improvement compared to immediately preoperatively. As no long-term DBS on vs. off comparisons have been published, it cannot be determined with certainty whether the loss of effect is due to loss of DBS efficacy or due to disease progression, although the latter seems more plausible. Only 1/22 patients failed to respond to DBS (<20% improvement), but in this particular patient the electrodes were removed within 1 month postoperatively, after continuously changing the settings. It is possible that insufficient time for effect wash-in was permitted [8]. The average UHDRS-MS reduction of approximately 50% is independent of the preoperative UHDRS-MS. There was no significant relationship between UHDRS-MS reduction and age or disease duration [60]. The majority of patients were able to taper their medication following DBS (total cessation of medication in 1/14) [60, 61].

Little is known about the mechanism behind DBS for ChAC. Bilateral striatal hypometabolism, as detected by fluoro-2-deoxyglucose positron emission tomography in ChAC patients, remained unchanged with DBS [74]. Seizures have been reported in one patient during DBS surgery (associated with a subdural hematoma) and in one patient 6 months after surgery. Given the predisposition for seizures in ChAC patients, the additional seizure risk caused by DBS appears to be low. Furthermore, one hardware infection resulting in a pallidotomy-like lesion, one lead pulled during an external trial, one Twiddler syndrome (i.e. malfunction due to manipulation of the device), and one sudden death 2 years post DBS implantation have been reported to date [60].

Conclusion

There is OCEBM level 4 evidence that GPi-DBS can improve chorea (UHDRS-MS, –50%; AIMS, –38%), dystonia, SMB, and functional status (UHDRS-IS, +37%; UHDRS-FCS, +76%) in ChAC patients. In the literature, >90% of cases responded to DBS. Medication can often be reduced. However, the improvement in chorea and dystonia vs. preoperatively is lost over approximately 5 years, most likely because of disease progression. Both high- and low-frequency stimulation can be beneficial for different motor components and therefore stimulation settings need to be individualized. The complication rate, including the risk of seizures, is low.

Lesch-Nyhan Disease

Pathophysiology and Clinical Features

Lesch–Nyhan disease (LND) is an X-linked recessive disorder associated with mutations in the *HPRT1* gene. This results in a complete deficiency of hypoxanthine–guanine phosphoribosyltransferase (HGPRT), which is a purine salvage enzyme [75, 76]. Clinically, LND expresses during early childhood with hyperuricemia leading to gout and nephrolithiasis, hypotonia evolving towards generalized dystonia, choreoathetosis, weakness and spasticity mainly in the lower limbs, and cognitive impairment. However, the most disabling symptoms are aggression and SMB, typically lip-biting or finger-chewing as soon as teeth are present [77, 78]. LND patients generally survive with a limited quality of life. Imaging studies [79] and neuropathological examinations [80] have not disclosed any abnormality except for striatal atrophy. Neurochemical analysis of post-mortem tissue and CSF revealed decreased levels of dopamine and its metabolite homovanillic acid,

while serotonin and 5-hydroxyindoleacetic levels vary. Abnormal monoaminergic transmission in the basal ganglia is likely to play a key role in the pathophysiology [81, 82].

Treatment of LND involves limiting hyperuricemia to avoid nephropathy and gout, but normalization of uric acid levels does not alter the neurological symptoms of the disease. Hypertonia is frequently treated with diazepam, baclofen, and/or intramuscular botulinum toxin injections [77]. As there is no specific treatment for the LND-associated SMB, these children often require removal of teeth as well as physical restraints including masks against spitting [76].

Patient Selection and Timing of Surgery

Since 2001, no more than nine LND patients treated with DBS have been reported. All patients were male, in line with the X-linked inheritance. The majority were operated in early adolescence (median 13 years, range 5–28 years). Exacerbation of SMB and severe dystonia were the principal indications for surgery.

Surgery

In the literature, only the GPi has been used as a DBS target for LND. An interesting question is whether or not stimulation of the limbic GPi (with connections to the frontal cortex [83]) specifically addresses SMB, wheras stimulation of the motor GPi (with connections to the motor cortex [83]) improves dystonia. Two groups have implanted two electrodes on each side, one targeting the motor GPi and one targeting the limbic GPi [84, 85]. The motor and limbic GPi may be discriminated electrophysiologically [85], and Cif *et al.* indeed report specific improvement of SMB with limbic GPi stimulation (but not with motor GPi stimulation) and dystonia with motor GPi stimulation (but not with limbic GPi stimulation) [84]. However, SMB can also be substantially or completely abolished when only one electrode is implanted, targeting the ventroposterior motor GPi [76]. It seems that stimulation in one part of the GPi also affects neurons in the other part, as the firing rate of motor GPi neurons altered with stimulation of the limbic GPi [86]. In LND patients, a firing rate of 10–15 Hz of has been reported in both motor and limbic GPi neurons, under propofol or sevoflurane anesthesia [76, 85, 86].

Programming and Follow-Up

In the published cases, only high-frequency stimulation (≥120 Hz) has been reported, although the pulse width varies widely (60–450 μs) between groups.

Outcome

The most disabling symptoms in LND are SMB and dystonia, and both are improved by DBS. Dystonia severity (BFMDRS-M) is reduced by 4–55% (median 33%), 1 year postoperatively. The effect on SMB is impressive, with complete resolution or significant improvement reported in 6/8 and 2/8 patients, respectively. Both dystonia and SMB improve within the first days until 2–3 months postoperatively [5, 75–77, 84]. When stimulation is ceased, dystonia returns within 10 days, and SMB after 1–3 weeks [84]. The evolution of BFMDRS-D 1 year post DBS was highly variable (ranging from 13% worsening to 50% improvement). However, many reports stress that physical restraints were no longer needed postoperatively [5, 75–77, 84] and that teeth extractions could be avoided [84]. This is paramount for social interaction, going to school, oral communication, and feeding. Moreover, mood and level of cooperation can also improve [75]. There have been no reports describing changes in cognition after DBS. Long-term experience is limited (with a follow-up of 2 and 5 years reported in three and one patients, respectively), but appears to be remarkably stable, both in terms of dystonia and SMB.

In 7/8 patients, dystonia was reduced substantially (>20%), while in 1/8 patients only a 16% BMFDRS-M improvement was obtained. Given the small cohort size and the heterogeneous way of outcome reporting, factors predicting responders cannot be reliably extracted. However, the improvement in SMB and dystonia is not larger per se in patients with four electrodes (targeting the motor and limbic GPi separately) than in patients with two electrodes. There is no obvious association with disease duration. Postoperatively, most reports describe a slow but substantial reduction in medication used to treat dystonia, and the complete cessation of anti-SMB drugs [75, 84, 85]. Given the selective effects of limbic and motor GPi stimulation, it seems plausible that DBS of the limbic and motor GPi alleviates SMB and dystonia, respectively. Nevertheless, SMB also improves with DBS targeting the motor GPi only. Interestingly, SMB may be a lateralized symptom, as it returned only on the left hemibody after a fracture of the right-sided GPi electrode [76]. In 2/9 patients, a lead fracture occurred [15, 76], which is a relatively high rate and potentially associated with SMB or with stress on the leads due to growth. A late infection occurred in one patient, necessitating unilateral system removal [15]. One sudden death, 1 year postoperatively, was reported [76].

Conclusion

There is OCEBM level 4 evidence that high-frequency GPi-DBS can substantially reduce dystonia (median BFMDRS-M reduction of 33%, range 4–55%) and completely or almost completely abolish SMB in patients with LND, with a remarkably sustained benefit. The reported response rate is very high. Lead fractures have been observed relatively frequently.

Kernicterus

Pathophysiology and Clinical Features

Severe hyperbilirubinemia, especially early in the newborn period, may result in bilirubin-induced neurological dysfunction (BIND). Structures commonly affected by bilirubin include the basal ganglia, hippocampus, geniculate bodies, cranial nerves, and cerebellum. Consequently, neurological manifestations of BIND are movement disorders including dystonia (often presenting as opisthotonus), spasticity and choreoathetosis, intellectual disability, and auditory and oculomotor dysfunction. Common non-neurological manifestations of kernicterus are gastroesophageal reflux, impaired digestion, and dysplasia or hypoplasia of the dental enamel. Treatment is focused on prevention by using phototherapy or exchange transfusions in newborns with hyperbilirubinemia. Baclofen, clonazepam, and trihexyphenidyl are commonly used for dystonia, spasticity, and choreoathetosis in BIND.

Patient Selection and Timing of Surgery

DBS has been reported in 14 patients with kernicterus, at a median age of 12 years (range 7–20 years). In all these cases, severe generalized dystonia, refractory to medical treatment, was the indication for surgery. One patient was operated during a dystonic storm [87]. Twelve patients were male, confirming the male predominance observed in kernicterus.

Surgery

MER was applied in the majority of patients, but no specific signal characteristics of GPi or STN neurons in patients with kernicterus have been published. Despite the fact that the basal ganglia and especially the GPi are pathologically and radiologically affected in kernicterus, 13/14 patients were treated with GPi-DBS (including one hemidystonia patient treated unilaterally). One patient underwent STN-DBS.

Programming and follow-up

Data on programming is limited, but as far as we know only high-frequency stimulation (≥120 Hz) has been applied. The longest reported follow-up is 3.5 years [88].

Outcome

Improvement in the dystonia severity and functional outcome after DBS has been variable but generally disappointing (median BFMDRS-M improvement of 7%, range +63% to –72% after a median of 1 year; median BFMDRS-D improvement of 3%, range +67% to –27% after a median of 1 year). Only 2/12 patients had a >30% BFMDRS-M improvement, and only 1/6 had a >20% BFMDRS-D improvement. Hence, the response rate of GPi-DBS for kernicterus is low. There are no reports on medication reduction after DBS for kernicterus. No complications have been published.

Conclusion

From the scarce publications on DBS for kernicterus, one may conclude that GPi-DBS is generally ineffective in reducing kernicterus-associated dystonia, with few exceptions, and that even in these successful cases the functional improvement is limited.

Glutaric aciduria type 1

Pathophysiology and Clinical Features

Glutaric aciduria type 1 (GA-1) is an autosomal-recessive disorder caused by a mutation in the *GCDH* gene encoding glutaryl-coenzyme A dehydrogenase. This enzyme is involved in degrading lysine, hydroxylysine, and tryptophan. The accumulation of their intermediate breakdown products including glutaric acid and 3-hydroxyglutaric acid, especially in the basal ganglia, causes neurological symptoms including intellectual disability, dystonia, choreoathetosis, and spasticity. Medical treatment involves carnitine and ascorbic acid substitution and a dietary restriction of lysine and tryptophan. Pallidotomy has been tried with variable success, even in an 18-month old child [89, 90].

Patient Selection and Timing of Surgery

We identified 10 GA-1 patients treated with DBS in the published literature. They were operated at a median age of 13 years (range 10–17 years). The indication was always generalized dystonia refractory to medical treatment.

Surgery

In all GA-1 patients, the GPi was targeted. At least half of the surgeries involved MER, although no specific neuronal characteristics have been reported.

Programming and Follow-Up

Stimulation parameters have been reported in only one patient. The longest follow-up was 1 year although one report states that the disability was initially stable but worsened in the long term [91].

Outcome

Overall, the reported outcome of GPi-DBS on dystonia in GA-1 has been poor, with a median BFMDRS-M and BADS reduction of 5% (range 0–15%) and 9% (range 0–18%), respectively. No studies have shown any change in disability as measured by BFMDRS-D. Interestingly, pain scores, as reported by the child and parents, child health-related quality of life, and caregiver burden were all substantially reduced after DBS in a single patient, despite unchanged BFMDRS-M and BFMDRS-D scores [13]. This was probably not observed in the other patients, as the depleted battery was not replaced in one patient and none of the other publications mentions a subjective improvement in pain or quality in life. As the maximal reduction in dystonia severity was <20%, the response rate is considered low. No changes in dystonia medication after DBS have been reported. One surgical complication (lead malposition requiring revision surgery) was reported.

Conclusion

Although the available data are limited, it appears that GPi-DBS does not substantially improve dystonia severity or disability in GA-1.

Other Metabolic Movement Disorders

With variable success rates, DBS has been explored in other metabolic movement disorder diseases, including Wilson disease, the neuronal ceroid lipofuscinoses, methylmalonic acidemia, GM1 gangliosidosis type 3, phenylketonuria, homocystinuria, McLeod syndrome, X-linked adrenoleukodystrophy, and glucose-6-phosphatase dehydrogenase deficiency.

Wilson Disease

Wilson disease is an autosomal-recessive inherited disease with mutations in *ATP7B*, resulting in copper accumulation and toxicity. Untreated Wilson disease inevitably leads to hepatic, neurologic, or psychiatric problems, in variable combinations. The timely initiation of chelation can reverse damage to the liver or brain. Neurological abnormalities can be seen in 20–75% of all patients. Traditionally, the neurological phenotype can be classified into four subtypes, with predominantly dysarthric, dystonic, pseudosclerotic (characterized by tremor), or parkinsonian manifestations. Even though a solitary neurological symptom may herald the onset of the disease, they commonly coexist in advanced stages of the disease, and dysarthria, in particular, is present in the majority of all patients [92]. Presence of dystonia is a negative prognostic factor in Wilson disease, and dystonia is also the symptom that is the most refractory to improvement after chelation therapy [92].

Excellent long-term tremor improvement has been reported after thalamotomy [93, 94] and has been replicated with Vim-DBS [92]. All three reports on GPi-DBS for Wilson disease-associated dystonia have been disappointing (0–14% BFMDRS reduction), although a subjective improvement in burden as reported by the caregiver and an improvement in ballistic movements upon arousal have been reported [11, 95].

Adenylyl Cyclase 5 Gene Mutations

Following the first phenotypic description of a family with autosomal-dominant inheritance of infantile onset paroxysmal or continuous hyperkinetic movements, dystonia, chorea, or a combination of these, in 2001, the underlying mutations in the adenylyl cyclase 5 gene (*ADCY5)* were identified in 2012. *ADCY5* encodes isoform 5 of adenylyl cyclase, which converts adenosine triphosphate to adenosine monophosphate. Isoform 5 is remarkably selectively expressed in the striatum, nucleus accumbens, and olfactory tubercle. Besides the aforementioned movement disorders, typical symptoms also involve sleep dysregulation, delayed milestones, hypotonia (especially in the face), and a distinct wide-based gait with adducted knees [96–98]. In four reported cases, GPi-DBS appeared to improve dystonia and hyperkinetic movements, as well as sleep and ambulation.

Non-PKAN Neurodegeneration with Brain Iron Accumulation

The most frequent type of neurodegeneration with brain iron accumulation (NBIA) is PKAN. However,

there are many other types of NBIA disorders, and for some the mutation has been identified (e.g. mutations in *PLA2G6*, aceruloplasminemia, neuroferritinopathy, mitochondrial membrane protein-associated neurodegeneration), whereas others are idiopathic. GPi-DBS in four cases of non-PKAN NBIA disorders, including one in Woodhouse–Sakati syndrome, resulted in variable dystonia reduction, probably as a result of the heterogeneous underlying causes [6, 51, 95, 99].

Neuronal Ceroid Lipofuscinoses

The neuronal ceroid lipofuscinoses are a group of neurodegenerative, lysosomal storage disorders. Batten disease, one of the juvenile forms of neuronal ceroid lipofuscinoses, is an inherited autosomal-recessive disease, caused by mutations in the *CLN3* gene (16p12). It is characterized by progressive vision loss, the deterioration of cognitive and motor functions, seizures, and, in a later stage, also the development of parkinsonism, dystonia, choreoathetosis, hemiballism, or myoclonus. In the course of neuronal ceroid lipofuscinoses, dystonic storms may eventually complicate the clinical picture. After the good effect of a bilateral pallidotomy in a dystonic patient with Batten disease, her sister, who suffered the same syndrome, underwent bilateral GPi-DBS during a dystonic storm, with a short-term reduction of 38% in the BFMDRS-M [100]. Kufs disease, the major adult form of NCL, can be either autosomal-recessive or -dominant, and is generally caused by mutations in the *CLN6* gene. Symptoms are usually milder than in juvenile forms and do not involve blindness. GPi-DBS in two of these adult cases resulted in a limited improvement of the hyperkinetic movements [95, 101].

Methylmalonic Acidemia

Methylmalonic acidemia (MMA) refers to a rare (1 in 50,000–169,000) heterogeneous disease resulting in the accumulation of methylmalonic acid in different body tissues and fluids. Patients generally present during the first years of life with failure to thrive, ketoacidosis, and neurological symptoms including hypotonia, seizures, encephalopathy, and generalized dystonia. Radiologically, a liquefaction of the pallidum (so-called autopallidotomy) appears as a T2 hyperintensity on MRI. To the best of our knowledge, only two MMA patients with generalized dystonia have been treated with DBS. Given the presumed absence of functional pallidal tissue, the Vim or STN were targeted. No reduction in dystonia severity was observed, although subjectively, functional status and mood improved after DBS [21, 95].

GM1 Gangliosidosis Type 3

GM1 gangliosidoses are rare autosomal-recessive lysosomal storage disorders caused by GM1 ganglioside accumulation, including in the striatum. Types 1 and 2 are severe infantile forms, whereas type 3 is a milder adult form, mainly presenting with a variable combination of muscle atrophy, corneal clouding, extrapyramidal signs, intellectual disability, and severe dystonia. GM1 gangliosidosis type 3 is caused by a mutation in the *GLB1* gene. In two type 3 patients, modest improvement in dystonia and parkinsonism [102] and stabilization of disability [91] were observed in the short term, although the benefit vs. preoperatively was diminished over time.

Phenylketonuria

Phenylketonuria (PKU) is an inborn deficiency of phenylalanine hydroxylase, which converts phenylalanine to tyrosine. Consequently, phenylalanine levels increase and accumulate in body tissues, accompanied by the typical musty odor of phenylacetic acid. Decreased levels of tyrosine (a melanin precursor) cause patients to have fair skin, blond hair, and light-colored eyes. The most profound characteristic of PKU is cognitive impairment, which has been associated with defective myelin synthesis during infancy. Other neurological signs include microcephaly, seizures, choreoathetosis, rigidity, ataxia, and tremor. A low-phenylalanine diet instituted early in life decreases the severity of the disease but does not guarantee normal neurological development. Approximately 25% of the PKU patients suffer from tremor, typically of the cerebellar type with postural and/or intention components. Vim-DBS substantially reduced tremor in a single case of PKU up to 30 months postoperatively [103].

Homocystinuria

Homocystinuria (HCU) is an autosomal-recessive disease, typically resulting in a defective sulfur amino acid metabolism. HCU may cause several neuropsychiatric, systemic, and ophthalmological symptoms. Exceptionally, movement disorders including dystonia, tremor, and chorea have been reported in HCU patients. In a single case report, bilateral GPi-

DBS resulted in a >90% reduction of BFMDRS-M, 7 months postoperatively [104].

McLeod Syndrome

McLeod syndrome (MLS) is a type of neuroacanthocytosis. MLS is an adult-onset X-linked recessive disorder, caused by mutations in the *XK* gene, encoding Kx, a secondary supportive protein for the Kell antigen on the erythrocyte surface. MLS may affect the central and peripheral nervous system, heart, muscles, and blood. Common neurological features include limb chorea, face and oromandibular dyskinesias, dystonia, hypotonia, postural instability seizures, peripheral neuropathy, dementia, and behavioral changes. In a single case report, 40-Hz GPi-DBS reduced chorea, dystonia, and dysarthria, 3 months postoperatively, although hypotonia continued to limit ambulation. Stimulation at 10 Hz was ineffective, while 130 Hz improved dystonia but worsened chorea and caused dysarthria [73].

X-Linked Adrenoleukodystrophy

X-linked adrenoleukodystrophy (X-ALD) is caused by mutations in *ABCD1*, encoding a peroxisomal membrane transporter protein. This results in the accumulation of very long chain fatty acids in different body tissues, of which the myelin in the central nervous system, the adrenal cortex, and the Leydig cells in the testis are most severely affected. Clinically, X-ALD presents very heterogeneously, but the majority of patients have a normal development in early childhood, followed by a rapid degeneration to a vegetative state (childhood cerebral form). A single patient affected by a less severe form of X-ALD, with mainly dystonic symptoms, did not show any benefit of bilateral GPi-DBS, and the system was eventually removed without any change in his clinical status [105].

Abetalipoproteinemia

Abetalipoproteinemia (also called Bassen–Kornzweig syndrome) is a rare autosomal-recessive disorder caused by a mutation in a microsomal triglyceride transfer protein gene (*MTTP*), thereby interfering with the normal absorption of fat and fat-soluble vitamins. The neurological sequelae likely result from vitamin E deficiency, and include retinal degeneration, hyporeflexia, reduced proprioception and sensation, ataxia, and, rarely, tremor. Bilateral Vim-DBS substantially reduced both tremor and ataxia severity in a single adult abetalipoproteinemia patient, but with a limited follow-up [106].

Glucose-6-Phosphatase Dehydrogenase Deficiency

Glucose-6-phosphatase dehydrogenase deficiency (G6PDD) is an X-linked recessive disorder predisposing to erythrocyte breakdown. Four hundred million people are affected globally, most often in Africa, Asia, the Mediterranean and the Middle East, potentially because carriers of the G6PDD allele may be partially protected against malaria. In a single pediatric G6PDD patient, the outcome of bilateral STN-DBS was called successful in treating dystonia, which most likely resulted from G6PDD through kernicterus, although this was not specified [107].

Conclusions

From this comprehensive literature review, we conclude that there is OCEBM level 4 evidence that bilateral GPi-DBS is effective to reduce dystonia in PKAN, especially the atypical type, and ChAc in the short term, and dystonia and SMB in LND in the long term. In contrast, GPi-DBS for dystonia associated with kernicterus and GA-1 is likely to be futile. DBS appears to be a promising treatment option for dystonia in forms of the NCLs and PKU; for dystonia, dyskinesia, and chorea-ballismus in *ADCY5*-associated movement disorders; and for tremor in PKU and abetalipoproteinemia.

Despite many efforts since the first publications in 2001, DBS for metabolic movement disorders is still considered as a treatment of last resort, and performed in very few centers. The evidence is restricted to case reports and small case series, often with unblinded and limited follow-up analyses. Furthermore, given the rarity of these disorders, the number of cases treated in a single center or even in a single country is too low to conduct well-powered trials. International prospective registries such as the Pediatric International Deep Brain Stimulation Registry Project (PEDiDBS) and German Registry of Paediatric Deep Brain Stimulation in Patients with Childhood-Onset Dystonia (GEPESTIM) may overcome this problem. Importantly, future trials should, after a stimulation optimization phase, include a blinded DBS on vs. off comparison with

sufficient wash-in and wash-out intervals, and outcomes should be measured with clinically meaningful scales optimized for symptoms and age group.

Key Points and Clinical Pearls

- There is Oxford Centre for Evidence-Based Medicine (OCEBM) level 4 evidence that bilateral globus pallidus internus deep brain stimulation (GPi-DBS) is effective to reduce dystonia in pantothenate kinase-associated neurodegeneration (PKAN), especially the atypical type, and choreoacanthocytosis (ChAc) in the short term, and dystonia and self-mutilating behavior in Lesch–Nyhan disease (NLD) in the long term.
- GPi-DBS for dystonia associated with kernicterus and glutaric aciduria type 1 is likely to be futile.
- DBS appears to be a promising treatment option for dystonia in forms of neuronal ceroid lipofuscinosis and phenylketonuria; for dystonia, dyskinesia and chorea-ballismus in *ADCY5*-associated movement disorders; and for tremor in phenylketonuria and abetalipoproteinemia.

Directions for Future Research

- International prospective registries such as the PEDiDBS and GEPESTIM may allow for eventual well-powered clinical trials.
- Future trials should, after a stimulation optimization phase, include a blinded DBS on vs. off comparison with sufficient wash-in and wash-out intervals.
- Outcomes should be measured with clinically meaningful scales optimized for symptoms and age group.

References

1. Thomas M, Hayflick SJ, Jankovic J. Clinical heterogeneity of neurodegeneration with brain iron accumulation (Hallervorden–Spatz syndrome) and pantothenate kinase-associated neurodegeneration. Mov Disord. 2004;**19**(1):36–42.
2. Cif L, Ruge D, Gonzalez V, et al. The influence of deep brain stimulation intensity and duration on symptoms evolution in an OFF stimulation dystonia study. Brain Stimul. 2013;**6**(4):500–5.
3. Shields DC, Sharma N, Gale JT, Eskandar EN. Pallidal stimulation for dystonia in pantothenate kinase-associated neurodegeneration. Pediatr Neurol. 2007;**37**(6):442–5.
4. Mariotti P, Fasano A, Contarino MF, et al. Management of status dystonicus: Our experience and review of the literature. Mov Disord. 2007;**22**(7):963–8.
5. Taira T, Kobayashi T, Hori T. Disappearance of self-mutilating behavior in a patient with Lesch–Nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus. Case report. J Neurosurg. 2003;**98**(2):414-6.
6. Timmermann L, Pauls KA, Wieland K, et al. Dystonia in neurodegeneration with brain iron accumulation: Outcome of bilateral pallidal stimulation. Brain. 2010;**133**(Pt 3):701-12.
7. Kefalopoulou Z, Zrinzo L, Aviles-Olmos I, et al. Deep brain stimulation as a treatment for chorea-acanthocytosis. J Neurol. 2013;**260**(1):303–5.
8. Ruiz PJ, Ayerbe J, Bader B, et al. Deep brain stimulation in chorea acanthocytosis. Mov Disord. 2009;**24**(10):1546–7.
9. Fujimoto Y, Isozaki E, Yokochi F, et al. A case of chorea-acanthocytosis successfully treated with posteroventral pallidotomy. Rinsho Shinkeigaku. 1997;**37**(10):891–4.
10. Monbaliu E, Himmelmann K, Lin JP, et al. Clinical presentation and management of dyskinetic cerebral palsy. Lancet Neurol. 2017;**16**(9):741–9.
11. Sidiropoulos C, Hutchison W, Mestre T, et al. Bilateral pallidal stimulation for Wilson's disease. Mov Disord. 2013;**28**(9):1292–5.
12. Darling A, Tello C, Marti MJ, et al. Clinical rating scale for pantothenate kinase-associated neurodegeneration: A pilot study. Mov Disord. 2017;**32**(11):1620–30.
13. Gimeno H, Tustin K, Selway R, Lin JP. Beyond the Burke–Fahn–Marsden Dystonia Rating Scale: Deep brain stimulation in childhood secondary dystonia. Eur J Paediatr Neurol. 2012;**16**(5):501–8.
14. Tsering D, Tochen L, Lavenstein B, et al. Considerations in deep brain stimulation (DBS) for pediatric secondary dystonia. Childs Nerv Syst. 2017;**33**(4):631–7.
15. Air EL, Ostrem JL, Sanger TD, Starr PA. Deep brain stimulation in children: Experience and technical pearls. J Neurosurg Pediatr. 2011;**8**(6):566–74.
16. Vayssiere N, Hemm S, Zanca M, et al. Magnetic resonance imaging stereotactic target localization for

deep brain stimulation in dystonic children. J Neurosurg. 2000;**93**(5):784–90.

17. Umemura A, Jaggi JL, Dolinskas CA, Stern MB, Baltuch GH. Pallidal deep brain stimulation for longstanding severe generalized dystonia in Hallervorden–Spatz syndrome. Case report. J Neurosurg. 2004;**100**(4):706–9.
18. Grandas F, Fernandez-Carballal C, Guzman-de-Villoria J, Ampuero I. Treatment of a dystonic storm with pallidal stimulation in a patient with *PANK2* mutation. Mov Disord. 2011;**26**(5):921–2.
19. Starr PA, Markun LC, Larson PS, et al. Interventional MRI-guided deep brain stimulation in pediatric dystonia: First experience with the ClearPoint system. J Neurosurg Pediatr. 2014;**14**(4):400–8.
20. Lumsden DE, Ashmore J, Charles-Edwards G, et al. Observation and modeling of deep brain stimulation electrode depth in the pallidal target of the developing brain. World Neurosurg. 2015;**83**(4):438–46.
21. Chakraborti S, Hasegawa H, Lumsden DE, et al. Bilateral subthalamic nucleus deep brain stimulation for refractory total body dystonia secondary to metabolic autopallidotomy in a 4-year-old boy with infantile methylmalonic acidemia: Case report. J Neurosurg Pediatr. 2013;**12**(4):374–9.
22. Pena C, Bowsher K, Samuels-Reid J. FDA-approved neurologic devices intended for use in infants, children, and adolescents. Neurology. 2004;**63**(7):1163–7.
23. Krause M, Fogel W, Tronnier V, et al. Long-term benefit to pallidal deep brain stimulation in a case of dystonia secondary to pantothenate kinase-associated neurodegeneration. Mov Disord. 2006;**21**(12):2255–7.
24. Johans SJ, Swong KN, Hofler RC, Anderson DE. A stepwise approach: Decreasing infection in deep brain stimulation for childhood dystonic cerebral palsy. J Child Neurol. 2017;**32**(10):871–5.
25. Kaminska M, Perides S, Lumsden DE, et al. Complications of deep brain stimulation (DBS) for dystonia in children: The challenges and 10 year experience in a large paediatric cohort. Eur J Paediatr Neurol. 2017;**21**(1):168–75.
26. Yianni J, Nandi D, Shad A, et al. Increased risk of lead fracture and migration in dystonia compared with other movement disorders following deep brain stimulation. J Clin Neurosci. 2004;**11**(3):243–5.
27. Lumsden DE, Ashmore J, Charles-Edwards G, et al. Accuracy of stimulating electrode placement in paediatric pallidal deep brain stimulation for primary and secondary dystonia. Acta Neurochir (Wien). 2013;**155**(5):823–36.
28. Yianni J, Nandi D, Ch M, et al. Failure of chronic pallidal stimulation in dystonic patients is a medical emergency. Neuromodulation. 2004;**7**(1):9–12.
29. Austin A, Lin JP, Selway R, Ashkan K, Owen T. What parents think and feel about deep brain stimulation in paediatric secondary dystonia including cerebral palsy: A qualitative study of parental decision-making. Eur J Paediatr Neurol. 2017;**21**(1):185–92.
30. Zhou B, Westaway SK, Levinson B, et al. A novel pantothenate kinase gene (*PANK2*) is defective in Hallervorden–Spatz syndrome. Nat Genet. 2001;**28**(4):345–9.
31. Hayflick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden–Spatz syndrome. N Engl J Med. 2003;**348**(1):33–40.
32. Gordon N. Pantothenate kinase-associated neurodegeneration (Hallervorden–Spatz syndrome). Eur J Paediatr Neurol. 2002;**6**(5):243–7.
33. Sethi KD, Adams RJ, Loring DW, el Gammal T. Hallervorden–Spatz syndrome: Clinical and magnetic resonance imaging correlations. Ann Neurol. 1988;**24**(5):692–4.
34. Savoiardo M, Halliday WC, Nardocci N, et al. Hallervorden–Spatz disease: MR and pathologic findings. AJNR Am J Neuroradiol. 1993;**14**(1):155–62.
35. Gregory A, Hayflick SJ. Pantothenate kinase-associated neurodegeneration. GeneReviews®. 2002; Aug 13 (updated Aug 3 2017).
36. Albright AL, Barry MJ, Fasick P, Barron W, Shultz B. Continuous intrathecal baclofen infusion for symptomatic generalized dystonia. Neurosurgery. 1996;**38**(5):934–8; discussion 8-9.
37. Justesen CR, Penn RD, Kroin JS, Egel RT. Stereotactic pallidotomy in a child with Hallervorden–Spatz disease. Case report. J Neurosurg. 1999;**90**(3):551–4.
38. Tsukamoto H, Inui K, Taniike M, et al. A case of Hallervorden–Spatz disease: Progressive and intractable dystonia controlled by bilateral thalamotomy. Brain Dev. 1992;**14**(4):269–72.
39. Balas I, Kovacs N, Hollody K. Staged bilateral stereotactic pallidothalamotomy for life-threatening dystonia in a child with Hallervorden–Spatz disease. Mov Disord. 2006;**21**(1):82–5.
40. De Vloo P, Lee DJ, Dallapiazza RF, et al. Deep brain stimulation for pantothenate kinase-associated neurodegeneration: A meta-analysis. Mov Disord. 2019;**34**(2):264–73.
41. Vidailhet M, Pollak P. Deep brain stimulation for dystonia: Make the lame walk. Ann Neurol. 2005;**57**(5):613–4.
42. Liu Z, Liu Y, Yang Y, et al. Subthalamic nuclei stimulation in patients with pantothenate kinase-associated neurodegeneration (PKAN). Neuromodulation. 2017;**20**(5):484–91.

43. Detante O, Vercueil L, Krack P, Off-period dystonia in Parkinson's disease but not generalized dystonia is improved by high-frequency stimulation of the subthalamic nucleus. Adv Neurol. 2004;**94**:309–14.
44. Holloway KL, Baron MS, Brown R, et al. Deep brain stimulation for dystonia: A meta-analysis. Neuromodulation. 2006;**9**(4):253–61.
45. Hinkelbein J, Kalenka A, Alb M. Anesthesia for patients with pantothenate-kinase-associated neurodegeneration (Hallervorden–Spatz disease): A literature review. Acta Neuropsychiatr. 2006; **18** (3-4): 168–72.
46. McClelland VM, Valentin A, Rey HG, et al. Differences in globus pallidus neuronal firing rates and patterns relate to different disease biology in children with dystonia. J Neurol Neurosurg Psychiatry. 2016;**87** (9):958–67.
47. Valentin A, Selway R, Lin JP, et al. Comparison of micro-electrode recordings from globus pallidus internus (GPi) in children with severe dystonia from NBIA1 and other syndromes: Recordings under general anesthesia (abstract). Mov Disord. 2008;May **15**;23(S1):S382.
48. Lim BC, Ki CS, Cho A, et al. Pantothenate kinase-associated neurodegeneration in Korea: Recurrent R440P mutation in *PANK2* and outcome of deep brain stimulation. Eur J Neurol. 2012;**19** (4):556–61.
49. Vasques X, Cif L, Gonzalez V, Nicholson C, Coubes P. Factors predicting improvement in primary generalized dystonia treated by pallidal deep brain stimulation. Mov Disord. 2009;**24**(6):846–53.
50. Castelnau P, Cif L, Valente EM, et al. Pallidal stimulation improves pantothenate kinase-associated neurodegeneration. Ann Neurol. 2005;**57**(5):738–41.
51. Lumsden DE, Kaminska M, Gimeno H, et al. Proportion of life lived with dystonia inversely correlates with response to pallidal deep brain stimulation in both primary and secondary childhood dystonia. Dev Med Child Neurol. 2013;**55**(6):567–74.
52. Adamovicova M, Jech R, Urgosik D, Spackova N, Krepelova A. Pallidal stimulation in siblings with pantothenate kinase-associated neurodegeneration: Four-year follow-up. Mov Disord. 2011;**26**(1):184–7.
53. Vercueil L, Pollak P, Fraix V, et al. Deep brain stimulation in the treatment of severe dystonia. J Neurol. 2001;**248**(8):695–700.
54. Isaac C, Wright I, Bhattacharyya D, Baxter P, Rowe J. Pallidal stimulation for pantothenate kinase-associated neurodegeneration dystonia. Arch Dis Child. 2008;**93** (3):239–40.
55. Muckschel M, Smitka M, Hermann A, von der Hagen M, Beste C. Deep brain stimulation in the globus pallidus compensates response inhibition deficits: Evidence from pantothenate kinase-associated neurodegeneration. Brain Struct Funct. 2016;**221** (4):2251–7.
56. Mahoney R, Selway R, Lin JP. Cognitive functioning in children with pantothenate-kinase-associated neurodegeneration undergoing deep brain stimulation. Dev Med Child Neurol. 2011;**53**(3):275–9.
57. Tierney TS, Lozano AM. Surgical treatment for secondary dystonia. Mov Disord. 2012;**27** (13):1598–605.
58. Koyama M, Yagishita A. Pantothenate kinase-associated neurodegeneration with increased lentiform nuclei cerebral blood flow. AJNR Am J Neuroradiol. 2006;**27**(1):212–3.
59. Hogarth P, Kurian MA, Gregory A, et al. Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). Mol Genet Metab. 2017;**120**(3):278–87.
60. Miquel M, Spampinato U, Latxague C, et al. Short and long term outcome of bilateral pallidal stimulation in chorea-acanthocytosis. PLoS One. 2013;**8**(11):e79241.
61. Burbaud P, Vital A, Rougier A, et al. Minimal tissue damage after stimulation of the motor thalamus in a case of chorea-acanthocytosis. Neurology. 2002;**59** (12):1982–4.
62. Fernandez-Pajarin G, Sesar A, Ares B, et al. Deep brain bilateral pallidal stimulation in chorea-acanthocytosis caused by a homozygous *VPS13A* mutation. Eur J Neurol. 2016;**23**(1):e4–5.
63. Edwards TC, Zrinzo L, Limousin P, Foltynie T. Deep brain stimulation in the treatment of chorea. Mov Disord. 2012;**27**(3):357–63.
64. Dobson-Stone C, Velayos-Baeza A, Filippone LA, et al. Chorein detection for the diagnosis of chorea-acanthocytosis. Ann Neurol. 2004;**56** (2):299–302.
65. Rampoldi L, Dobson-Stone C, Rubio JP, et al. A conserved sorting-associated protein is mutant in chorea-acanthocytosis. Nat Genet. 2001;**28**(2):119–20.
66. Wihl G, Volkmann J, Allert N, et al. Deep brain stimulation of the internal pallidum did not improve chorea in a patient with neuro-acanthocytosis. Mov Disord. 2001;**16**(3):572–5.
67. Nakano N, Miyauchi M, Nakanishi K, et al. Successful combination of pallidal and thalamic stimulation for intractable involuntary movements in patients with neuroacanthocytosis. World Neurosurg. 2015;**84** (4):1177e1–7.
68. Syeda S, Bharadwaj S. Is dexmedetomidine a miracle drug for sedation in patients with neuroacanthocytosis with involuntary movements? J Neurosurg Anesthesiol. 2018;**30**(4):382–3.

69. Lim TT, Fernandez HH, Cooper S, Wilson KM, Machado AG. Successful deep brain stimulation surgery with intraoperative magnetic resonance imaging on a difficult neuroacanthocytosis case: Case report. Neurosurgery. 2013;**73**(1):E184–7; discussion E8.
70. Shin H, Ki CS, Cho AR, et al. Globus pallidus interna deep brain stimulation improves chorea and functional status in a patient with chorea-acanthocytosis. Stereotact Funct Neurosurg. 2012;**90**(4):273–7.
71. Smith KM, Spindler MA. Uncommon applications of deep brain stimulation in hyperkinetic movement disorders. Tremor Other Hyperkinet Mov (NY). 2015;**5**:278.
72. Machado A, Haber S, Sears N, et al. Functional topography of the ventral striatum and anterior limb of the internal capsule determined by electrical stimulation of awake patients. Clin Neurophysiol. 2009;**120**(11):1941–8.
73. Guehl D, Cuny E, Tison F, et al. Deep brain pallidal stimulation for movement disorders in neuroacanthocytosis. Neurology. 2007;**68**(2):160–1.
74. Li P, Huang R, Song W, et al. Deep brain stimulation of the globus pallidus internal improves symptoms of chorea-acanthocytosis. Neurol Sci. 2012;**33**(2):269–74.
75. Piedimonte F, Andreani JC, Piedimonte L, et al. Remarkable clinical improvement with bilateral globus pallidus internus deep brain stimulation in a case of Lesch–Nyhan disease: Five-year follow-up. Neuromodulation. 2015;**18**(2):118–22; discussion 22.
76. Abel TJ, Dalm BD, Grossbach AJ, et al. Lateralized effect of pallidal stimulation on self-mutilation in Lesch–Nyhan disease. J Neurosurg Pediatr. 2014;**14**(6):594–7.
77. Deon LL, Kalichman MA, Booth CL, Slavin KV, Gaebler-Spira DJ. Pallidal deep-brain stimulation associated with complete remission of self-injurious behaviors in a patient with Lesch–Nyhan syndrome: A case report. J Child Neurol. 2012;**27**(1):117–20.
78. Torres RJ, Puig JG. Hypoxanthine–guanine phosophoribosyltransferase (HPRT) deficiency: Lesch–Nyhan syndrome. Orphanet J Rare Dis. 2007;**2**:48.
79. Harris JC, Lee RR, Jinnah HA, et al. Craniocerebral magnetic resonance imaging measurement and findings in Lesch–Nyhan syndrome. Arch Neurol. 1998;**55**(4):547–53.
80. Watts RW, Spellacy E, Gibbs DA, Clinical, post-mortem, biochemical and therapeutic observations on the Lesch–Nyhan syndrome with particular reference to the neurological manifestations. Q J Med. 1982;**51**(201):43–78.
81. Lloyd KG, Hornykiewicz O, Davidson L, et al. Biochemical evidence of dysfunction of brain neurotransmitters in the Lesch–Nyhan syndrome. N Engl J Med. 1981;**305**(19):1106–11.
82. Silverstein FS, Johnston MV, Hutchinson RJ, Edwards NL. Lesch–Nyhan syndrome: CSF neurotransmitter abnormalities. Neurology. 1985;**35**(6):907–11.
83. Lumsden DE, Kaminska M, Ashkan K, Selway R, Lin JP. Deep brain stimulation for childhood dystonia: Is "where" as important as in "whom"? Eur J Paediatr Neurol. 2017;**21**(1):176–84.
84. Cif L, Biolsi B, Gavarini S, et al. Antero-ventral internal pallidum stimulation improves behavioral disorders in Lesch–Nyhan disease. Mov Disord. 2007;**22**(14):2126–9.
85. Pralong E, Pollo C, Coubes P, et al. Electrophysiological characteristics of limbic and motor globus pallidus internus (GPi) neurons in two cases of Lesch–Nyhan syndrome. Neurophysiol Clin. 2005; **35** (5-6): 168–73.
86. Pralong E, Pollo C, Villemure JG, Debatisse D. Opposite effects of internal globus pallidus stimulation on pallidal neurones activity. Mov Disord. 2007;**22**(13):1879–84.
87. Franzini A, Cordella R, Rizzi M, et al. Deep brain stimulation in critical care conditions. J Neural Transm (Vienna). 2014;**121**(4):391–8.
88. Keen JR, Przekop A, Olaya JE, Zouros A, Hsu FP. Deep brain stimulation for the treatment of childhood dystonic cerebral palsy. J Neurosurg Pediatr. 2014;**14**(6):585–93.
89. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM. Primary dystonia is more responsive than secondary dystonia to pallidal interventions: Outcome after pallidotomy or pallidal deep brain stimulation. Neurosurgery. 2004;**54**(3):613–19; discussion 9-21.
90. Rakocevic G, Lyons KE, Wilkinson SB, Overman JW, Pahwa R. Bilateral pallidotomy for severe dystonia in an 18-month-old child with glutaric aciduria. Stereotact Funct Neurosurg. 2004; **82** (2-3): 80–3.
91. Meoni S, Fraix V, Castrioto A, et al. Pallidal deep brain stimulation for dystonia: A long term study. J Neurol Neurosurg Psychiatry. 2017;**88**(11):960–7.
92. Hedera P. Treatment of Wilson's disease motor complications with deep brain stimulation. Ann N Y Acad Sci. 2014;**1315**:16–23.
93. Dwarakanath S, Zafar A, Yadav R, et al. Does lesioning surgery have a role in the management of multietiological tremor in the era of deep brain stimulation? Clin Neurol Neurosurg. 2014;**125**:131–6.
94. Starikov AS. Electrical stimulation of the brain in Wilson–Konovalov hepatocerebral dystrophy (a neuromorphological and neurophysiological analysis). Neurosci Behav Physiol. 2002;**32**(3):255–7.

95. Beaulieu-Boire I, Aquino CC, Fasano A, et al. Deep brain stimulation in rare inherited dystonias. Brain Stimul. 2016;**9**(6):905–10.

96. Chang FC, Westenberger A, Dale RC, et al. Phenotypic insights into *ADCY5*-associated disease. Mov Disord. 2016;**31**(7):1033–40.

97. Dy ME, Chang FC, Jesus SD, et al. Treatment of *ADCY5*-associated dystonia, chorea, and hyperkinetic disorders with deep brain stimulation: A multicenter case series. J Child Neurol. 2016;**31**(8):1027-35.

98. Meijer IA, Miravite J, Kopell BH, Lubarr N. Deep brain stimulation in an additional patient with *ADCY5*-related movement disorder. J Child Neurol. 2017;**32**(4):438–9.

99. FitzGerald JJ, Rosendal F, de Pennington N, et al. Long-term outcome of deep brain stimulation in generalised dystonia: A series of 60 cases. J Neurol Neurosurg Psychiatry. 2014;**85**(12):1371–6.

100. Elkay M, Silver K, Penn RD, Dalvi A. Dystonic storm due to Batten's disease treated with pallidotomy and deep brain stimulation. Mov Disord. 2009;**24**(7):1048–53.

101. Hasegawa H, Alkufri F, Munro N, et al. GPi deep brain stimulation for palliation of hemidystonia and hemibody jerking in a patient with suspected adult onset neuronal ceroid lipofuscinosis. J Neurol Sci. 2016;**362**:228–9.

102. Roze E, Navarro S, Cornu P, Welter ML, Vidailhet M. Deep brain stimulation of the globus pallidus for generalized dystonia in GM1 type 3 gangliosidosis: Technical case report. Neurosurgery. 2006;**59**(6):E1340; discussion E.

103. Payne MS, Brown BL, Rao J, Payne BR. Treatment of phenylketonuria-associated tremor with deep brain stimulation: Case report. Neurosurgery. 2005;**56**(4):E868; discussion E.

104. Aydin S, Abuzayed B, Varlibas F, et al. Treatment of homocystinuria-related dystonia with deep brain stimulation: A case report. Stereotact Funct Neurosurg. 2011;**89**(4):210–3.

105. van Karnebeek C, Horvath G, Murphy T, et al. Deep brain stimulation and dantrolene for secondary dystonia in X-linked adrenoleukodystrophy. JIMD Rep. 2015;**15**:113–6.

106. Mammis A, Pourfar M, Feigin A, Mogilner AY. Deep brain stimulation for the treatment of tremor and ataxia associated with abetalipoproteinemia. Tremor Other Hyperkinet Mov (NY). 2012;**2**.

107. Sriganesh K, Manikandan S. Anesthetic management of a child with severe dystonia and G6PD deficiency for deep brain stimulation. J Neurosurg Anesthesiol. 2015;**27**(3):271–2.

Chapter

32

Novel Therapeutic Approaches to Metabolic Movement Disorders

Gabriella A. Horvath and Clara D. van Karnebeek

Introduction

Movement disorders are common symptoms in patients with inborn errors of metabolism (IEMs), and have a serious impact on their quality of life. Treatment of the movement disorder is usually causal, i.e. aimed at the underlying condition. More and more therapeutic strategies are emerging for many IEMs, varying from dietary restriction/supplementation, enzyme cofactor/vitamin supplementation, enzyme-replacement, substrate inhibition, substrate reduction, bone marrow or hematopoietic stem-cell transplantation (HSCT), gene therapy, or newer symptomatic treatment modalities. Dietary manipulations typically aim at substrate reduction, i.e. decreasing the intake of toxic precursors or providing the deficient product. Vitamins and cofactors are used because in some disorders the synthesis of these is affected, while in others these catalyze residual enzyme activity and stability, or act as chaperones.

Enzyme-replacement therapy (ERT) has been used mainly in lysosomal storage disorders and is based on the ability of most cells to take up the deficient enzyme. Over the last few years, efforts have been made to target the brain better with intrathecal ERT. Substrate reduction therapy is also applied for the treatment of lysosomal storage disorders and aims to reduce the synthesis of the substrate of the mutant enzyme or its precursor.

Organ transplantation, specifically liver transplants, has been used mainly in small molecule disorders, especially urea cycle defects. The goal of this treatment is to replace the missing enzyme by replacing the whole organ. HSCT has been used for some lysosomal storage disorders and X-linked adrenoleukodystrophy (X-ALD). Some novel therapeutic approaches include chaperone molecules and proteostasis regulators, read-through drugs, cell therapies, ex vivo and in vivo gene therapy, RNA targeting, and genome editing (CRISPR/Cas9).

In some cases of IEMs, the movement disorder occurs after an acute metabolic decompensation, such as in glutaric aciduria type 1, and prompt management can prevent this life-altering complication. Since the introduction of expanded newborn screening in many countries, early diagnosis and treatment has dramatically reduced the disease burden in patients with IEMs.

The growing interest from the pharmaceutical industry in the field of rare disorders is also contributing to major breakthroughs in the development of clinical trials in IEMs.

Here, we will review novel therapies for movement disorders in IEMs that have emerged over the past decade, some of them proven to be effective, others failed after clinical trials, and some in ongoing trials. This may not be a comprehensive review of all the novel treatment modalities due to the large number of ongoing clinical trials, but it is intended to represent the rapidly expanding field of new treatments in rare diseases [1–11].

Treatment Modalities for IEMs

Natural Treatments

Natural treatments with antioxidants, natural compounds, and vitamins for IEMs began in the late twentieth century. These included vitamin E, selenium, curcumin, antioxidants, endoplasmic reticulum modifiers such as trimethylamine-N-oxide and N-tert-butyl-hydroxylamine derivative (NtBuHA), among others. Unfortunately these approaches address only the secondary consequences of the disease and not the underlying cause [12, 13].

Novel Approaches Using Available Drugs

Sodium benzoate, phenylacetate, and sodium phenylbutyrate are used for treatment in urea cycle disorders, but their side effect of decreasing branched-

chain amino acid levels have been investigated in the treatment of **maple syrup urine disease** patients. A double-blinded, randomized, placebo-controlled trial of phenylbutyrate in the treatment of maple syrup urine disease (ClinicalTrials.gov registration number: NCT01529060) has been completed, with results pending.

In a particular murine model of **Leigh syndrome**, specifically in *Ndufs4* knockout mice, it was found that mTOR was activated in the brain. Administration of an mTOR inhibitor, rapamycin conferred neuroprotection in these mice [14].

In **argininosuccinic aciduria** (**ASA**) there is nitric oxide (NO) deficiency, and patients develop long term hypertension and neurocognitive deficits. Supplementation of NO in patients with ASA controlled hypertension and improved cardiac hypertrophy [15, 16].

Anti-Inflammatories

Some lysosomal storage disorders have an abnormal inflammatory response in their pathobiology. The use of anti-inflammatories has been addressed in cases of the neuronal ceroid lipofuscinoses (NCLs) (ClinicalTrials.gov NCT01399047). Ten children participated in a double-blinded, randomized, 22-week crossover study of mycophenolate mofetil vs. placebo; no serious side effects were found but outcomes have not yet been reported.

Cofactor Administration

Molybdenum Cofactor Deficiency Type A

Molybdenum cofactor deficiency (MoCD) is caused by a deficiency in one of the molybdenum-dependent enzymes, sulfite oxidase, xanthine oxidase, and aldehyde dehydrogenase. Mutations in *MOCS1* cause impaired sulfite oxidase enzyme activity leading to a deficiency in the first intermediate in the biosynthetic pathway, the cyclic pyranopterin monophosphate (cPMP), and it is classified as MoCD type A. It is characterized by sulfite accumulation. Defects in *MOCS2* cause accumulation of cPMP and it is classified as MoCD type B. The very rare type C form is associated with mutations in *GPHN*. The natural history of the disease is that of neurodegeneration leading to severe epileptic encephalopathy, brain atrophy, severe disability, and death. Later-onset cases have been also described, presenting with parkinsonism and dystonia, and even, in rare cases, infantile onset with status dystonicus [17, 18]. Treatment had been confined to supportive and palliative care until recently when **cyclic pyranopterin monophosphate** (**cPMP**) substitution was shown to be effective in improving the neurodevelopmental outcome of patients. In 2002, Lee et al. produced a molybdenum cofactor-deficient mouse model that resembles the human phenotype [19]. The same group later rescued the mouse phenotype with a biosynthetic precursor developed from *Escherichia coli* [20]. This substance was cPMP. The first few case reports demonstrated a favorable outcome in newborns treated early with daily intravenous injections of cPMP, reporting improved alertness, seizure control, and biochemical parameters [21, 22]. In 2015, there was a report on the efficacy and safety of cPMP in 16 neonates diagnosed with MoCD types A and B who received intravenous cPMP following a standardized protocol. They were enrolled in an observational prospective cohort study and the drug was provided based on a compassionate-use program. There were no drug-related serious adverse events reported and the disease biomarkers, urinary S-sulfocysteine, xanthine, and urate almost normalized. The longest follow up was 5 years; patients with type A had significant improvement in clinical outcome, and three patients who started treatment early were completely seizure-free and had near-normal development. Patients with type B had no improvements in biochemical or clinical parameters. cPMP remains an effective treatment option in early diagnosed MoCD type A patients; however, the daily intravenous administration and cost limit its feasibility and accessibility at this time [23].

Chelation

Neurodegeneration with Brain Iron Accumulation

Neurodegeneration with brain iron accumulation (NBIA) syndromes are a heterogeneous group of neurological disorders caused by excessive iron deposition in the brain (PKAN, PLAN, MPAN, BPAN, CoPAN, FAHN, Kufor–Rakeb syndrome, aceruloplasminemia, neuroferritinopathy; see Chapter 16). Because these disorders are individually very rare, controlled clinical trials are challenging.

Use of chelation therapy in the brain iron overload diseases has been tried since the 1960s but systemic iron chelation limited its use. The role of iron in the neurodegenerative process, however, is still not completely understood and the therapeutic potential of

chelation is not well documented. Several case reports and safety and efficacy trials with the chelator deferiprone have shown a decrease in brain iron levels; however, a clinical benefit was not evident in most cases [24–27].

Findings in the *Drosophila* PKAN model of bypassing the defective enzyme PANK2 with the supplement pantethine, an active form of pantothenic acid (also known as vitamin B5), for coenzyme A (CoA) synthesis led to trials in humans, but because of its instability in serum and difficulties in passing the blood–brain barrier, its use is limited [28–30]. Newer derivatives of pantethine may be explored in the future. Fosmetpantothenate (also known as RE-024) has shown some promising results in animal studies [31].

Trials with small molecule product replacement and gene transfer therapy in mouse models of NBIA are underway (NCT03570931 using a compound RT001, which is deuterated linoleic acid, or using DHA (docosahexanoic acid) [32, 33]. Although evidence-based guidelines are limited, in 2017 an international expert panel published a consensus clinical management guideline for PKAN [34]. There are a few clinical trials in progress (ClinicalTrials.gov), including double-blinded, placebo-controlled studies of fosmetpantothenate, a phosphopantothenate replacement, and deferiprone in PKAN. These trials include open-label extensions.

Dietary Manipulations

GLUT1 Deficiency

Glucose is the main metabolic substrate for the brain. It provides energy for neurons via glycolysis and the tricarboxylic acid (TCA) cycle. In glucose transporter type 1 (GLUT1) deficiency there is decreased glucose transport through the blood–brain barrier and less glucose is available as a substrate for the various biochemical transformations, including anapleurosis, which is the act of replacing the TCA intermediates used for biosynthesis. The main treatment for GLUT1 deficiency has been the ketogenic diet, which offers an alternative energy source for brain metabolism in the form of ketone bodies. However, its efficacy is only about 75% in patients with severe epilepsy and patients may remain with neurological deficits, especially movement disorders. Triheptanoin, a seven-carbon fatty acid triglyceride that can yield three molecules of heptanoate, can refill TCA intermediates via anapleurosis. One clinical trial enrolled 14 patients with GLUT1 deficiency (children and adults) and gave open-label supplementation with food-grade triheptanoin for 3 months [35]. The primary outcome of the study was a decrease in seizures on EEG and improved neurocognitive performance and brain metabolic rate. There were no reported serious adverse events and patients tolerated the oil well, manifesting only some minor or transient digestive discomfort or diarrhea. There was marked subjective motor and cognitive improvement in all participants as well as EEG seizure reduction and favorable neuropsychological results in receptive and expressive vocabulary.

Another open-label study performed in patients with GLUT1 deficiency presenting with non-epileptic paroxysmal movement disorder enrolled eight patients (children and adults) treated with triheptanoin 1 g/kg per day [36]. They performed three phases of two months each: baseline, treatment, and withdrawal, and used patient diaries to record motor and non-motor paroxysmal events. Treatment with triheptanoin resulted in a 90% improvement in non-epileptic paroxysmal manifestations. Larger, controlled studies need to be done to be able to offer an alternative therapy to the ketogenic diet, which is not always feasible in some patients.

SPG5

Spastic paraplegia type 5 (SPG5) is an autosomal-recessive disorder due to mutations in the *CYP7B1* gene causing neurodegeneration resulting from alterations in lipid homeostasis. The protein product of *CYP7B1* is a cytochrome P450 7α-hydroxylase, implicated in cholesterol metabolism. A recent therapeutic trial in 12 patients with SPG5 showed an improved bile acid profile and plasma oxysterol levels using chenodeoxycholic acid and atorvastatin. The trial was a randomized, placebo-controlled, double-blinded study consisting of a three-period, three-treatment crossover study and the six different sequences of three treatments were randomized. The study concluded that atorvastatin decreased plasma 27-hydroxycholesterol but did not change the 27-hydroxycholesterol to total cholesterol ratio or 25-hydroxycholesterol levels. The bile acid profile normalized on treatment [37].

Another publication described a long-term benefit in one patient treated with a statin (simvastatin) and ezetimibe (which lowers cholesterol by inhibiting its absorption in the small intestine) and one patient with ezetimibe alone, followed for 12 months and 24

months, respectively. The long-term administration of cholesterol-lowering drugs reduced serum 27-hydroxycholesterol by about 50%. They found intolerable side effects when adding chenodeoxycholic acid (diarrhea and elevation of liver enzymes). Although further long-term studies are needed, the investigators concluded that cholesterol-lowering drugs should be considered in SPG5 [38].

Ketogenic Diet

The ketogenic diet has been used widely in children with epilepsy since the 1990s. In GLUT1 deficiency and pyruvate dehydrogenase complex deficiency the ketogenic diet is the therapy of choice. Other inherited metabolic disorders have been the target of trials with the ketogenic diet, such as some of the mitochondrial disorders. Ketone bodies have several salutary properties: they reduce the proportion of mutated mitochondrial DNA (mtDNA) and improve respiratory chain function in cultured cells; they decrease cytochrome C oxidase-negative muscle fibers and induce mitochondrial biogenesis in an animal model for late-onset mitochondrial myopathy; they decrease production of reactive oxygen species in rats; and they increase citrate synthase along with complex I and catalase activity in neuronal cell lines.

There are 135 current clinical trials with the ketogenic diet listed on the ClinicalTrials.gov website, mostly for the treatment of epileptic seizures. One trial is listed as a synergistic intervention in gangliosidoses using a combination of ketogenic diet and miglustat, a substrate reduction therapy (SRT). The authors hypothesize that the ketogenic diet will minimize or prevent the gastrointestinal side effects of miglustat, and will also improve the central nervous system response to miglustat therapy as well as improving seizure control (NCT02030015).

The ketogenic diet has been suggested as a method of treatment in other IEMs, such as mitochondrial disorders with or without seizures, and targeting the epilepsy in other IEMs such as non-ketotic hyperglycinemia, argininosuccinate lyase deficiency, adenosylsuccinate lyase deficiency, and succinic semialdehyde dehydrogenase (SSADH) deficiency [39].

Neuromodulation

SSADH Deficiency

The deterioration of the SSADH-deficient mouse model after weaning lead to a trial of 18 patients with the amino acid taurine in 18 patients. Taurine has numerous neuromodulatory roles, including protection against free radical damage. The study was an open-label study that lasted for 12 months. Outcome was measured with the Adaptive Behavior Assessment Scale and the results showed no significant change in the adaptive behavior scores after taurine treatment [40].

A double-blinded, crossover, phase 2 clinical trial has completed recruitment using the experimental compound SGS-742, a gamma-aminobutyric acid (GABA) B receptor antagonist that has been shown to be safe and well tolerated in clinical trials in adults with cognitive impairment (NCT02019667). The SSADH knockout mouse model has shown benefits from it. The primary outcome measure will be a change in the Auditory Comprehension subtest of the Neuropsychological Assessment Battery Language Module score; the secondary outcome measure will be a change in cortical excitation and inhibition measured by transcranial magnetic stimulation. Additional evaluations include neurological and neuropsychological examinations and CSF collection to measure GABA levels.

Chaperone Therapy

Chaperone therapy is a molecular therapeutic approach to treat protein misfolding diseases. Major targets for researching these compounds are the various lysosomal storage disorders. Lysosomal storage disorders are often caused by mutations that destabilize native folding and impair the trafficking of enzymes, leading to premature endoplasmic reticulum-associated degradation, deficiency of hydrolytic functions, and storage of material in lysosomes. **Chemical or pharmaceutical chaperones** are low-weight molecular compounds that stabilize the mutant protein and induce the expression of its biological activity in the cell, hence restoring trafficking and increasing enzyme activity and substrate production. They can reach the brain, crossing the blood–brain barrier and are often used in disorders with neurological manifestations [41].

Another class of molecules able to influence the fate of misfolded proteins are the **proteostasis regulators**. These facilitate protein folding by increasing the function of molecular chaperones and/or by activating the protein quality-control system. Examples of these are: the antitumor antibiotic geldanamycin, antiseizure drugs (i.e. carbamazepine), histone deacetylase inhibitors, and the proteasome inhibitor bortezomib [42, 43].

Gaucher Disease (Neuronopathic)

The efficacy of enzyme-replacement and substrate reduction therapies in treating the neurological manifestations of neuronopathic Gaucher disease is negligible; hence, the development of pharmaceutical chaperone therapies is an alternative approach.

Ambroxol is such a compound, which is commonly used as an expectorant. Results of an open-label pilot study using high-dose ambroxol in combination with enzyme-replacement therapy in five patients showed that ambroxol had good safety and tolerability, significantly increased lymphocyte glucocerebrosidase activity, crossed the blood–brain barrier, and decreased the glucosylsphingosine levels in the CSF. Clinically, patients had improvement in myoclonus, seizures, and the pupillary light reflex. These results are promising but further clinical trials are needed [44].

There are several studies using high-throughput screening for small molecule therapy in Gaucher disease, using either the wild-type enzyme or patient tissue as the source of mutant glucocerebrosidase [45, 46].

Other small molecules have been used in trials in neuronopathic Gaucher disease, either in Gaucher cell lines [47, 48] or patients (molecule AT2101 – isofagomine tartrate).

Unmodified iminosugars are also considered to be good pharmacological chaperones, behaving as competitive inhibitors of the target lysosomal enzyme. Isofagomine (IFG) is one compound that has shown promising results in ex vivo and in vivo experiments, increasing enzyme activity. However, dosing experiments in a mouse model have shown that it gets transported to the endoplasmic reticulum (ER) inefficiently. Iminosugars with alkyl chains of varying lengths, i.e N-butyl- and N-nonyl-deoxynojirimycin, which are forms of the iminosugar miglustat, an SRT, have better ER permeability and bind to the enzyme better. The search for suitable pharmaceutical chaperones has used the concept to conjugate an iminosugar with a lipophilic moiety. Diverse technologies using large libraries of glycomimetics, or using delta-lactams, have been implemented by several research groups. Other compounds researched are C-alkylated iminosugars, sp^2-iminosugars, aminocyclitols, and aminosugars [5].

Phase II trials with arimoclomol, a heat shock protein inducer, are planned.

GM1 Gangliosidosis

GM1 gangliosidosis is caused by mutations in the *GLB1* gene, encoding lysosomal beta-galactosidase. Only three types of beta-D-galactosidase inhibitors have been investigated as potential pharmacological chaperones in this disorder: carbasugar N-octyl-epivalienamine (NOEV), selected unbranched analogs, and iminosugars with various structural modifications. Suzuki and coworkers explored chaperone therapy in GM1 gangliosidosis with the galacto-configured iminosugar 1-deoxy-galactonojirimycin (DGJ) and its N-butyl derivative (NB-DGJ) [49]. They showed a significant increase in enzyme activity in mouse fibroblasts expressing human mutations and in patients' fibroblasts; however, relatively high doses were needed, limiting its use in clinical trials. Further work led to the identification of other compounds that significantly increased residual beta-galactosidase activity: DLHex-DGJ, NN-DGJ, and C-glycoside iminosugar derivatives [5]. The same group also pioneered the work on NOEV that represented a hallmark in the field of pharmaceutical chaperone therapy [50]. Mice expressing human mutations showed an increase in enzyme activity and a decrease in GM1 ganglioside accumulation in the brainstem and cerebral cortex. NOEV treatment starting in the early stage of the disease arrested the neurological progression of GM1 within a few months and significantly prolonged survival. Other research groups modified the structure of NOEV to improve its chaperone properties, which led to an increase in the enzyme activity in mice harboring certain human mutations [5].

Another new family of experimental pharmacological chaperones has been described, the aminocyclopentane-based carbasugars [51]. These are powerful inhibitors of beta-D-galactosidase with increase of enzyme activity several fold in human mutant cells.

Clinical trials of these chaperone therapies are pending.

GM2 Gangliosidosis

Pyrimethamine was found to be an effective chaperone molecule in cells from patients with late-onset GM2 gangliosidosis. Many mutations in either the alpha or beta subunit of hexosaminidase A were partially rescued. An open-label clinical trial with pyrimethamine in eight patients with late-onset GM2 gangliosidosis examined the effect of escalating doses. The activity of the hexosaminidase A enzyme was increased four-fold at doses of 50 mg per day. Doses of 75 mg or above caused significant side effects. Expanded studies have been withdrawn due to lack of funding [52].

Peroxisomal Disorders

There are no curative therapies for peroxisomal disorders. Several compounds have been tried in a small number of patients, such as the plasmalogen precursor batyl alcoho or oral bile acid supplementation (chenodeoxycholic acid, ursodeoxycholic acid, cholic acid), and although the biochemical parameters improved, there was no improvement in clinical outcome [53]. Several other pharmacological therapies are under development, such as plasmalogen precursor therapy other than alkylglycerol (PPI-1011) [54]. Proliferation of peroxisomes in Zellweger disease fibroblasts using 4-phenylbutyrate and related compounds has been achieved in cell lines from patients who have an intermediate or mild phenotype. This resulted in improved peroxisome enzyme function [55, 56]. Geneticin (G418), a nonsense suppressor aminoglycoside also has been shown to promote peroxisome recovery in fibroblast cell lines from patients with *PEX2* and *PEX12* mutations [57]. Chemical chaperone drugs, such as arginine and betaine, improved peroxisome biogenesis and functions in cell lines with *PEX1*, *PEX6*, and *PEX12* mutations. Trials are ongoing utilizing betaine (trimethylglycine) in patients with *PEX1* mutations. The misfolded protein in the *PEX1* Gly843Asp mutation has residual function and treatment with betaine recovered peroxisome function in cultured cells. Clinical trial outcomes have included the measurements of biochemical markers, the C26/C22 ratio, and developmental outcomes. Thus far, clinical improvement has not been demonstrated, and reasons could include the small numbers of patients, the testing of plasma biomarkers possibly being less sensitive than direct measurement in cells, or a high variability of patients' phenotypes.

Enzyme-Replacement Therapy

New investigational enzyme-replacement therapy is ongoing in several lysosomal disorders. A number of preclinical studies with recombinant enzyme-replacement therapy have been performed in **infantile neuronal ceroid lipofuscinosis** (INCL) and **late-infantile neuronal ceroid lipofuscinosis** (LINCL). Intravenous, intrathecal, and intraventricular methods of delivery have been used. Some of these studies led to an ERT clinical trial for the treatment of LINCL (NCT01907087). Twenty-four patients were enrolled between the ages of 3 years and 16 years, and received intraventricular infusion of cerliponase alfa every 2 weeks. Treatment was limited to 300 mg/dose. The results have been published and concluded that intraventricular infusion of cerliponase alfa in patients with CLN2 disease resulted in less decline in motor and language function compared to historical controls. Serious adverse events included failure of the intraventricular device and device-related infections [58].

The challenging obstacle in the treatment of lysosomal storage disorders has been penetrating the blood–brain barrier. **Peptide modification** is one approach that has been used to overcome this. Some studies have used modified TPP1 protein by altering its glycosylation profile or combining its peptide sequence with a specific region of the apolipoprotein E receptor, both resulting in increased blood–brain barrier penetrance [59, 60]. This method is called the "Trojan horse" approach and utilizes natural cellular pathways to deliver proteins across the blood–brain barrier [61, 62]. Another way to deliver drugs across the blood–brain barrier is by using **nanocarriers**, including liposomes [63]. One advantage of nanocarriers is targeted cell delivery, using antibodies to different receptors expressed on endothelial cells of the blood–brain barrier.

Substrate Reduction Therapy

The conventional therapy for lysosomal storage disorders is to use enzyme-replacement therapy but since Radin introduced the concept of SRT in 1996, this approach has been expanded and many SRT drugs have been approved: miglustat for Gaucher disease and Niemann–Pick disease type C (NPC), eliglustat tartrate for Gaucher disease, and genistein for mucopolysaccharidoses. To overcome some of the side effects of these drugs, second-generation compounds are under evaluation.

An open-label multicentre clinical trial is underway for studying the tolerability, pharmacokinetics, pharmacodynamics, and efficacy of a compound venglustat in combination with ERT (imiglucerase) in adult patients with Gaucher disease type 3.

Trials are underway to explore synergistic therapy with miglustat and the ketogenic diet for the treatment of childhood-onset gangliosidosis, with a proposed study duration of 5 years and with the primary outcome of duration of survival of each participant and the rate of change in neurocognitive functioning. (NCT02030015).

Gene suppression technologies as tools for substrate reduction have been introduced in the last decade. One of the most promising techniques seems to

be RNA interference, and phase 3 clinical trials are underway for various neurological and non-neurological conditions. Antisense oligonucleotides for gene knockdown have been used and are under clinical evaluation. Small interfering RNAs have been used to reduce glycosaminoglycan synthesis in mucopolysaccharidosis type III (MPS III) mice and patient fibroblasts [64].

Vorinostat, a histone deacetylase inhibitor has been shown to increase mutant NPC1 protein levels in vivo and to reverse the cellular accumulation of unesterified cholesterol. An open-label phase 1/2 study of vorinostat in NPC has been completed and posted on the ClinicalTrials.gov website. Twelve adult participants were enrolled and 11 finished the study. Trial participants were treated with vorinostat, utilizing a 3 days on/4 days off regimen to limit toxicity. The primary outcome measure was tolerability and secondary outcomes were measures of biochemical efficacy (NCT02124083).

Another approach to treating lysosomal storage disorders is with recombinant heat-shock protein 70 (rHSP70). Exposure to rHSP70 led to a significant reductions in cellular lysosome enlargement, suggesting that rHSP70 aids in diminishing the build-up of metabolites within lysosomes. Subsequently, rHSP70 treatment was tested in genetic mouse models of NPC leading to diminished lipid metabolite storage in the central nervous system. This reduction in lipid accretion was accompanied by improvements in ataxic gait and general physical activity [65]. In separate experiments, NPC mice treated with the small molecule inducer of HSP70 arimoclomol also demonstrated a reduction in lysosomal enlargement and an improvement in neurological and behavioral symptoms. A double-blind, randomized, placebo-controlled study in pediatric patients with NPC is in progress (NCT02612129).

Another type of inhibition of substrate accumulation is using 2-hydroxypropyl-beta-cyclodextrin (HPβCD) in NPC. In mice, administration of this compound led to a delayed clinical onset, extended lifespan, and reduced unesterified cholesterol and glycolipid accumulation within the central nervous system and other organs [66].

A phase 2b/3 prospective, randomized, double-blinded, sham-controlled three-part trial of VTS-270 (2-hydroxypropyl-beta-cyclodextrin) intrathecal injections in subjects with neurological manifestations of NPC is also in progress (NCT 02534844).

Umbilical Cord Blood Cell Transplantation and Hematopoietic Stem-Cell Therapy

X-Linked Adrenoleukodystrophy

Allogenic HSCT is an established long-term treatment method for boys with childhood cerebral X-ALD. The mechanism of action is replacing the defective microglia by bone marrow-derived long-lived macrophages of the allogeneic donor. Recently, lentivirus-based ex vivo gene therapy has been introduced as a treatment option. Both HSCT and gene therapy are effective when performed early in the course of childhood cerebral X-ALD [67, 68].

Mucopolysaccharidosis II

Although there is enzyme-replacement therapy for MPS II, it does not cross the blood–brain barrier, limiting treatment of the neurological complications of the disease. HSCT is the treatment of choice in MPS I, but has not been recommended for MPS II. The clinical experience with HSCT in MPS II is limited and no systematic or well-designed clinical trials have been conducted. However, the overall outcome suggests that the neurological deterioration can be halted or slowed in the few cases who had HSCT. Well-designed clinical trials are needed to confirm this assumption [69].

Niemann–Pick Disease Type C

Evidence is limited to one case report on presymptomatic cord blood transplantation in a child with NPC whose older brother died of complications of the disease at the age of 3 years. The patient was transplanted at the age of 5 months; there was some neurological deterioration at the age of 4 years but by age 8 years he was severely affected, with loss of ambulation, ataxia, and generalized myoclonus [70].

Neuronal Ceroid Lipofuscinoses

A number of NCL mouse model and patient studies have been used to explore the benefits of HSCT, with limited success [71–73]. Other studies have used a combination with gene therapy in *Ppt-/-* mice and this showed significant improvement. Neural stem-cell therapy has also been proven to be effective and the results of a clinical trial with human central nervous system stem cells in six children tested in an open-label dose escalation phase 1 trial showed that the procedure is well tolerated. There were no results

on efficacy since the children enrolled were all in advanced stages of the disease [74].

Leukodystrophies

Currently, presymptomatic HSCT is the only therapeutic modality that alleviates Krabbe disease-induced central nervous system injury. However, all HSCT-treated patients exhibit severe deterioration in peripheral nervous system function, and patients still present with major motor and expressive language dysfunction. Studies in mice studies, using an aggressive busulfan conditioning regimen, have shown an extended life span after HSCT [75]. The same authors have also demonstrated that combining this protocol with lentiviral vector-based gene therapy did not significantly change the outcome.

A review of the last 20 years' experience on cord blood transplantation in patients with leukodystrophies, such as metachromatic leukodystrophy (MLD), globoid-cell leukodystrophy (Krabbe disease), and X-ALD found that factors associated with higher overall survival included presymptomatic status, well-matched cord blood units, and a higher baseline performance status (PS). Long-term survival was best in patients who were presymptomatic and had a performance status of >80. Of these patients, 50% remained stable, 20% declined to PS 60–80, and 30% to <60 [6].

A review on late mortality in patients transplanted for IEMs, including 264 patients (104 with X-ALD, 96 with MPS I, 28 with MLD, and 36 with other diseases), found that the 10-year overall survival exceeded 85% [76].

Gene Therapy

Gene therapy is a direct approach to the treatment of genetic diseases regardless of how well the underlying pathophysiology is understood, as it delivers a normal gene to a diseased cell or organ, resulting in the expression of the normal protein. The severe adverse reactions in the early stages of gene therapy halted the progression of these types of intervention, but recently, newer techniques and vectors for delivery have been proven to be safer. Encouraging short-term safety and efficacy studies have been published in **X-ALD and aromatic L-amino acid decarboxylase** (**AADC**) **deficiency**. Delivery of the gene can be done by non-viral transfer or by viral gene delivery, such as using simple retrovirus, lentivirus, adenovirus, and adeno-associated virus (AAV) vectors. Vectors capable of targeted integration and DNA editing exist and have shown promising results in some in vitro and preclinical studies. Improvements in immunosuppression regimens will also improve safety and efficacy of using viral vectors in the future [7].

Twenty-eight clinical trials have been reported in 2017 based on the local delivery of AAV vectors for lysosomal storage disorders [2]. Most of them use intraparenchymal injections; one was based on intrathecal (Batten disease) and one on intravenous injection (MPSIIIA). Unfortunately, some of the gene therapies for severe neurodegenerative disorders, such as **Canavan disease** or **LINCL**, although successfully expressing the normal protein in the brain, have shown little clinical improvements. These trials have demonstrated the safety of recombinant AAV (rAAV)-mediated gene delivery through direct brain injections but failed to achieve a substantial rescue (NCT00151216, NCT01161576).

Ex vivo gene therapy uses reprogrammed isolated patient cells for functional protein synthesis. For example, in an X-ALD gene therapy trial, the bone marrow cells were genetically reprogrammed using a lentiviral vector carrying the missing *ABCD1* gene and reinjected into the patients. Follow-up studies have shown that demyelination was halted 14–16 months after treatment, and, 24–30 months later, ABCD1 protein expression was still present in several cell types [77, 78].

A combination of HSCT and gene therapy is recruiting in a phase 1/2 trial aiming at the assessment of the safety and efficacy of arylsulfatase A (*ARSA*)/adenosine-triphosphate-binding cassette, subfamily D (*ABCD1*) gene transfer into hematopoietic stem/progenitor cells for the treatment of **MLD** and **X-ALD**, respectively, after an Italian group conducted a gene therapy clinical trial based on autologous HSCT and advanced generation lentiviral vectors for patients affected by the most severe, early-onset forms of the disease (HCT01560182). The safety and efficacy of this gene therapy approach in MLD patients was evaluated. During 3 years of follow-up, they reported multilineage ARSA expression and an ability to prevent and correct neurological disease manifestations. In a newer study, the investigators will recruit symptomatic patients for transduced cluster of differentiation 34 positive (CD34+) HSCT treatment. In the treated patients, the short-term and long-term safety of the administration of the autologous transduced hematopoietic stem cells, their long-term engraftment, the expression of vector-derived ARSA or ABCD1, and the ability of the transduced cells to provide a clinical benefit to the patients will be studied. The treated patients will be followed for 3 years and thereafter

monitored for the safety of gene therapy for an additional 5 years. If successful, this study will provide key results on the safety and efficacy of gene therapy for MLD and X-ALD patients (NCT02559830). A phase 1/2, open-labelled, monocentric study of direct intracranial administration of a replication deficient AAV gene transfer vector expressing the human ARSA complementary DNA (cDNA) to five children with MLD has been conducted, but results are not yet available (NCT01801709).

Another phase 2/3 trial assesses the efficacy and safety of autologous CD34+ hematopoietic stem cells, transduced ex-vivo with the Lenti-D lentiviral vector, for the treatment of **cerebral ADL**. A subject's blood stem cells were collected and modified (transduced) using the Lenti-D lentiviral vector encoding human ADL protein. After modification (transduction) with the Lenti-D lentiviral vector, the cells were transplanted back into the subject following myeloablative conditioning. This interventional open-label trial started in 2013 with the goal of recruiting 30 participants (NCT01896102) and was recently published [79], with positive results.

A single-stage, adaptive, open-label, dose escalation safety and efficacy study of gene therapy of **AADC deficiency** was first posted on the ClinicalTrials.gov website in 2016. This trial is a single treatment arm interventional open-label trial with the goal of recruitment of six participants between the ages of 5 years and 18 years, using the AAV2 vector. The AAV2-hAADC dose is infused via MRI-guided infusion in both the left and right substantia nigra pars compacta and ventral tegmental areas (NCT02852213).

A similar study was previously done with some promising results (NCT01395641). Ten patients were enrolled and received bilateral intraputaminal injections of AAV2-hAADC through stereotactic brain surgery. Primary efficacy outcomes were an increase in the Peabody Developmental Motor Scale, 2nd edition (PDMS-2) score of greater than 10 points, and an increase in homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations in the CSF, 12 months after the gene therapy. All patients met the primary efficacy endpoint: 12 months after gene therapy the PDMS-2 scores were increased by a median of 62 points and HVA concentrations by a median of 25 nmol/L. There were 101 adverse effects reported, the most common being pyrexia (16%) and orofacial dyskinesia (10%). Twelve serious side effects occurred, including one death (treatment-unrelated influenza-B encephalitis) [80]. An expansion of this study is offering this clinical trial to patients who are not enrolled in the phase 1/2 trial with a slightly increased dosage (NCT02926066).

LYS-SAF302 has been also approved for a phase 2/3 single arm clinical trial in children with **MPS III type A**. This is an open-label, single arm, interventional study using intracerebral administration of AAV serotype rh.10 carrying human N-sulfoglucosamine sulfohydrolase cDNA. In addition, a phase 1/2 clinical trial of scAAV9.U1a.hSGSH for MPS III type A is administering the vector in a peripheral vein is also in progress (NCT02716246).

Another phase 1/2, dose escalation interventional trial for **MPS III type B** uses AAV serotype 9 carrying the human alpha-N-acetylglucosaminidase (NAGLU) gene under the control of a cytomegalovirus (CMV) enhancer/promoter (rAAV9.CMV.hNAGLU) (NCT03315182).

Specific gene therapies for IEMs with particular mutations have been also tried in cell lines. An example is a particular mutation in *ALDH7A1*, causing **pyridoxine-dependent epilepsy**. Perez et al. used antisense therapy in a patient's lymphoblast cell line harbouring the c.75 C>T mutation, a novel splicing mutation, creating a new donor site inside exon 1, and this was successful [81].

Genome editing with site-specific endonucleases, such as zinc-finger nucleases and the CRISPR/Cas9 system, in combination with delivery vectors engineered to target disease tissue, have been successful in correcting mutations in murine models, in a number of IEMs, including tyrosinemia type I, ornithine transcarbamylase deficiency, and lysosomal storage disorders [82–87].

An important safety issue for genome editing is the accurate assessment of the off-target cleavage by endonucleases and mitigating the effects of non-specific activity. Overall, the better understanding of the CRISPR/Cas9 mechanisms have led to improved technology. However, considerable work is needed before genome editing becomes a common therapeutic avenue in IEMs [8].

Read-Through Drugs

These drugs allow the ribosome to selectively read through nonsense mutations to generate functional proteins by preventing messenger RNA degradation by nonsense-mediated decay. Ataluren is such a drug and has been proposed for treatment in several IEMs: lysosomal storage diseases [88], the NCLs [89], and

phenylalanine hydroxylase deficiency [90], among others.

Lysosomal Modulators

Accumulation of lysosomal material can be cleared by modulating the lysosome. TFEB, a transcription factor, can achieve this by altering the expression of different lysosomal genes. Studies have identified a number of TFEB activators that reduce storage accumulation in patients' fibroblasts [91–93]. Other compounds that have been shown to modulate the lysosomes of lysosomal storage disorders include delta-tocopherol [94].

Small Molecules and Alternatively Targeted Pathways

One small molecule, the collapsing response mediator protein-2, has been recently identified to be associated with neurodegenerative diseases, including the NCLs. Targeting this molecule with various compounds (i.e. lanthionine ketimine, lacosamide) may be a therapeutic option [95–98]. Another small molecule, N-tert-(butyl) hydroxylamine, was used in INCL cell lines and a mouse model with promising results [99]. Other small molecules, cysteamine bitartrate and N-acetylcysteine, have been also used in models of INCL.

Mitochondrial Disease

Treatment in mitochondrial disorders is most challenging due to the extreme clinical heterogeneity, multiple organ involvement, and the unique genetic make-up of the mitochondria.

Primary mitochondrial disorders can be attributed to mutations in both mitochondrial and nuclear genomes. For many decades patients with mitochondrial disorders have been treated with vitamins, cofactors, and nutritional supplements, with no proven benefit.

Therapies to improve mitochondrial dysfunction, to decrease the amount of reactive oxygen and nitrogen species that result in redox imbalance and glutathione deficiency, have been used in clinical trials in recent years, and the results published in a recent update by Enns et al., 2017 [9]. The therapies with EPI-743 (alpha-tocotrienol quinone) and RP103 (cysteamine bitartrate) have the theoretical potential to improve redox balance by increasing intracellular glutathione. There have been five clinical trials with EPI-743 (four open-label and one randomized, double-blinded, placebo-controlled) completed in primary mitochondrial disorders and the outcomes show clinical improvement, reversal or arrested disease progression, and/or decreased rates of hospitalization. There has been a cysteamine open-label clinical trial (NCT02023866) for short-term safety and efficacy in children with mitochondrial disease, including Leigh syndrome, with continuation to a long-term extension study (NCT02473445), but unfortunately this has been prematurely terminated due to lack of efficiency in the baseline study.

New therapeutic approaches have emerged with some benefit, some in preclinical animal models and others in clinical trials [10, 11]. The therapeutic strategies can be categorized into non-specific and disease-specific strategies.

The **non-specific, general treatment strategies** include new protein delivery, stimulation of mitochondrial biogenesis, regulating execution pathways, improving mitochondrial dynamics, or bypassing respiratory chain defects.

These general treatment strategies have a wide applicability and address common disease mechanisms, could be potentially cost-effective, but often present with challenges such as off-target effects.

In the new protein delivery category there is systemic protein delivery enhancing nucleotide metabolism by transfusing platelets or erythrocyte-encapsulated thymidine phosphorylase, for treatment of mitochondrial neuro-gastro-intestinal encephalopathy (MNGIE); however, neither of these approaches have proven to have sustained clinical benefits [100–102]. Direct enzyme-replacement therapy would be an approach to improve long-term outcomes, which has been done in animal models, but the reported antibody generation means that these protocols require modification [103]. Another approach in animal models (*Tymp-/-* and *Tk2-/-*) is to rescue nucleotide imbalance and mtDNA instability with supplementation of deoxycytidine or tetrahydrouridine (inhibitor of cytidine deaminase in the case of the *Tymp-/-* mouse model), or with deoxycytidine monophosphate and deoxythimidine monophosphate (in the case of *Tk2-/-* mouse model) [104, 105].

The stimulation of mitochondrial biogenesis is achieved with several approaches, such as aminoimidazolecarboxamide ribotide (AICAR), nicotinic acid, bezafibrates, and resveratrol. Mitochondrial biogenesis is regulated mainly by the transcription coactivator peroxisome proliferator-activated receptor-γ1

(PGC1), which interacts with several transcription factors, which in turn control the expression of genes involved in oxidative phosphorylation. PGC1 is activated with either deacetylation by the protein sirtuin 1 (Sirt1) or phosphorylation by AMP-dependent kinase (AMPK). AICAR, an adenosine monophosphate analogue, activates AMPK. Nicotinamide riboside increases NAD^+ levels, which activates Sirt1. Administration of AICAR and nicotinic acid in mouse models of mitochondrial myopathy has been shown to induce mitochondrial biogenesis and ameliorate clinical phenotypes [106–108].

Bezafibrate is a pan-agonist for the PGC1, upregulating its gene expression. Its use has generated controversial reports, with improvement observed in the muscle-specific *Cox10* knock-out mouse, which later was not reproducible in other mouse models [107, 109].

Resveratrol increases NAD^+ levels enhancing Sirt1 activation. It has been shown to improve mitochondrial function in fibroblasts [110] and in Friedreich ataxia (NCT01339884) [111]. Inhibition of the NAD^+-consuming enzyme poly-ADP polymerase 1 (PARP1) increases NAD^+ availability, Sirt1 activity, and oxidative metabolism. Experiments in animal models have shown efficacy [106, 112].

Tripeptides that penetrate cells and accumulate in mitochondria, binding to cardiolipin, a lipid component of the inner mitochondrial membrane, can change the shape of the mitochondrial cristae. The mechanism is linked to modulating Opa1 activity, which is a dynamin-like GTPase of the inner membrane [113].

Single-peptide enzymes derived from yeast, called xenogenes, have been used to bypass the block of respiratory chain due to specific complex deficiencies, for example NADH reductase [114, 115].

Inhibiting autophagy is another general strategy, which is achieved by using the mammalian target of rapamycin (mTOR) inhibitor, rapamycin, although long-term side effects may limit its use in mitochondrial disease [116]. Lithium chloride has also been used as autophagy modulator [117].

Disease-specific therapies have been designed for several nuclear and mtDNA mutations in the form of stem-cell therapies and other strategies directed at manipulating DNA. There are quite a few case reports and small studies on treatments with allogeneic hematopoietic stem-cell transplantations in MNGIE and a clinical trial in progress (NCT02427178). Endogenous stem cells that contain less mutated mtDNA than mature post-mitotic skeletal muscle cells have been transfused for mtDNA mutations; however, there were no clinical benefits. More recently, in vitro experiments have used a somatic-cell nuclear transfer approach to correct the metabolic disturbance in these disorders, using induced pluripotent stem cells [118].

The other forms of targeted treatment approaches are based on manipulating DNA. This can be achieved by the restriction endonuclease approach, which would recognize specific DNA sequences, produce double-stranded DNA breaks, and initiate target molecule degradation. In theory, a single treatment would suffice to correct the biochemical defect in mutated cells. Unfortunately, there are not many human pathogenic mutations that create restriction sites enabling the use of this approach more widely. To circumvent this problem, special custom-designed restriction endonucleases have been used in some preclinical trials especially for eliminating the m8993 T>G mutation (causing Leigh syndrome or neuropathy ataxia retinitis pigmentosa, [NARP]). One of the examples of such endonucleases is the zinc finger nuclease (ZFN) consisting of tandem repeat zinc fingers. Unfortunately, early experiments found that ZNFs cause significant cytotoxicity and hence are not suitable for human trials, but continuing efforts have been made to improve their design [119].

Other approaches are with target specific DNA nucleases (TALENs), which are more potent than ZFNs, but larger in size, limiting their use with AAV vectors [120] and with Cas9 nuclease. This latter is targeted, using a shorter RNA sequence CRISPR [121, 122], and is not hindered by context-specific binding characteristics for ZFNs and TALENs. MitoTALENs have been used in oocytes in recent years to reduce germline transmission of mutated mtDNA responsible for Leber hereditary optic neuropathy (LHON) and NARP [123].

Manipulating transfer RNA (tRNA) with tRNA synthases has been used to partially rescue the mitochondrial dysfunction in mitochondrial tRNA defects, but human trials are needed [124, 125].

Gene therapy for nuclear mitochondrial diseases has been tried in several murine models, such as ethylmalonic aciduria (caused by mutations in the *ETHE1* gene), MNGIE, and mutations in *MPV17*, using AAV vector approaches [126–128]. However, several challenges have not been addressed mainly because of tissue specificity and the fact that the vector was targeted to liver and did not reach skeletal muscle or brain.

Delivering gene therapy for mtDNA disorders presents an even greater challenge. The mitochondrial membrane is relatively impermeable and there are thousands of affected mitochondria in each individual cell. Alternative approaches of adding an engineered targeting peptide presequence to the AAV vector have emerged. This method has been used in preclinical experiments in LHON caused by the mtDNA m.11778 G>A mutation. This has been expanded to murine trials using intraocular injections of the human nuclear *ND4* gene constructs expressed by AAV [129]. However, it has not yet been demonstrated that the allotopically expressed proteins can integrate in the respiratory chain. Human clinical trials have been either recently completed or are currently recruiting LHON patients for AAV-vector gene therapy. A safety and efficacy study (NCT01267422) with a single intravitreal injection of recombinant AAV-NADH dehydrogenase, subunit 4 (complex I) (rAAV2-ND4) has been completed in nine patients with LHON. The visual acuity of the injected eyes of six patients improved by at least 0.3 on the LogMAR chart after 9 months of follow-up. In these six patients, the visual field was enlarged but the retinal nerve fibre layer remained relatively stable. No other outcome measure was significantly changed. None of the nine patients had local or systemic adverse events related to the vector during the 9-month follow-up period. The study was terminated early because of a limited number of participants [130]. Several similar studies are underway (NCT03153293, NCT02064569).

Neurotransmitter Therapy

Movement disorders can be a hallmark of the **monoamine neurotransmitter disorders**. This is a heterogeneous group of neurological disorders characterized by primary and secondary defects in the biosynthesis, degradation, and transport of dopamine, norepinephrine, epinephrine, and serotonin. The deficiency of dopamine and serotonin will cause characteristic neurological features, including pyramidal and extrapyramidal movement disorders. Treatment strategies include the replacement of the monoamines with their precursors and the inhibition of their degradation. The primary neurotransmitter disorders have been addressed elsewhere in this book; there are also a host of secondary neurotransmitter deficiencies. Many IEMs have low levels of CSF HVA and 5-HIAA, including untreated phenylketonuria, Lesch–Nyhan disease, mitochondrial disorders, and different leukodystrophies. Many of these patients will have low levels of HVA in the CSF and will present with dyskinesia, tremor, dystonia, and eye movement disorders, similar to what is seen in primary monoamine disorders. The possibility of symptomatic treatment with levodopa and/or 5-hydroxytryptophan should be considered to improve brain maturation and neurological outcome [131].

Surgical Treatment

Surgical management of severe movement disorders, specifically **deep brain stimulation** has been discussed in detail in the previous chapter. Disorders associated with benefit using this novel therapeutic approach include PKAN, Lesch–Nyhan disease, glutaric aciduria type 1 after severe encephalopathic episodes, and methylmalonic acidemia.

Conclusions

The treatment of rare diseases is a rapidly expanding field in medicine. Clinical trials are numerous and in various stages, and can be searched online at the ClinicalTrials.gov website (www.clinicaltrials.gov). A wide range of disease-specific and non-specific approaches have become available with a variety of approaches, including substrate reduction therapy, enzyme-replacement therapy, and gene therapy.

Key Points and Clinical Pearls

- Emerging therapeutic strategies include dietary restriction/supplementation, enzyme cofactor/vitamin supplementation, enzyme replacement, substrate inhibition, substrate reduction, bone marrow or hematopoietic stem-cell transplantation, gene therapy, or newer symptomatic treatment modalities.
- Enzyme-replacement and substrate-reduction therapies have focused especially on lysosomal storage disorders and are based on the ability of most cells to take up the deficient enzyme.
- Organ transplantation, specifically liver transplantation, has been used mainly in small molecule disorders, especially urea cycle defects. The goal of this treatment is to replace the missing enzyme by replacing the whole organ.

- Hematopoietic stem-cell transplantation has been used for some lysosomal storage disorders and X-linked adrenoleukodystrophy.
- Novel therapeutic approaches are using chaperone molecules and proteostasis regulators, read-through drugs, cell therapies, ex vivo and in vivo gene therapy, RNA targeting, and genome editing (CRISPR/Cas9).
- Mitochondrial disorders are especially challenging due to clinical heterogeneity, multiple organ involvement, and the unique genetic make-up of the mitochondria.

Directions for Future Research

- Preclinical studies of non-specific and disease-specific interventions are expected to rapidly evolve into clinical trials.
- Selection of measurable and meaningful clinical endpoints are a challenge in clinical trial development.
- Safer approaches to viral-mediated gene therapy and gene editing will invariably lead to increasing clinical trials and applicability of novel therapeutic strategies to inborn errors of metabolism.

Bibliography

1. Ginocchio VM, Brunetti-Pierri N. Progress toward improved therapies for inborn errors of metabolism. Hum Mol Genet. 2016;**25**(R1):R27–35.
2. Piguet F, Alves S, Cartier N. Clinical gene therapy for neurodegenerative diseases: Past, present, and future. Hum Gene Ther. 2017;**28**(11):988–1003.
3. Geraets RD, Koh S, Hastings ML, et al. Moving towards effective therapeutic strategies for neuronal ceroid lipofuscinosis. Orphanet J Rare Dis. 2016;**11**:40.
4. Pastores GM. Therapeutic approaches for lysosomal storage diseases. Ther Adv Endocrinol Metab. 2010;**1**(4):177–88.
5. Sanchez-Fernandez EM, Garcia Fernandez JM, Mellet CO. Glycomimetic-based pharmacological chaperones for lysosomal storage disorders: Lessons from Gaucher, GM1-gangliosidosis and Fabry diseases. Chem Commun (Camb). 2016;**52**(32):5497–515.
6. van den Broek BTA, Page K, Paviglianiti A, et al. Early and late outcomes after cord blood transplantation for pediatric patients with inherited leukodystrophies. Blood Adv. 2018;**2**(1):49–60.
7. Chandler RJ, Venditti CP. Gene therapy for metabolic diseases. Transl Sci Rare Dis. 2016;**1**(1):73–89.
8. Schneller JL, Lee CM, Bao G, Venditti CP. Genome editing for inborn errors of metabolism: Advancing towards the clinic. BMC Med. 2017;**15**(1):43.
9. Enns GM, Cohen BH. Clinical trials in mitochondrial disease: An update on EPI-743 and RP103. J Inborn Error Metab Screen. 2017;**5**:2326409817733013.
10. Viscomi C. Toward a therapy for mitochondrial disease. Biochem Soc Trans. 2016;**44**(5):1483–90.
11. Nightingale H, Pfeffer G, Bargiela D, Horvath R, Chinnery PF. Emerging therapies for mitochondrial disorders. Brain. 2016;**139**(Pt 6):1633–48.
12. Yoon DH, Kwon OY, Mang JY, et al. Protective potential of resveratrol against oxidative stress and apoptosis in Batten disease lymphoblast cells. Biochem Biophys Res Commun. 2011;**414**(1):49–52.
13. Wei H, Kim SJ, Zhang Z, et al. ER and oxidative stresses are common mediators of apoptosis in both neurodegenerative and non-neurodegenerative lysosomal storage disorders and are alleviated by chemical chaperones. Hum Mol Genet. 2008;**17**(4):469-77.
14. Johnson SC, Yanos ME, Kayser EB, et al. mTOR inhibition alleviates mitochondrial disease in a mouse model of Leigh syndrome. Science. 2013;**342**(6165):1524–8.
15. Nagamani SC, Campeau PM, Shchelochkov OA, et al. Nitric-oxide supplementation for treatment of long-term complications in argininosuccinic aciduria. Am J Hum Genet. 2012;**90**(5):836–46.
16. Brunetti-Pierri N, Erez A, Shchelochkov O, Craigen W, Lee B. Systemic hypertension in two patients with ASL deficiency: A result of nitric oxide deficiency? Mol Genet Metab. 2009; **98** (1–2): 195–7.
17. Alkufri F, Harrower T, Rahman Y, et al. Molybdenum cofactor deficiency presenting with a parkinsonism–dystonia syndrome. Mov Disord. 2013;**28**(3):399–401.
18. Carman KB, Yildirim GK, Kiral E, et al. Status dystonicus: A rare presentation of molybdenum cofactor deficiency. Int J Clin Pediatr. 2017; **6** (3-4): 51–3.
19. Lee HJ, Adham IM, Schwarz G, et al. Molybdenum cofactor-deficient mice resemble the phenotype of

human patients. Hum Mol Genet. 2002;**11**(26):3309–17.

20. Schwarz G, Santamaria-Araujo JA, Wolf S, et al. Rescue of lethal molybdenum cofactor deficiency by a biosynthetic precursor from *Escherichia coli*. Hum Mol Genet. 2004;**13**(12):1249–55.
21. Veldman A, Santamaria-Araujo JA, Sollazzo S, et al. Successful treatment of molybdenum cofactor deficiency type A with cPMP. Pediatrics. 2010;**125**(5):e1249–54.
22. Hitzert MM, Bos AF, Bergman KA, et al. Favorable outcome in a newborn with molybdenum cofactor type A deficiency treated with cPMP. Pediatrics. 2012;**130**(4):e1005–10.
23. Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: A prospective cohort study. Lancet. 2015;**386**(10007):1955–63.
24. Zorzi G, Zibordi F, Chiapparini L, et al. Iron-related MRI images in patients with pantothenate kinase-associated neurodegeneration (PKAN) treated with deferiprone: Results of a phase II pilot trial. Mov Disord. 2011;**26**(9):1756–9.
25. Hayflick SJ, Hogarth P. As iron goes, so goes disease? Haematologica. 2011;**96**(11):1571–2.
26. Schneider SA, Dusek P, Hardy J, et al. Genetics and pathophysiology of neurodegeneration with brain iron accumulation (NBIA). Curr Neuropharmacol. 2013;**11**(1):59–79.
27. Hogarth P. Neurodegeneration with brain iron accumulation: Diagnosis and management. J Mov Disord. 2015;**8**(1):1–13.
28. Rana A, Seinen E, Siudeja K, et al. Pantethine rescues a *Drosophila* model for pantothenate kinase-associated neurodegeneration. Proc Natl Acad Sci USA. 2010;**107**(15):6988–93.
29. Brunetti D, Dusi S, Giordano C, et al. Pantethine treatment is effective in recovering the disease phenotype induced by ketogenic diet in a pantothenate kinase-associated neurodegeneration mouse model. Brain. 2014;**137**(Pt 1):57–68.
30. TIRCON (Treat Iron-Related Childhood-Onset Neurodegeneration). Report summary: Project ID 277984, funded by FP7-HEALTH. June 5, 2017. Available from: https://cordis.europa.eu/project/id/277984/reporting/de.
31. Elbaum D, Beconi MG, Monteagudo E, et al. Fosmetpantotenate (RE-024), a phosphopantothenate replacement therapy for pantothenate kinase-associated neurodegeneration: Mechanism of action and efficacy in nonclinical models. PLoS One. 2018;**13**(3):e0192028.
32. Mazzocchi-Jones D. Impaired corticostriatal LTP and depotentiation following iPLA2 inhibition is restored following acute application of DHA. Brain Res Bull. 2015;**111**:69–75.
33. Schneider SA, Kurian MA. What the future holds for the genetic diagnosis for neurodegeneration with brain iron accumulation syndromes? Expert Opinion on Orphan Drugs. 2015;**3**(4):353–6.
34. Hogarth P, Kurian MA, Gregory A, et al. Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). Mol Genet Metab. 2017;**120**(3):278–87.
35. Pascual JM, Liu P, Mao D, et al. Triheptanoin for glucose transporter type I deficiency (G1D): Modulation of human ictogenesis, cerebral metabolic rate, and cognitive indices by a food supplement. JAMA Neurol. 2014;**71**(10):1255–65.
36. Mochel F, Hainque E, Gras D, et al. Triheptanoin dramatically reduces paroxysmal motor disorder in patients with GLUT1 deficiency. J Neurol Neurosurg Psychiatry. 2016;**87**(5):550–3.
37. Schols L, Rattay TW, Martus P, et al. Hereditary spastic paraplegia type 5: Natural history, biomarkers and a randomized controlled trial. Brain. 2017;**140**(12):3112–27.
38. Mignarri A, Malandrini A, Del Puppo M, et al. Treatment of SPG5 with cholesterol-lowering drugs. J Neurol. 2015;**262**(12):2783–5.
39. Scholl-Burgi S, Holler A, Pichler K, et al. Ketogenic diets in patients with inherited metabolic disorders. J Inherit Metab Dis. 2015;**38**(4):765–73.
40. Pearl PL, Schreiber J, Theodore WH, et al. Taurine trial in succinic semialdehyde dehydrogenase deficiency and elevated CNS GABA. Neurology. 2014;**82**(11):940–4.
41. Mohamed FE, Al-Gazali L, Al-Jasmi F, Ali BR. Pharmaceutical chaperones and proteostasis regulators in the therapy of lysosomal storage disorders: Current perspective and future promises. Front Pharmacol. 2017;**8**:448.
42. Balch WE, Morimoto RI, Dillin A, Kelly JW. Adapting proteostasis for disease intervention. Science. 2008;**319**(5865):916–9.
43. Singh LR, Gupta S, Honig NH, Kraus JP, Kruger WD. Activation of mutant enzyme function in vivo by proteasome inhibitors and treatments that induce Hsp70. PLoS Genet. 2010;**6**(1):e1000807.
44. Narita A, Shirai K, Itamura S, et al. Ambroxol chaperone therapy for neuronopathic Gaucher disease: A pilot study. Ann Clin Transl Neurol. 2016;**3**(3):200–15.
45. Motabar O, Huang W, Marugan JJ, et al. Identification of modulators of the n370s mutant form of

glucocerebrosidase as a potential therapy for gaucher disease: Chemotype 1. 2010;Mar 24 (updated May 5, 2011). In Probe Reports from the NIH Molecular Libraries Program. Bethesda, MD: National Center for Biotechnology Information (US). Available from: www-ncbi-nlm-nih-gov.ezp-prod1.hul.harvard.edu/books/NBK63601/.

46. Goldin E, Zheng W, Motabar O, et al. High throughput screening for small molecule therapy for Gaucher disease using patient tissue as the source of mutant glucocerebrosidase. PLoS One. 2012;**7**(1):e29861.

47. Steet RA, Chung S, Wustman B, et al. The iminosugar isofagomine increases the activity of N370S mutant acid beta-glucosidase in Gaucher fibroblasts by several mechanisms. Proc Natl Acad Sci USA. 2006;**103**(37):13813–8.

48. Aflaki E, Moaven N, Borger DK, et al. Lysosomal storage and impaired autophagy lead to inflammasome activation in Gaucher macrophages. Aging Cell. 2016;**15**(1):77–88.

49. Tominaga L, Ogawa Y, Taniguchi M, et al. Galactonojirimycin derivatives restore mutant human beta-galactosidase activities expressed in fibroblasts from enzyme-deficient knockout mouse. Brain Dev. 2001;**23**(5):284–7.

50. Matsuda J, Suzuki O, Oshima A, et al. Chemical chaperone therapy for brain pathology in G(M1)-gangliosidosis. Proc Natl Acad Sci USA. 2003;**100**(26):15912–7.

51. Schalli M, Weber P, Tysoe C, et al. A new type of pharmacological chaperone for GM1-gangliosidosis related human lysosomal beta-galactosidase: N-substituted 5-amino-1-hydroxymethyl-cyclopentanetriols. Bioorg Med Chem Lett. 2017;**27**(15):3431–5.

52. Clarke JT, Mahuran DJ, Sathe S, et al. An open-label phase I/II clinical trial of pyrimethamine for the treatment of patients affected with chronic GM2 gangliosidosis (Tay–Sachs or Sandhoff variants). Mol Genet Metab. 2011;**102**(1):6–12.

53. Argyriou C, D'Agostino MD, Braverman N. Peroxisome biogenesis disorders. Transl Sci Rare Dis. 2016;**1**(2):111–44.

54. Wood PL, Khan MA, Smith T, et al. In vitro and in vivo plasmalogen replacement evaluations in rhizomelic chrondrodysplasia punctata and Pelizaeus–Merzbacher disease using PPI-1011, an ether lipid plasmalogen precursor. Lipids Health Dis. 2011;**10**:182.

55. Wei H, Kemp S, McGuinness MC, Moser AB, Smith KD. Pharmacological induction of peroxisomes in peroxisome biogenesis disorders. Ann Neurol. 2000;**47**(3):286–96.

56. Li X, Baumgart E, Dong GX, et al. PEX11alpha is required for peroxisome proliferation in response to 4-phenylbutyrate but is dispensable for peroxisome proliferator-activated receptor alpha-mediated peroxisome proliferation. Mol Cell Biol. 2002;**22**(23):8226–40.

57. Dranchak PK, Di Pietro E, Snowden A, et al. Nonsense suppressor therapies rescue peroxisome lipid metabolism and assembly in cells from patients with specific *PEX* gene mutations. J Cell Biochem. 2011;**112**(5):1250–8.

58. Schulz A, Ajayi T, Specchio N, et al. Study of intraventricular cerliponase alfa for CLN2 disease. N Engl J Med. 2018;**378**(20):1898–907.

59. Meng Y, Sohar I, Wang L, Sleat DE, Lobel P. Systemic administration of tripeptidyl peptidase I in a mouse model of late infantile neuronal ceroid lipofuscinosis: Effect of glycan modification. PLoS One. 2012;**7**(7):e40509.

60. Meng Y, Sohar I, Sleat DE, et al. Effective intravenous therapy for neurodegenerative disease with a therapeutic enzyme and a peptide that mediates delivery to the brain. Mol Ther. 2014;**22**(3):547–53.

61. Boado RJ, Pardridge WM. The Trojan horse liposome technology for nonviral gene transfer across the blood–brain barrier. J Drug Deliv. 2011;**2011**:296151.

62. Pardridge WM. Molecular Trojan horses for blood–brain barrier drug delivery. Discov Med. 2006;**6**(34):139-43.

63. Muro S. New biotechnological and nanomedicine strategies for treatment of lysosomal storage disorders. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2010;**2**(2):189–204.

64. Coutinho MF, Santos JI, Matos L, Alves S. Genetic substrate reduction therapy: A promising approach for lysosomal storage disorders. Diseases. 2016;**4**(4).

65. Kirkegaard T, Gray J, Priestman DA, et al. Heat shock protein-based therapy as a potential candidate for treating the sphingolipidoses. Sci Transl Med. 2016;**8**(355):355ra118.

66. Davidson CD, Fishman YI, Puskas I, et al. Efficacy and ototoxicity of different cyclodextrins in Niemann–Pick C disease. Ann Clin Transl Neurol. 2016;**3**(5):366–80.

67. Kuhl JS, Suarez F, Gillett GT, et al. Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy. Brain. 2017;**140**(4):953–66.

68. Kuhl JS, Kupper J, Baque H, et al. Potential risks to stable long-term outcome of allogeneic hematopoietic stem cell transplantation for children with cerebral X-linked adrenoleukodystrophy. JAMA Netw Open. 2018;**1**(3):e180769.

69. Barth AL, Horovitz DDG. Hematopoietic stem cell transplantation in mucopolysaccharidosis type II: A literature review and critical analysis. J Inborn Error Metab Screen. 2018;**6**:2326409818779097.

70. Mercati O, Pichard S, Ouachee M, et al. Limited benefits of presymptomatic cord blood transplantation in neurovisceral acid sphingomyelinase deficiency (ASMD) intermediate type. Eur J Paediatr Neurol. 2017;**21**(6):907–11.

71. Lonnqvist T, Vanhanen SL, Vettenranta K, et al. Hematopoietic stem cell transplantation in infantile neuronal ceroid lipofuscinosis. Neurology. 2001;**57**(8):1411–6.

72. Lake BD, Henderson DC, Oakhill A, Vellodi A. Bone marrow transplantation in Batten disease (neuronal ceroid-lipofuscinosis). Will it work? Preliminary studies on coculture experiments and on bone marrow transplant in late infantile Batten disease. Am J Med Genet. 1995;**57**(2):369–73.

73. Yuza Y, Yokoi K, Sakurai K, et al. Allogenic bone marrow transplantation for late-infantile neuronal ceroid lipofuscinosis. Pediatr Int. 2005;**47**(6):681–3.

74. Selden NR, Al-Uzri A, Huhn SL, et al. Central nervous system stem cell transplantation for children with neuronal ceroid lipofuscinosis. J Neurosurg Pediatr. 2013;**11**(6):643–52.

75. Hu P, Li Y, Nikolaishvili-Feinberg N, et al. Hematopoietic stem cell transplantation and lentiviral vector-based gene therapy for Krabbe's disease: Present convictions and future prospects. J Neurosci Res. 2016;**94**(11):1152–68.

76. Wadhwa A, Chen Y, Holmqvist A, et al. Late mortality after allogeneic blood or marrow transplantation for inborn errors of metabolism: A report from the Blood or Marrow Transplant Survivor Study-2 (BMTSS-2). Biol Blood Marrow Transplant. 2019;**25**(2):328–34.

77. Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al. Lentiviral hematopoietic cell gene therapy for X-linked adrenoleukodystrophy. Methods Enzymol. 2012;**507**:187–98.

78. Nagabhushan Kalburgi S, Khan NN, Gray SJ. Recent gene therapy advancements for neurological diseases. Discov Med. 2013;**15**(81):111–9.

79. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. N Engl J Med. 2017;**377**(17):1630–8. doi:10.1056/NEJMoa1700554. Epub 2017 Oct 4.

80. Chien YH, Lee NC, Tseng SH, et al. Efficacy and safety of *AAV2* gene therapy in children with aromatic L-amino acid decarboxylase deficiency: An open-label, phase 1/2 trial. Lancet Child Adolesc Health. 2017;**1**(4):265–73.

81. Perez B, Gutierrez-Solana LG, Verdu A, et al. Clinical, biochemical, and molecular studies in pyridoxine-dependent epilepsy. Antisense therapy as possible new therapeutic option. Epilepsia. 2013;**54**(2):239–48.

82. Yin H, Xue W, Chen S, et al. Genome editing with Cas9 in adult mice corrects a disease mutation and phenotype. Nat Biotechnol. 2014;**32**(6):551–3.

83. Yin H, Song CQ, Dorkin JR, et al. Therapeutic genome editing by combined viral and non-viral delivery of CRISPR system components in vivo. Nat Biotechnol. 2016;**34**(3):328–33.

84. Pankowicz FP, Barzi M, Legras X, et al. Reprogramming metabolic pathways in vivo with CRISPR/Cas9 genome editing to treat hereditary tyrosinaemia. Nat Commun. 2016;**7**:12642.

85. Nygaard S, Barzel A, Haft A, et al. A universal system to select gene-modified hepatocytes in vivo. Sci Transl Med. 2016;**8**(342):342ra79.

86. Yang Y, Wang L, Bell P, et al. A dual AAV system enables the Cas9-mediated correction of a metabolic liver disease in newborn mice. Nat Biotechnol. 2016;**34**(3):334–8.

87. Sharma R, Anguela XM, Doyon Y, et al. In vivo genome editing of the albumin locus as a platform for protein replacement therapy. Blood. 2015;**126**(15):1777–84.

88. Brooks DA, Muller VJ, Hopwood JJ. Stop-codon read-through for patients affected by a lysosomal storage disorder. Trends Mol Med. 2006;**12**(8):367–73.

89. Miller JN, Chan CH, Pearce DA. The role of nonsense-mediated decay in neuronal ceroid lipofuscinosis. Hum Mol Genet. 2013;**22**(13):2723-34.

90. Ho G, Reichardt J, Christodoulou J. In vitro read-through of phenylalanine hydroxylase (*PAH*) nonsense mutations using aminoglycosides: A potential therapy for phenylketonuria. J Inherit Metab Dis. 2013;**36**(6):955–9.

91. Medina DL, Fraldi A, Bouche V, et al. Transcriptional activation of lysosomal exocytosis promotes cellular clearance. Dev Cell. 2011;**21**(3):421–30.

92. Song W, Wang F, Savini M, et al. TFEB regulates lysosomal proteostasis. Hum Mol Genet. 2013;**22**(10):1994–2009.

93. Moskot M, Montefusco S, Jakobkiewicz-Banecka J, et al. The phytoestrogen genistein modulates lysosomal metabolism and transcription factor EB (TFEB) activation. J Biol Chem. 2014;**289**(24):17054–69.

94. Xu M, Liu K, Swaroop M, et al. delta-Tocopherol reduces lipid accumulation in Niemann–Pick type C1 and Wolman cholesterol storage disorders. J Biol Chem. 2012;**287**(47):39349–60.

95. Hensley K, Venkova K, Christov A, Gunning W, Park J. Collapsin response mediator protein-2: An emerging pathologic feature and therapeutic target for neurodisease indications. Mol Neurobiol. 2011;**43**(3):180–91.

96. Khanna R, Wilson SM, Brittain JM, et al. Opening Pandora's jar: A primer on the putative roles of CRMP2 in a panoply of neurodegenerative, sensory and motor neuron, and central disorders. Future Neurol. 2012;**7**(6):74–71.

97. Hensley K, Christov A, Kamat S, et al. Proteomic identification of binding partners for the brain metabolite lanthionine ketimine (LK) and documentation of LK effects on microglia and motoneuron cell cultures. J Neurosci. 2010;**30**(8):2979–88.

98. Beyreuther BK, Freitag J, Heers C, et al. Lacosamide: A review of preclinical properties. CNS Drug Rev. 2007;**13**(1):21–42.

99. Sarkar C, Chandra G, Peng S, et al. Neuroprotection and lifespan extension in Ppt1(-/-) mice by NtBuHA: Therapeutic implications for INCL. Nat Neurosci. 2013;**16**(11):1608–17.

100. Lara MC, Weiss B, Illa I, et al. Infusion of platelets transiently reduces nucleoside overload in MNGIE. Neurology. 2006;**67**(8):1461–3.

101. Hussein E. Non-myeloablative bone marrow transplant and platelet infusion can transiently improve the clinical outcome of mitochondrial neurogastrointestinal encephalopathy: A case report. Transfus Apher Sci. 2013;**49**(2):208–11.

102. Moran NF, Bain MD, Muqit MM, Bax BE. Carrier erythrocyte entrapped thymidine phosphorylase therapy for MNGIE. Neurology. 2008;**71**(9):686–8.

103. Levene M, Coleman DG, Kilpatrick HC, et al. Preclinical toxicity evaluation of erythrocyte-encapsulated thymidine phosphorylase in BALB/c mice and beagle dogs: An enzyme-replacement therapy for mitochondrial neurogastrointestinal encephalomyopathy. Toxicol Sci. 2013;**131**(1):311–24.

104. Camara Y, Gonzalez-Vioque E, Scarpelli M, et al. Administration of deoxyribonucleosides or inhibition of their catabolism as a pharmacological approach for mitochondrial DNA depletion syndrome. Hum Mol Genet. 2014;**23**(9):2459–67.

105. Garone C, Garcia-Diaz B, Emmanuele V, et al. Deoxypyrimidine monophosphate bypass therapy for thymidine kinase 2 deficiency. EMBO Mol Med. 2014;**6**(8):1016–27.

106. Cerutti R, Pirinen E, Lamperti C, et al. NAD(+)-dependent activation of Sirt1 corrects the phenotype in a mouse model of mitochondrial disease. Cell Metab. 2014;**19**(6):1042–9.

107. Viscomi C, Bottani E, Civiletto G, et al. In vivo correction of COX deficiency by activation of the AMPK/PGC-1alpha axis. Cell Metab. 2011;**14**(1):80–90.

108. Khan NA, Auranen M, Paetau I, et al. Effective treatment of mitochondrial myopathy by nicotinamide riboside, a vitamin B3. EMBO Mol Med. 2014;**6**(6):721–31.

109. Wenz T, Diaz F, Spiegelman BM, Moraes CT. Activation of the PPAR/PGC-1alpha pathway prevents a bioenergetic deficit and effectively improves a mitochondrial myopathy phenotype. Cell Metab. 2008;**8**(3):249–56.

110. Bastin J, Lopes-Costa A, Djouadi F. Exposure to resveratrol triggers pharmacological correction of fatty acid utilization in human fatty acid oxidation-deficient fibroblasts. Hum Mol Genet. 2011;**20**(10):2048–57.

111. Yiu EM, Tai G, Peverill RE, et al. An open-label trial in Friedreich ataxia suggests clinical benefit with high-dose resveratrol, without effect on frataxin levels. J Neurol. 2015;**262**(5):1344–53.

112. Felici R, Cavone L, Lapucci A, et al. PARP inhibition delays progression of mitochondrial encephalopathy in mice. Neurotherapeutics. 2014;**11**(3):651–64.

113. DeVay RM, Dominguez-Ramirez L, Lackner LL, et al. Coassembly of Mgm1 isoforms requires cardiolipin and mediates mitochondrial inner membrane fusion. J Cell Biol. 2009;**186**(6):793–803.

114. Dassa EP, Dufour E, Goncalves S, et al. Expression of the alternative oxidase complements cytochrome C oxidase deficiency in human cells. EMBO Mol Med. 2009;**1**(1):30–6.

115. Fernandez-Ayala DJ, Sanz A, Vartiainen S, et al. Expression of the Ciona intestinalis alternative oxidase (AOX) in *Drosophila* complements defects in mitochondrial oxidative phosphorylation. Cell Metab. 2009;**9**(5):449–60.

116. Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol. 2011;**13**(2):132–41.

117. Peng M, Ostrovsky J, Kwon YJ, et al. Inhibiting cytosolic translation and autophagy improves health in mitochondrial disease. Hum Mol Genet. 2015;**24**(17):4829–47.

118. Ma H, Folmes CD, Wu J, et al. Metabolic rescue in pluripotent cells from patients with mtDNA disease. Nature. 2015;**524**(7564):234–8.

119. Gammage PA, Rorbach J, Vincent AI, Rebar EJ, Minczuk M. Mitochondrially targeted ZFNs for selective degradation of pathogenic mitochondrial genomes bearing large-scale deletions or point mutations. EMBO Mol Med. 2014;**6**(4):458–66.

120. Bacman SR, Williams SL, Pinto M, Peralta S, Moraes CT. Specific elimination of mutant mitochondrial genomes in patient-derived cells by mitoTALENs. Nat Med. 2013;**19**(9):1111–3.

121. Hsu PD, Lander ES, Zhang F. Development and applications of CRISPR–Cas9 for genome engineering. Cell. 2014;**157**(6):1262–78.

122. Cox DB, Platt RJ, Zhang F. Therapeutic genome editing: Prospects and challenges. Nat Med. 2015;**21**(2):121–31.

123. Reddy P, Ocampo A, Suzuki K, et al. Selective elimination of mitochondrial mutations in the germline by genome editing. Cell. 2015;**161**(3):459–69.

124. Hornig-Do HT, Montanari A, Rozanska A, et al. Human mitochondrial leucyl tRNA synthetase can suppress non cognate pathogenic mt-tRNA mutations. EMBO Mol Med. 2014;**6**(2):183–93.

125. Perli E, Giordano C, Pisano A, et al. The isolated carboxy-terminal domain of human mitochondrial leucyl-tRNA synthetase rescues the pathological phenotype of mitochondrial tRNA mutations in human cells. EMBO Mol Med. 2014;**6**(2):169–82.

126. Di Meo I, Auricchio A, Lamperti C, et al. Effective AAV-mediated gene therapy in a mouse model of ethylmalonic encephalopathy. EMBO Mol Med. 2012;**4**(9):1008–14.

127. Torres-Torronteras J, Viscomi C, Cabrera-Perez R, et al. Gene therapy using a liver-targeted AAV vector restores nucleoside and nucleotide homeostasis in a murine model of MNGIE. Mol Ther. 2014;**22**(5):901–7.

128. Bottani E, Giordano C, Civiletto G, et al. AAV-mediated liver-specific *MPV17* expression restores mtDNA levels and prevents diet-induced liver failure. Mol Ther. 2014;**22**(1):10-7.

129. Yu H, Koilkonda RD, Chou TH, et al. Gene delivery to mitochondria by targeting modified adenoassociated virus suppresses Leber's hereditary optic neuropathy in a mouse model. Proc Natl Acad Sci USA. 2012;**109**(20):E1238–47.

130. Wan X, Pei H, Zhao MJ, et al. Efficacy and safety of rAAV2-ND4 treatment for Leber's hereditary optic neuropathy. Sci Rep. 2016;**6**:21587.

131. Kurian MA, Gissen P, Smith M, Heales S, Jr., Clayton PT. The monoamine neurotransmitter disorders: An expanding range of neurological syndromes. Lancet Neurol. 2011;**10**(8):721–33.

Closing Remarks: A Clinical Approach to Inherited Metabolic Movement Disorders

Darius Ebrahimi-Fakhari and Phillip L. Pearl

As editors and authors, we reflect on this project, conceptualized to blend the salient clinical and exciting scientific advances that are on full display, from common to unique, in the field of inherited metabolic movement disorders. It is the province of the neurologist (pediatric *and* adult), geneticist, movement disorder specialist, developmentalist, radiologist, pathologist, physiatrist, therapist, educator, parent, advocate . . . indeed, the scope of this work is beyond provincial but instead universal. We have endeavored to encapsulate in this monograph a comprehensive approach to the somewhat peculiar but frankly permeating intersection of the inherited errors of metabolism and movement disorders.

In order to accomplish this goal, we divided this book into three major sections. First, there is a series of chapters using a phenomenology-based approach. Movement disorders, after all, represent a phenomenology-based school in neurology. This is a time-honored approach, and is well honed by those neurologists engrossed in the evaluation and management of Parkinson disease and the many forms of parkinsonism and its comorbidities including dementia, cerebral palsy and its own prominent comorbidities, and a host of explained and unexplained diseases with abnormal, and typically excessive, movements. The book begins with general principles including the importance of movement disorders in inborn errors of metabolism and vice versa, imaging aspects, and biochemical and genetic testing. The section leads off with a "top 10" list of those metabolic movement disorders that have inherent treatability, yet the specific diagnosis and targeted therapy are both required, typically in a timely fashion, to effect a change, and a profound change at that, in outcome. While the list of these designated entities can be challenged, and certainly enlarged, the principles and "hidden prevalence" of each warrant special recognition in our view. While listed in descending order, the entities starting from the "top" of the list are a veritable Who's Who of movement disorders and metabolic disease: Segawa dopa-responsive dystonia, Wilson disease, glucose-1-transporter deficiency, ataxia with vitamin E deficiency, biotin–thiamine-responsive basal ganglia disease, cerebral creatine deficiency, glutaric aciduria type 1, cerebrotendinous xanthomatosis, manganese transporter defects, and Niemann–Pick disease type C. Clearly a compelling list of enigmatic entities that rivet our attention!

This is then followed by phenomenology-based chapters, each devoted to a single significant area of movement disorders and authored by a recognized panoply of international luminaries. Whole chapters are devoted to ataxia, dystonia, parkinsonism, spasticity, and myoclonus.

The next section shifts to a metabolically based approach, and is organized by traditional as well as emerging inborn errors of metabolism that are permeated by movement disorders in their manifestations and morbidity. These include the amino acidopathies and lysosomal storage diseases, the latter with chapters devoted to Niemann–Pick type C and the neuronal ceroid lipofuscinoses. There is a series of chapters covering metal storage disorders, including neurodegeneration with brain iron accumulation (NBIA) syndromes, copper and manganese pathway disorders, and primary familial brain calcification. The area of post-translational modification, with the congenital disorders of glycosylation, is a burgeoning one, and there is an additional chapter on newly recognized disorders of autophagy. There is a section on neurotransmitter disorders, with a chapter devoted to dopamine metabolism and another to gamma-aminobutyric acid (GABA). A variant of hyperphenylalaninemia as an emerging chaperone disorder is covered as well, highlighting future trends in the field. There is coverage of vitamin-responsive disorders, from vitamin E to biotin and thiamine, and cerebral folate deficiency. This is followed by disorders of cholesterol metabolism, in particular cerebrotendinous xanthomatosis, and disorders of purine and pyrimidines, e.g. Lesch–Nyhan disease, and

creatine metabolism. This section closes with a chapter on inborn errors of metabolism associated with hereditary spastic paraplegia.

The final section encompasses conclusions and future directions. This includes chapters on next-generation sequencing and its applications to metabolic movement disorders, deep brain stimulation as an established intervention in more common movement disorders and an emerging one for specific rare metabolic disorders, and other novel therapeutic approaches targeted to metabolomics and in multiple clinical trials.

Overall, this is a challenging area of medicine, and requires a considerable degree of expertise and collaboration by clinical and laboratory specialists and investigators. The phenomenological approach of the traditional movement disorder neurologist must be combined with the biochemical–genetic orientation of the metabolism-based expert. The amount of new diseases being delineated by next-generation sequencing, advancing our understanding of metabolism and its disorders, is staggering. While most of the diseases covered in this book have early life onset, including the neonatal and infantile periods, there are also metabolic movement disorders with adult onset, or showing significant phenotypic variation and evolution over the course of the lifespan. Each chapter has been supplied with boxes of key points and future directions. It is our fervent hope that our approach to organizing this material will promote clinical care and advance the field of inherited metabolic movement disorders.

Appendix: Video Captions

Video 9.1 Patient with compound heterozygous variants in *GCH1*.

Video 9.2 Patient with *SLC30A10*-associated hypermanganesemia.

Video 9.3 Patient with Tay–Sachs disease presenting with parkinsonism. (With permission, from: Ebrahimi-Fakhari D, Hildebrandt C, Davis PE, Rodan LH, Anselm I, Bodamer O. The Spectrum of Movement Disorders in Childhood-onset Lysosomal Storage Diseases. Mov Disord Clin Pract. 2018;5:149–155.)

Videos 17.1 and 17.2 Movement disorder observed in a patient with SLC30A10 deficiency showing upper limb dystonia and dysdiadochokinesis (Video 17.1), and a characteristic high-stepping gait (also known as cock-walk gait) (Video 17.2). From: Stamelou M, Tuschl K, Chong WK, Burroughs AK, Mills PB, Bhatia KP, et al. Dystonia with brain manganese accumulation resulting from *SLC30A10* mutations: A new treatable disorder. Mov Disord. 2012;27(10):1317–22.

Videos 17.3 and 17.4 An individual with SLC39A14 deficiency before (Video 17.3) and after (Video 17.4) chelation therapy with disodium calcium edetate. Pre-treatment, the girl shows significant axial and limb hypotonia, dystonic posturing of the lower limbs, bradykinesia, hypomiymia, and inability to walk. Following 6 months of chelation therapy, her tone and posture have improved with residual lower limb dystonia, and she has regained her ability to walk with the aid of foot orthoses. From: Tuschl K, Meyer E, Valdivia LE et al. Mutations in *SLC39A14* disrupt manganese homeostasis and cause childhood-onset parkinsonism–dystonia. Nat Commun. 2016 May 27;7:11601.

Video 19.1 Video showing the characteristic hyperkinetic movement disorder of a patient with N-glycanase 1 deficiency.

Video 23.1 A 6-month-old patient with SSADH deficiency with active choreoathetosis.

Video 23.2 An Adolescent patient with SSADH deficiency with exertional dyskinesia.

Video 23.3 A 20-month-old patient with GABA-T deficiency with virtually constant choreoathetosis and myoclonus during the awake state. Reproduced with permission from Koenig MK, Hodgeman R, Riviello JJ, Chung W, Bain J, Chiriboga CA, et al. Phenotype of GABA-transaminase deficiency. Neurology. 2017;88(20):1919–24.

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