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Chapter 22

Inborn errors of metabolism

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Abstract

Inborn errors of metabolism, also known as inherited metabolic diseases, constitute an important group of conditions presenting with neurologic signs in newborns. They are individually rare but collectively common. Many are treatable through restoration of homeostasis of a disrupted metabolic pathway. Given their frequency and potential for treatment, the clinician should be aware of this group of conditions and learn to identify the typical manifestations of the different inborn errors of metabolism. In this review, we summarize the clinical, laboratory, electrophysiologic, and neuroimaging findings of the different inborn errors of metabolism that can present with florid neurologic signs and symptoms in the neonatal period.

INTRODUCTION

The first inborn error of metabolism (IEM) was described by Garrod (1902). Nowadays, there are estimated to be more than 700 inborn errors of metabolism (Illsinger and Das, 2010). Defined as genetic disorders that cause disruption of a metabolic pathway, IEMs can lead to disease either by accumulation of a toxic substrate proximal to the metabolic block (for example, excessive leucine in maple syrup urine disease), a deficiency of the product distal to the block (as in serine biosynthetic disorders), or a diversion of the substrate to an alternative pathway (for example in D-hydroxyglutaric aciduria type 2, where α-ketoglutarate is diverted from the Krebs cycle into the formation of D-2-hydroxyglutarate). Although each disorder in isolation is rare, as a group they represent somewhat common disorders, with an overall prevalence of 1 in 784 individuals in the West Midlands, United Kingdom (Sanderson et al., 2006), 1 in 2500 in British Columbia, Canada (Applegarth et al., 2000), and 1 in 2555 in Italy (Dionisi-Vici et al., 2002). IEMs can be classified in various ways, as small-molecule diseases (such as aminoacidopathies, urea cycle disorders, organic acidemias, fatty acid oxidation disorders, purine and pyrimidine disorders, and disorders of metal metabolism) and large-molecule diseases (such as lysosomal storage disorders, glycogen storage disorders, peroxisomal disorders, and congenital disorders of glycosylation) (Lanpher et al., 2006). In turn, the small-molecule diseases can be classified into intoxication disorders (such as organic acidemias, urea cycle disorders, or aminoacidopathies, caused by accumulation of a toxic compound), or disorders of energy deficiency (such as fatty acid oxidation disorders, disorders of pyruvate metabolism and gluconeogenesis, and mitochondrial disorders) (Illsinger and Das, 2010).

Some inborn errors of metabolism are treatable (van Karnebeek and Stockler, 2012), and thus many are included in newborn screening programs in various countries. In fact, the number of treatable IEMs continues to increase with time, and care for conditions that are already treatable continues to improve. It has been argued that the most important development contributing to improved care is the increased access to knowledge of

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IEMs (Campeau et al., 2008). Online tools exist to facilitate the diagnosis (Lee et al., 2017b) or aid in the nutritional treatment of IEMs (Ho et al., 2016), while other available tools can provide help with both diagnosis and treatment of these conditions (van Karnebeek et al., 2012b).

Many IEMs present with neurologic symptoms in the neonatal period, some predominantly with encephalopathy, others with neonatal seizures, or still others with neonatal hypotonia, or a combination of these findings. Some can have characteristic EEG changes, such as the comb-like rhythm in maple syrup urine disease (MSUD) (Tharp, 1992; van Karnebeek et al., 2018). Certain IEMs can be accompanied by structural brain anomalies, such as a dysgenetic corpus callosum seen commonly in pyruvate dehydrogenase complex deficiency or in glycine encephalopathy (Nissenkorn et al., 2001). Brain magnetic resonance spectroscopy can sometimes aid the correct diagnosis of an IEM, as has been seen in cases of GABA transaminase deficiency (Tsuji et al., 2010), fatty acid oxidation disorders (Ferreira et al., 2016), or glycine encephalopathy (McAdams and Richards, 2009). In this chapter, we provide an overview of the clinical symptoms, biochemical and genetic defects, and treatment of IEMs that present with neurologic features during the neonatal period. We also provide a tabular summary of the main clinical (neurologic and extraneurologic), laboratory, EEG, brain MRI, and brain MRS findings for the different groups of IEMs, in order to raise awareness and facilitate their rapid recognition by the busy clinician (see Table 22.1).

UREA CYCLE DISORDERS

Clinical symptoms

The age at which urea cycle disorders (UCDs) first present clinically is variable, but they are more likely to present in the neonatal period, during late infancy, and around puberty. The early symptoms are often not specific and therefore easily overlooked. Nevertheless, it is important to think of and actively test for hyperammonemia to establish the diagnosis quickly and reduce complications.

Immediately after birth, babies suffering one of these inherited metabolic diseases generally appear normal but within days to weeks, due to the hyperammonemia, they typically become progressively unwell, with poor feeding, vomiting, lethargy, temperature instability, irritability, and tachypnea. If left untreated, neonates may rapidly deteriorate, develop neurologic and autonomic problems, including encephalopathy and/or epilepsy, vasomotor instability, intracranial hemorrhages, apnea, and coma. For ornithine transcarbamylase (OTC) deficiency, which is an X-linked disorder, hyperammonia is usually severe and often fatal during the neonatal period; for females the clinical picture depends on X-inactivation pattern in the liver with severe symptoms/encephalopathy in the neonatal period in less than 15% of cases. For argininosuccinic aciduria, neurologic and hepatic problems occur despite good control of ammonia levels; this is due to the accumulation of argininosuccinic acid in the brain and other organs. Arginase deficiency differs clinically from the other UCDs; often misdiagnosed as cerebral palsy (Leach et al., 2014), it presents most commonly at a later age with spastic diplegia and intellectual disability due to high guanidinoacetate levels (Amayreh et al., 2014). However, some patients may indeed present with a subacute encephalopathy and/or seizures.

Genes

The genes involved in UCD encode the urea cycle enzymes and those crucial to proper functioning of those enzymes: *NAGS* encoding *N*-acetylglutamate synthase, *CPS1* encoding carbamylphosphate synthetase I, *OTC* encoding ornithine transcarbamylase (the defect of which leads to the most common urea cycle defect, an X-linked disorder with an incidence of 1 in 14,000), *ASS* encoding argininosuccinate synthetase (the deficiency of which leads to citrullinemia type 1), *ASL* encoding argininosuccinate lyase, *ARG1* encoding arginase, *CA5A* encoding carbonic anhydrase VA, and *SLC25A15* encoding the mitochondrial ornithine translocator (the deficiency of which is associated with hyperornithinemia, hyperammonemia, and homocitrullinuria syndrome).

Biochemical defects and pathophysiology

The main detoxification mechanism of ammonia (NH_3) arising from amino acid metabolism is its conversion to urea in the liver. Carbamoyl phosphate synthetase 1 is the enzyme catalyzing the initial condensation of ammonia and bicarbonate. It requires activation by *N*-acetylglutamate, which itself is formed by *N*-acetylglutamate synthase. Ornithine transcarbamylase acts as a carrier molecule, binding carbamylphosphate to ornithine. The citrulline that is then formed is transported out of the mitochondrion and bound to aspartate by argininosuccinate synthetase. The resulting argininosuccinate is split by argininosuccinate lyase into fumarate and arginine. Subsequently, the latter is hydrolyzed by arginase into ornithine and urea, which are both harmless. Urea carries two nitrogen residues and is excreted in the urine, while ornithine is transported back into the

Table22.1

Summary of clinical, laboratory, EEG, and neuroimaging findings of IEMs.

IEM	Neurologic	Extraneurologic	Laboratory	EEG	Brain MRI	Bran MRS
Urea cycle disorders	Encephalopathy	Liver disease (sometimes)	Hyperammonemia. Respiratory alkalosis. Increased glutamine	Slow background	Cortical and subcortical edema. BG T2-hyperintensity with thalamic sparing. Scalloped ribbon of DWI restriction at insular gray–white interface	Prominent Glx peak
Organic acidemias	Encephalopathy. Choreoathetosis	Cytopenias. Pancreatitis. Cardiomyopathy (PA). Renal disease (MMA)	Hyperammonemia. High-anion gap metabolic acidosis. Ketotic hyperglycinemia	Slow background. Burst suppression possible	Diffuse swelling neonatally; delayed myelination and globi pallidi lesions later	Prominent Glx peak
Disorders of biotin metabolism	Encephalopathy	Erythroderma or ichthyosis	Hyperammonemia. High-anion gap metabolic acidosis. Lactic acidosis. Ketosis	Burst suppression	Intraventricular hemorrhage. Subependymal cysts	Lactate peak
MSUD	Encephalopathy; opisthotonus; bicycling/ fencing movements	Sweet (maple syrup) smell	Ketosis. Hypernatremia. Increased BCAAs and BCKAs	Comb-like rhythm	Increased signal and cytotoxic edema myelinated structures, vasogenic edema of unmyelinated tracts	BCAA/BCKA peak (0.9 ppm)
Fatty acid oxidation defects	Encephalopathy (Reye syndrome)	Lipid storage myopathy. Liver disease. Renal cysts (GA2)	Hypoketotic hypoglycemia	Slow background	T2 hyperintensities in periventricular and subcortical WM (GA2)	Lipid peak (0.9 and 1.3 ppm)
Primary lactic acidosis	Encephalopathy. Infantile Parkinsonism (PC deficiency)	Dysmorphic features (PDH deficiency)	Lactic acidosis	Slow background, multifocal spikes	T2 hyperintensities and DWI restriction of dorsal brainstem, cerebral peduncles, corticospinal tracts; subependymal cysts	Lactate peak
Glycine encephalopathy	Seizures	None	High CSF glycine and CSF/ plasma glycine ratio	Burst suppression	Agenesis of the CC. T2 hyperintensities and DWI restriction of myelinated tracts	Glycine peak (3.55 ppm)
Molybdenum cofactor/ sulfite oxidase deficiency	Seizures. hyperekplexia	None	Elevated S-sulfocysteine; low cysteine, high taurine. Increased AASA and pipecolic acid	Burst suppression	Diffuse swelling followed by cystic changes	*S*-sulfocysteine peak (3.61 ppm); taurine peak (3.24 and 3.42 ppm)
Disorders of GABA metabolism	Seizures. Hypersomnolence. Choreoathetosis	Overgrowth	Elevated urine 4-hydroxybutyric acid (SSADH); elevated GABA, beta-alanine, and homocarnosine (GABAT)	Slow background, multifocal spikes, burst suppression	T2 hyperintensities of globi pallidi, dentate, and subthalamic nucleus (SSADH)	GABA peak (2.2–2.4 ppm; GABAT)

Continued

Table22.1

Continued

IEM	Neurologic	Extraneurologic	Laboratory	EEG	Brain MRI	Bran MRS
PDE	Seizures	None	Increased AASA and pipecolic acid	Slow background, multifocal spikes, burst suppression	Usually normal; can have dysgenetic CC	Decreased NAA peak (over time)
Serine biosynthesis disorders	Microcephaly. Seizures	Ichthyosis. Ectropion, eclabion (Neu–Laxova)	Low serine in plasma and CSF	Multifocal spikes; hypsarrhythmia	Hypomyelination	Decreased NAA peak; increased choline peak
Lysosomal storage disorders	Neurodegeneration. Hypotonia (Pompe)	Hydrops fetalis. Dermal melanosis. Ichthyosis (Gaucher type 2)	Increased CK (Pompe)	Fast central spikes (Tay-Sachs); vertex sharp waves (sialidosis)	Thick optic nerves and intracranial calcifications (Krabbe)	Broad peak centered around 3.7 ppm
Peroxisonal disorders	Hypotonia. Seizures	Cholestasis; renal cysts; epiphyseal stippling. Dysmorphic features	Elevated VLCFA, phytanic acid, bile acid intermediates, pipecolic acid, low plasmalogens	Multifocal spikes; hypsarrhythmia	Perisylvian polymicrogyria and pachygyria; hypomyelination; subependymal cysts	Lipid peak (0.9 and 1.3 ppm)
Cholesterol biosynthesis disorders (SLO)	Microcephaly. Hypotonia	Dysmorphic features. Photosensitivity	Low cholesterol (90%); elevated 7DHC	Interictal epileptiform discharges common	Holoprosencephaly (5%)	Lipid peak (0.9 and 1.3 ppm)
Congenital disorders of glycosylation	Hypotonia. Seizures	Inverted nipples. Abnormal fat pads	Elevated transaminases; coagulopathy; endocrine abnormalities	Multifocal epileptic discharges	Pontocerebellar hypoplasia	Decreased NAA peak
Disorders of copper metabolism	Seizures	Pili torti. Cutis laxa. Bladder diverticula. Metaphyseal lesions	Low serum copper and ceruloplasmin; high urine copper	Burst suppression	Arterial tortuosity. Subdural collections	Decreased NAA peak
GLUT1 deficiency	Seizures. Abnormal eye movements	Hemolytic anemia, pseudohyperkalemia, cataracts (specific mutations)	Low CSF glucose and lactose; low CSF/serum glucose ratio	Variable depending on type of seizure	Normal	Normal

Abbreviations: *7DHC*, 7-dehydrocholesterol; *AASA*, α-aminoadipic semialdehyde; *BCAAs*, branched-chain amino acids; *BCKAs*, branched-chain ketoacids; *BGF*, basal ganglia; *CC*, corpus callosum; *DWI*, diffusion-weighted imaging; *GA2*, glutaric aciduria type 2; *GABAT*, GABA transaminase; *Glx*, glutamine/glutamate; *MSUD*, maple syrup urine disease; *NAA*, *N*-acetylaspartate; *PA*, propionic acidemia; *PC*, pyruvate carboxylase; *PDE*, pyridoxine-dependent epilepsy; *PDH*, pyruvate dehydrogenase; *SLO*, Smith–Lemli–Opitz syndrome; *WM*, white matter.

mitochondrion by the ornithine transporter, thus completing the urea cycle.

Additionally, hepatic NH_3 detoxification occurs (in low capacity) through the action of glutamine synthetase at the perivenous area of the hepatic lobule. Transport defects involving the dibasic amino acids cause a deficiency of intramitochondrial ornithine, and accumulation of carbamoyl phosphate and hyperammonemia. Additionally, a liver bypass (e.g., open ductus venosus in the neonate) causes hyperammonemia with insufficient formation of both urea and glutamine, as can also be seen with insufficient arginine intake (e.g., parenteral nutrition). Carbonic anhydrase VA provides bicarbonate to the proximal urea cycle enzyme CPS1, as well as three other enzymes active in intermediary metabolism, resulting in hyperammonemia as well as lactic acidosis and hypoglycemia (pyruvate carboxylase) and accumulation of organic aciduria metabolites (propionyl-CoA carboxylase and 3-methylcrotonyl-CoA carboxylase) (van Karnebeek et al., 2014).

For ASL deficiency, there is accumulation of argininosuccinic acid that is damaging to all organs and may result in intellectual disability and psychiatric symptoms, as well as abnormal hair, hepatomegaly, and hepatic fibrosis, which are unique features of this disorder.

Other genetic defects of ammonia detoxification that can present during the neonatal period include: hyperinsulinism-hyperammonemia syndrome due to gain-of-function mutations in glutamate dehydrogenase; lysinuric protein intolerance, caused by deficiency of a dibasic amino acid transporter—encoded by *SLC7A7*—resulting in a lack of substrates (ornithine and arginine) for the urea cycle; and glutamine synthetase deficiency, associated with severe neonatal encephalopathy.

In addition to the ammonia, plasma amino acids and urine organic acids are required for pinpointing the type of UCD. It must be noted that metabolic abnormalities might be fluctuating and inconsistent. Therefore enzymatic and/or molecular analyses are required to confirm the diagnosis.

Treatment and outcomes

The main management principles of acute hyperammonemia include cessation of protein intake, administration of enough calories to avoid catabolism, and use of ammonia scavengers such as sodium benzoate and/or sodium phenylbutyrate. Protein cessation should not exceed 24 h; otherwise muscle breakdown will ensue, with a consequent rise in ammonia production from protein catabolism. Intravenous fluids (such as D10W) at 1.5 times the calculated maintenance rate—and if necessary intravenous lipids—are typically administered to minimize endogenous protein breakdown and reliance on amino acid oxidation for energy. If these measures are insufficient, one could consider hemodialysis or continuous venous–venous hemofiltration. For the proximal UCDs, intravenous arginine is administered, while citrulline is given enterally for distal UCDs. Chronic management is based on the same but less rigorous principles, with a low-protein diet and amino acid supplementation, enteral medications and, in case of illness, an emergency formula to avoid a metabolic decompensation. Detailed diagnostic and management guidelines have been published (Häberle et al., 2012).

Outcomes are highly variable and depend on the type and severity of the particular UCD or secondary cause of hyperammonemia. Equally important is the age at diagnosis, as irreversible damage and neurologic sequelae correlate closely with the ammonia level and the duration during which it is elevated, especially for the neonates and young infants whose brains are most vulnerable to the damaging effects of hyperammonemia and other toxins inherent to specific UCDs. The overall metabolic control and (lack of) decompensation also contribute to the outcome of UCD patients. Most frequent complications include intellectual disability, psychiatric disease, failure to thrive, and liver disease.

ORGANIC ACIDURIAS

Clinical symptoms

Organic acidurias are disorders of intermediary metabolism with characteristic accumulation of carboxylic acids identified by gas chromatography/mass spectroscopy (GC/MS) analysis of urine. During the neonatal period, the most common and relevant OAs are those involving branched-chain amino acid metabolism–propionic aciduria (PA), methylmalonic aciduria (MMA), isovaleric aciduria (IVA) and lysine/tryptophan metabolism, glutaric aciduria type 1 (GA1). Most patients present with systemic illness (classical organic acidurias) but some conditions, such as GA1, have only cerebral abnormalities. The latter presents with macrocephaly, frontotemporal atrophy on MRI, acute encephalopathic crisis (usually between the ages of 6 and 18 months) with destruction of the striatum, which results in severe dystonic–dyskinetic movement disorder, subdural hematomas, and leukoencephalopathy in adulthood.

For the other three acidurias there are several phenotypes. The neonatal form presents with metabolic encephalopathy. Lethargy and feeding problems with dehydration are early symptoms. Truncal hypotonia with limb hypertonia occur, as well as myoclonic jerks. Cerebral edema results in coma and death. Pancytopenia and myelodysplasia are seen in PA and MMA. Multiorgan failure is possible. An unusual sweaty feet odor may be diagnostic for isovaleric acidemia. The chronic,

intermittent form of aciduria can manifest later in life, up to adulthood, with recurrent episodes of ketoacidotic coma, lethargy and ataxia, focal neurologic signs, stupor, coma, and Reye syndrome. Patients with PA can also present with cardiomyopathy and prolongation of the QT interval. Finally, the chronic progressive form presents with failure to thrive, chronic vomiting, anorexia, osteoporosis, hypotonia, psychomotor retardation, and recurrent infections.

Pathophysiology and biochemical defects

The three aforementioned organic acidurias are the result of enzymatic defects in branched-chain amino acid catabolism. The mitochondrial accumulation of CoA metabolites is an important difference between many organic acidurias and the aminoacidopathies.

Specifically, IVA is caused by a defect in isovaleryl-CoA dehydrogenase, a FAD-dependent enzyme in the leucine catabolic pathway. In PA, propionyl-CoA accumulates due to propionyl-CoA carboxylase deficiency, inhibiting enzymes of the tricarboxylic acid cycle, the urea cycle, and other pathways. Of note, this is a biotin-dependent enzyme, although no biotin-responsive patients have been described.

MMA is the result of methylmalonyl-CoA mutase deficiency. Secondary deficiency of this enzyme may also be caused by insufficient metabolism of its cofactor cobalamin, or nongenetic factors such as vitamin B12 deficiency. Finally, GA1 is caused by a defect of an enzyme active in the lysine and tryptophan catabolism pathway, glutaryl-CoA dehydrogenase.

Biochemically, patients present with a high-anion gap metabolic acidosis, lactate accumulation along with ketones and tricyclic acid intermediates, hypoglycemia, and hyperammonemia. For neonates, ketonuria is always abnormal and should prompt investigations for organic acidurias and other IEMs. Specific metabolic investigations are required to confirm the diagnosis. Acylcarnitines show low total carnitine for all four organic acidurias: C2 acetylcarnitine (indicative of ketosis), C3 propionylcarnitine elevations for PA and MMA, C5 isovalerylcarnitine for isovaleric aciduria, and C5DC glutarylcarnitine for glutaric aciduria type 1. Organic acid analysis will reveal elevations of 3-hydroxypropionate, methylcitrate, tiglylglycine, and propionylgycine in patients with PA, methylmalonic acid in MMA, 3-hydroxyisovaleric acid and isovalerylglycine in IVA, and 3-hydroxyglutaric acid and glutaric acid in GA1. Amino acids show elevated glycine in patients with PA, MMA, and IVA. It must be noted that metabolic abnormalities might be fluctuating and inconsistent, so enzymatic and/or molecular analyses are required to confirm the diagnosis.

Genes

PCCA and *PCCB* encode the two subunits of propionyl-CoA carboxylase. *MUT* encodes methylmalonyl-CoA mutase; *IVD* encodes isovaleryl-CoA dehydrogenase; and *GCDH* encodes glutaryl-CoA dehydrogenase.

Therapy and outcomes

Prompt intervention is paramount in acute phase organic acidurias. Therapy comprises the interruption of the catabolic state with high-dose glucose infusion (with intravenous insulin, if necessary) and lipid infusion, stopping protein intake for no longer than 24 h; counteraction of the acidosis; removal of ammonia (if required, with use of carglumic acid or dialysis); and supplementation of levocarnitine to increase acid excretion. Long-term treatment comprises dietary protein restriction and supplementation of carnitine. An emergency protocol (with extra fluids and calories, but further restriction of protein) in case of illness, fasting for surgery, or other catabolic states is imperative for all organic acidurias. Guidelines are in place for the diagnosis and management of PA and MMA (Baumgartner et al., 2014).

The outcome of organic acidurias depends on the timing of diagnosis and intervention, as well as the severity of disease (in most cases, correlating with the type of mutation). Complications of organic acidurias are many, varying from demyelination, striatal necrosis, nephritis (in MMA), pancreatitis, dermatoses/epidermolysis, osteoporosis, and cardiomyopathy (in PA).

Other organic acidurias—diagnosed via urine organic acid profile and treated symptomatically unless otherwise indicated—include:

1. 3-methylglutaconic aciduria of different types, of which the most relevant for the neonatal neurologist is type 2, also known as Barth syndrome, an X-linked disorder caused by mutations in *TAZ*, and characterized by skeletal and cardiac myopathy, growth retardation, and neutropenia. Type 3, also known as Costeff syndrome, is caused by mutations in *OPA3* and presents with optic atrophy, extrapyramidal signs, and spasticity.
2. D-2-hydroxyglutaric acidurias type 1 (D-2-hydroxyglutarate dehydrogenase deficiency) and type 2 (isocitrate dehydrogenase 2 superactivity) presenting with a variable phenotype (from asymptomatic to developmental delay, epilepsy, hypotonia, cardiomyopathy, or dysmorphic features).
3. L-2-hydroxyglutaric aciduria (L-2-hydroxyglutarate dehydrogenase deficiency) presenting with psychomotor delay, epilepsy, cerebellar ataxia, and macrocephaly. It often progresses slowly. Neuroimaging findings include peripheral leukodystrophy, with

symmetric T2-weighted hyperintensities of the dentate nucleus and pallidum.

4. Ethylmalonic encephalopathy (caused by mutations in *ETHE1*) presenting with (often lethal) neurodevelopmental regression, pyramidal and extrapyramidal tract signs, seizures, petechiae, orthostatic acrocyanosis, and chronic diarrhea.
5. 2-Methyl-3-hydroxybutyric aciduria, an X-linked condition presenting in males with progressive neurodegeneration, loss of skills, choreoathetosis, epilepsy, blindness, mild acidosis in catabolic states, and cardiomyopathy. Females may have nonprogressive intellectual disability.
6. Malonic aciduria (caused by mutations in *MLYCD*) presenting with relatively mild clinical features including intellectual developmental delay, epilepsy, and recurrent vomiting. Treatment includes carnitine supplementation and a low-fat, high-carbohydrate diet.
7. Canavan disease, or aspartoacylase deficiency, presenting with progressive psychomotor delay, progressive epileptic encephalopathy, macrocephaly, leukodystrophy (particularly of subcortical U-fibers), and optic atrophy.

DISORDERS OF BIOTIN METABOLISM (MULTIPLE CARBOXYLASE DEFICIENCY)

Clinical symptoms

The neonatal form of multiple carboxylase deficiency presents with intrauterine growth restriction (IUGR), hypotonia, feeding and breathing difficulties, and encephalopathy. Skin manifestations are typical and include erythroderma-like dermatitis, or even ichthyosis with a collodion membrane (Arbuckle and Morelli, 2006). Laboratory findings include severe metabolic acidosis with lactic acidosis and ketosis, hyperammonemia, and a common pattern of organic aciduria.

Typical neuroimaging findings, seen in 86% of patients, include ventriculomegaly, intraventricular hemorrhage, and subependymal cysts (Bandaralage et al., 2016).

Genes

HLCS is the gene causative of the neonatal form of multiple carboxylase deficiency, while *BTD* is the gene typically responsible for a later-onset form of the disease. A founder mutation in *HLCS* is present in the Faroe Islands, with an estimated carrier frequency of 1 in 20 (Lund et al., 2007). The human sodium-dependent multivitamin transporter (SMVT) that transports biotin through the plasma membrane is encoded by the *SLC5A6* gene, and mutations in the latter were recently associated with human disease (Subramanian et al., 2017).

Biochemical defects and pathophysiology

Multiple carboxylase deficiency results either from biotinidase deficiency or from holocarboxylase synthetase deficiency. Biotinidase deficiency is usually associated with a later onset of symptoms, while the neonatal form of multiple carboxylase deficiency is caused by a lack of holocarboxylase synthetase. While biotinidase is necessary for cleaving biotin from biotin-dependent holocarboxylases so it can be recycled for new use, holocarboxylase synthetase is responsible for incorporating biotin into the apocarboxylases, to form the fully active holocarboxylases. There are five biotin-dependent carboxylases: propionyl-CoA carboxylase (PCC), pyruvate carboxylase, 3-methylcrotonyl-CoA carboxylase (3-MCC), acetyl-CoA carboxylase-alpha, and acetyl-CoA carboxylase-beta. Lactic acidosis in this condition results from a deficiency of pyruvate carboxylase, while the characteristic pattern of urine organic acid excretion is that of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine from 3-MCC deficiency, and 3-hydroxypropionic acid, methylcitrate, and tiglylglycine from PCC deficiency. These characteristic urine metabolites, however, can be masked by the presence of gross ketosis in urine organic analysis by GC/MS (Carpente et al., 2000).

Newborn screening by tandem MS reveals elevated C5OH (3-hydroxyisovalerylcarnitine) on dried blood spots, although elevation of C3 (propionylcarnitine) can also be found. However, cases can be missed or even misdiagnosed as isolated 3-MCC deficiency (Donti et al., 2016).

In addition to its aforementioned cytosolic and mitochondrial role in metabolism, holocarboxylase synthetase also fulfills a putative role in histone biotinylation and has a moonlighting function as a nuclear coregulator of gene transcription (León-Del-Río et al., 2017). Indeed, patients with holocarboxylase synthetase deficiency were found to have decreased histone biotinylation (Narang et al., 2004).

Treatment and outcomes

Therapy for disorders of biotin metabolism involves biotin supplementation. Although most patients respond favorably to biotin, some patients show an incomplete response (Wilson et al., 2005). Biotin-unresponsive mutations typically exhibit reduced affinity for the substrate (Mayende et al., 2012). For poorly responsive cases, some authors advocate measuring biotin plasma levels to ensure that the biotin dose is sufficient to saturate the K_m of the mutant enzyme (Van Hove et al., 2008).

Doses of up to 200 mg of biotin have been administered in holocarboxylase synthetase deficiency, unlike the lower doses of 5–10 mg given to patients with biotinidase deficiency. Maternal administration of biotin prenatally has led to improved growth in a fetus with IUGR due to holocarboxylase synthetase deficiency (Yokoi et al., 2009). The solubility of the formulation should be taken into account, as poorly soluble forms might not be absorbed or might even lead to a biotin pharmacobezoar (De Castro et al., 2015).

MAPLE SYRUP URINE DISEASE

Clinical symptoms

MSUD presents within a few days of life, many times even before the return of newborn screening results, with poor feeding, hypertonia, seizures, and progressive neurologic deterioration. The presence of severe spasticity with opistothonus has occasionally led to a misdiagnosis of neonatal tetanus (Kültürsay et al., 1994). Stereotypic movements such as "fencing" and "bicycling" are typical. The characteristic maple syrup smell can be appreciated first in cerumen and later in other bodily secretions, such as urine.

Laboratory findings include ketosis and hyponatremia, the latter from an increase in vasopressin (Strauss et al., 1993), thus representing an example of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Hypoglycemia and hyperammonemia are not common.

A characteristic EEG pattern, described as a comb-like rhythm, is diagnostic of the neonatal form of MSUD (see left side of Fig. 22.1, obtained from a 3-week-old patient) (Estivill et al., 1985; Tharp, 1992).

Neuroimaging reveals cerebral edema. Diffusion-weighted imaging is useful in the acute setting of MSUD, as it shows hyperintensity with decreased apparent diffusion coefficient (ADC) values—consistent with cytotoxic edema—in the cerebellar white matter, dorsal brainstem, cerebral peduncles, thalami, posterior limbs of the internal capsules, and centrum semiovale (Cavalleri et al., 2002; Parmar et al., 2004), while the unmyelinated white matter reveals an increase in ADC, consistent with vasogenic edema (Ha et al., 2004). Magnetic resonance spectroscopy reveals a large peak at 0.9 ppm from the methyl resonance of branched-chain amino acids and ketoacids (see arrow on right side of Fig. 22.1, obtained from the same patient as previously) (Jan et al., 2003; Sato et al., 2014).

Genes

MSUD is caused by a deficiency in branched-chain ketoacid dehydrogenase (BCKDH). The BCKDH complex is composed of three subunits: E1, E2, and E3. The decarboxylase (E1 subunit) is in turn composed of an α subunit (encoded by *BCKDHA*) and a β subunit (encoded by *BCKDHB*). The dihydrolipoamide branched-chain transacylase (E2 subunit) is encoded by *DBT*, while the dihydrolipoamide dehydrogenase (E3 subunit) is encoded by *DLD*. In addition, phosphorylation of the complex inactivates it, while dephosphorylation by a phosphatase makes it active. Mutations in *BCKDHA* cause MSUD type 1A, and are responsible for 33% of cases, while mutations in *BCKDHB* cause MSUD type 1B, responsible for 38% of cases, and mutations in *DBT* cause MSUD type 2, responsible for 19% of all MSUD cases (Nellis and Danner, 2001). A founder mutation in *BCKDHA* is present in Old Order Mennonites, where the incidence of the disease reaches 1 in 150 individuals (Carleton et al., 2010). Mutations in *DLD* cause a different condition, E3 deficiency, sometimes called MSUD type 3. Finally, a mutation in *PPM1K*, encoding for the BCKDH phosphatase, has been associated with a mild variant of MSUD (Oyarzabal et al., 2013).

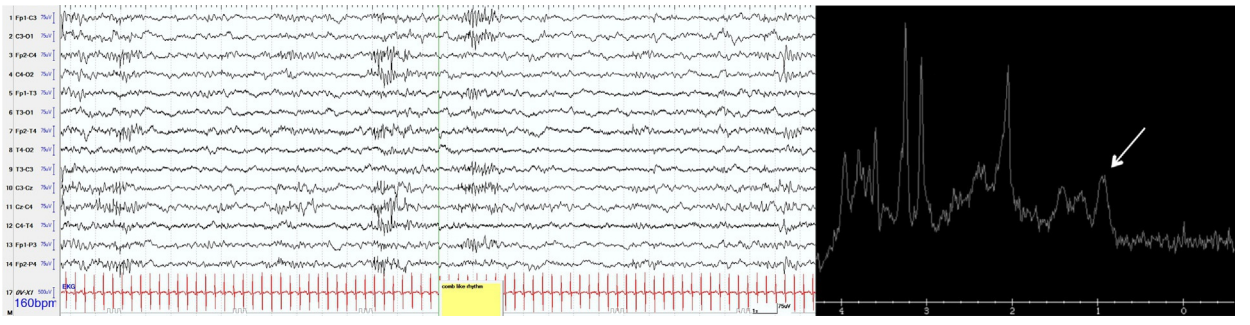

Fig. 22.1. Electroencephalogram showing comb-like rhythm in a newborn with MSUD (*left*). Brain magnetic resonance spectroscopy on the same patient with voxel placed over the left basal ganglia, showing a dominant peak at 0.9 ppm and other collection of peaks downstream spanning to 1.5 ppm, corresponding to BCAAs and BCKAs (*right*).

Biochemical defects and pathophysiology

MSUD is associated with elevation of branched-chain amino acids, leucine, isoleucine, and valine, as well as alloisoleucine, the latter being a pathognomonic finding for MSUD. Their corresponding ketoacids are also elevated, including α-Ketoisocaproic acid, α-keto-β-methylvaleric acid, and α-Ketoisovaleric acid.

Patients with the neonatal form of DLD deficiency can also have additional biochemical findings, including lactic acidosis and elevated urinary α-ketoglutrate, since the E3 subunit is shared with the pyruvate dehydrogenase complex and the α-ketoglutarate dehydrogenase complex.

The informative marker in newborn screening is XLE, which measures the combined concentration of leucine, isoleucine, and alloisoleucine. Hydroxyproline, however, also contributes to the XLE peak (Staufner et al., 2016).

The branched-chain amino acids compete with seven other large, neutral amino acids for crossing the blood–brain barrier via the same transporter, LAT1 (Strauss et al., 2010), thus interfering with neuronal protein synthesis. In addition, the α-Ketoisocaproic acid interferes with transamination reactions, thus leading to deficiency of neurotransmitters such as glutamate and GABA (Strauss et al., 1993). In addition, the accumulated α-Ketoisocaproic acid inhibits the Krebs cycle and causes ATP depletion which, in turn, likely leads to cerebral edema via failure of the Na+/K+ ATPase (Zinnanti et al., 2009).

Treatment and outcomes

The main aim of treatment is to control the plasma leucine concentration. In the acute setting, the provider should strive for a balance between enough protein intake to allow for growth, while at the same time avoiding protein excess and its consequent leucine elevation. A formula deprived of branched-chain amino acids is necessary, although supplementation of isoleucine and valine is also required, as these compete against neuronal intake of leucine. Sufficient calories should be administered in order to avoid catabolism; otherwise, muscle breakdown would lead to a paradoxical increase in leucine. Thus although dextrose infusions are often needed, hypotonic solutions should be avoided, as the hyponatremia associated with the metabolic crisis can worsen the cerebral edema. Hemodialysis or hemofiltration has often been used, in order to quickly remove branched-chain amino acids from circulation.

Some patients show response to thiamine supplementation, but this phenotype is caused by specific mutations in *DBT*, where at least one missense mutation falls in the inner core domain and produces a full-length mutant E2 (Chuang et al., 2006).

Approximately 9%–13% of the whole-body BCKDH activity is found in the liver (Suryawan et al., 1998). Thus a liver transplant is curative of the disease (Strauss et al., 2006).

FATTY ACID OXIDATION DEFECTS

Clinical symptoms

Typical presenting symptoms of fatty acid oxidation defects (FAODs) during the neonatal period include severe neonatal lactic acidosis, cardiomyopathy, and hepatopathy and may resemble a mitochondrial respiratory defect. Neurologically, the children may be encephalopathic, but there are no specific signs or symptoms. Overall, there is considerable phenotypic heterogeneity for FAODs. In infancy or early childhood, the key presenting feature is hypoketotic hypoglycemia, sometimes accompanied by signs of liver failure with hyperammonemia. Milder defects of long-chain fatty acid oxidation and the carnitine shuttle may affect skeletal muscle and become manifest in adolescence or early adulthood as recurrent myopathy and rhabdomyolysis or cause acute or chronic cardiomyopathies.

Genes

The very long-chain acyl-CoA dehydrogenase (VLCAD) is encoded by *ACADVL*, the medium-chain acyl-CoA dehydrogenase (MCAD) by *ACADM*, the LCHAD by *HADHA*, and the trifunctional protein by *HADHB*. The genes encoding proteins of the carnitine shuttle include *SLC22A5* (encoding the carnitine plasma membrane transporter), *CPT1A* (encoding carnitine palmitoyltransferase type 1), *SLC2520* (encoding the mitochondrial carnitine-acylcarnitine translocase, or CACT), and *CPT2* (encoding carnitine palmytoyltransferase 2).

All disorders in this group are inherited in an autosomal recessive fashion though heterozygotes can occasionally express symptoms, such as carrier mothers of long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency being at high risk of severe preeclampsia, acute fatty liver of pregnancy or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.

Biochemical defects and pathophysiology

Fatty acids are oxidized in the mitochondrial matrix. Although short- and medium-chain fatty acids can freely enter the mitochondrial matrix, long-chain fatty acids need to be bound to carnitine for entry inside the

mitochondria. Carnitine enters the cell via a plasma membrane transporter and is then bound to a fatty acid via the action of CPT1 at the outer mitochondrial matrix; subsequently, this fatty acid–bound carnitine (i.e., acylcarnitine) is transported inside the mitochondrial matrix by CACT, so that the fatty acid can be separated from carnitine by CPT2. Once this unbound fatty acid is available in the mitochondrial matrix, it undergoes four subsequent oxidation steps that culminate with the cleavage of two carbons in the form of acetyl-CoA. The oxidative enzymes are length dependent and thus there are specific enzymes for short-chain, medium-chain, and long-chain fatty acid oxidation. SCAD, MCAD, and VLCAD all participate in the first oxidative step (acting upon fatty acids of different carbon lengths), while LCHAD participates in the third oxidative step.

The inability to obtain energy from the oxidation of fatty acids leads to hypoglycemia. The lack of fatty acid oxidation leads to their increase in circulation and to a concomitant decrease in ketone body production, as fatty acid oxidation gives rise to acetyl-CoA, the substrate for ketone body synthesis. In cases of hypoglycemia, rapid determination of fatty acids (elevated) and ketones (low) is usually sufficient for recognition of FAODs. Acylcarnitine profiling in plasma is usually diagnostic, and urine acylglycines can be particularly sensitive for diagnosis. Specific dicarboxylic acids can be identified on organic acid analyses. Enzyme studies (leukocytes, fibroblasts) and molecular studies are required for confirmation.

Central in the pathophysiology of FAODs is both the energy deficiency and the intoxication. The mitochondrial respiratory dysfunction in FAODs is caused by the accumulation of toxic long-chain acylcarnitines, particularly in long-chain fatty acid oxidation disorders. The hypoketotic hypoglycemia seen in neonates and young children is caused by insufficient ketone body production in combination with inhibition of gluconeogenesis by low acetyl-CoA during catabolic states. The renal excretion of large amounts of acylcarnitines can lead to secondary carnitine deficiency and the consequent decrease in long-chain fatty acid oxidation.

Treatment and outcomes

When there is a diagnostic suspicion during the acute phase, avoid fasting and aim for anabolism by providing high-dose glucose. Intravenous lipids are contraindicated, as they will cause a rise in fatty acids, which cannot be oxidized due to the metabolic block. For long-chain FAODs, medium-chain triglycerides are administered, as these bypass the metabolic block.

If there is a persistent severe reduction of serum carnitine concentrations, then consider carnitine supplementation (up to 50–100 mg/kg/day); please note this may be detrimental in disorders of long-chain fatty acid oxidation or the carnitine cycle (as long-chain acylcarnitines can be cardiotoxic). Carnitine supplementation is not usually necessary for MCAD deficiency.

As with other IEMs, early diagnosis and treatment are essential for good outcomes. Currently, in many countries tandem mass spectrometry (MS/MS) in newborn screening programs identifies many of the fatty acid oxidation defects. Not surprisingly, when identified presymptomatically, many of the disorders have a mild phenotype. Patients with the long-chain enzyme defects can still suffer considerable symptoms, which include cardiomyopathy, hepatopathy, and recurrent rahbdomyolysis, despite early detection and treatment.

PRIMARY LACTIC ACIDOSIS

Clinical symptoms

The most common cause of primary lactic acidosis is pyruvate dehydrogenase (PDH) complex deficiency. The more severe form of the disease presents with intractable lactic acidosis at birth, leading to neonatal death. The lactic acidosis is accompanied by respiratory distress. Milder forms of the disease present with more moderate lactic acidosis, and common findings later in the clinical course include developmental delay, hypotonia, seizures, microcephaly, and ataxia (Patel et al., 2012). Typical dysmorphisms include a prominent forehead, wide nasal bridge, anteverted nares, and long philtrum with thin vermillion of the upper lip, reminiscent of the dysmorphic features seen in fetal alcohol syndrome. Structural brain anomalies can be detected in utero via fetal MRI, and include paraventricular pseudocysts, hypoplastic corpus callosum, ventriculomegaly, and delayed gyration, while IUGR can be seen on prenatal ultrasound (Pirot et al., 2016). About 27% of patients with PDH complex deficiency have neuroimaging findings consistent with Leigh syndrome (Patel et al., 2012).

Leigh syndrome, also known as subacute necrotizing encephalomyelopathy, is a neurodegenerative disorder characterized by focal, bilateral, symmetric lesions in one or more areas of the central nervous system, including the basal ganglia, thalamus, and brainstem. Clinically, it is accompanied by periods of stepwise developmental regression in the setting of intercurrent illness. Typical onset is between 3 and 12 months of age, with a median of 7 months, although perinatal onset is seen in 13.1% of patients (Sofou et al., 2014). The most common neurologic features include abnormal motor findings in 99% (with hypotonia in 75% and dystonia in 45% of patients), abnormal ocular findings in 61%

(with nystagmus in 24%, strabismus in 19%, and optic atrophy in 15% of patients), seizures in 39%, and intellectual disability in 37%. Extraneurologic features include feeding difficulties in 45%, respiratory dysfunction in 38%, and cardiac dysfunction in 18% (Sofou et al., 2014).

Pyruvate carboxylase deficiency can present with three different phenotypes. The most severe form is the French phenotype or type B, in which neonates present within the first 3 days of life with hypothermia, tachypnea, and severe truncal hypotonia. Nemaline rods can be seen on muscle biopsy (Unal et al., 2013). A hypokinetic-rigid syndrome of neonatal onset is also seen with this form of the disease, accompanied by high-amplitude tremor, hypokinesia, and abnormal eye movements (García-Cazorla et al., 2006). Hepatomegaly and failure to thrive can also be a part of this phenotype, which typically has a poor prognosis, with death within the first few months of life. The type A form is also known as the North American phenotype, as it is seen more commonly in native North American Ojibwa, Cree, and Micmac tribes of the Algonquin-speaking peoples, where the carrier frequency is as high as 1 in 10 (Carbone et al., 1998). Patients with this phenotype present at 2–5 months of age with failure to thrive, developmental delay, seizures, pyramidal signs, ataxia, and nystagmus; renal tubular acidosis has also been described (Marin-Valencia et al., 2010). The progressive course of this phenotype also leads to death within a few years of life. The mildest form of the disease is type C, or intermittent phenotype, that shows no clear ethnic predilection. Development is near normal, and patients present with recurrent episodes of lactic acidosis and ketoacidosis.

All of the aforementioned disorders present with lactic acidosis. The lactate/pyruvate (L/P) ratio is reflective of the redox state (NADH/NAD ratio) of the cytosol, while the beta-hydroxybutyrate/acetoacetate (BHB/AcAc) ratio reflects the NADH/NAD ratio inside the mitochondria. PDH deficiency and pyruvate carboxylase deficiency types A and C have a normal L/P molar ratio (<20); pyruvate carboxylase deficiency type B presents with an elevated L/P ratio but a decreased BHB/AcAc ratio (<0.8); and respiratory chain disorders present with an elevated L/P ratio with a normal or elevated BHB/AcAc ratio (Marin-Valencia et al., 2010). It should be noted that the sensitivity and specificity of the L/P ratio in differentiating these various etiologies of lactic acidosis increases with higher lactate concentrations, while the ratio is not useful with lactate values of <2.5 mmol/L (Debray et al., 2007). Other laboratory findings in the type B form of pyruvate carboxylase deficiency include paradoxical postprandial ketosis, high concentrations of lysine, proline, and citrulline, and hyperammonemia with low glutamine levels.

Genes

Conditions in which lactic acidosis is a primary feature of the disease process include PDH complex deficiency, pyruvate carboxylase deficiency, and other disorders of gluconeogenesis, disorders of the Krebs cycle, and mitochondrial respiratory chain defects.

The PDH complex is composed of an E1 component (also called pyruvate decarboxylase), E2 component (also called dihydrolipoamide acetyltransferase), E3 subunit (common to that of BCKDH and α-ketoglutarate dehydrogenase), and an E3 binding protein, also known as component X. The complex is regulated by phosphorylation, where a kinase inactivates it, while a phosphatase activates the complex by dephosphorylation. The E1 component is composed of an E1-α subunit, encoded by *PDHA1*, and an E1-β subunit, encoded by *PDHB*. E2 is encoded by *DLAT*, E3BP is encoded by *PDHX*, and the phosphatase is encoded by *PDP1*. Mutations in either of these genes cause PDH complex deficiency, but the most common form is caused by mutations in *PDHA1*, accounting for 84% of cases (Patel et al., 2012). The *PDHA1* gene is located in the X chromosome, so the most common form of PDH complex deficiency is X-linked dominant, with females being more severely affected than males. The other, rarer forms of PDH complex deficiency are inherited in an autosomal recessive manner.

A deficiency of 3-hydroxyisobutyryl-CoA hydrolase (encoded by *HIBCH*) or of short-chain enoyl-CoA hydratase deficiency (encoded by *ECHS1*) can also be accompanied by lactic acidosis (Reuter et al., 2014; Ganetzky et al., 2016), as the accumulated methylacrylyl-CoA metabolites cause secondary inhibition of the PDH complex (Peters et al., 2015).

Leigh syndrome can be caused by mutations in dozens of different genes, giving rise to nuclear-encoded or mitochondrial DNA-encoded subunits of any of the mitochondrial respiratory chain complexes (Rahman and Thorburn, 1993; Thorburn et al., 1993; Ruhoy and Saneto, 2014).

Other conditions that can present with primary neonatal lactic acidosis include Sengers syndrome, given a decrease in the expression of the adenine nucleotide translocator (Mayr et al., 2012), mitochondrial pyruvate carrier deficiency (Brivet et al., 2003), or primary CoQ10 deficiency caused by mutations in the *COQ9* gene (Danhauser et al., 2016).

Pyruvate carboxylase is encoded by *PC*.

Biochemical defects and pathophysiology

PDH complex deficiency and mitochondrial respiratory chain deficiencies lead to disease resulting from energy

depletion (insufficient ATP synthesis). In PDH deficiency in particular, pyruvate cannot be converted to acetyl-CoA, which, in addition to oxaloacetate, represents one of the substrates for citrate synthesis. The similarities in dysmorphic facial features described in PDH complex deficiency and those of fetal alcohol syndrome are likely explained by the fact that acetaldehyde, a metabolite of ethanol, is known to inhibit PDH activity (Hard et al., 2001).

Pyruvate carboxylase deficiency represents not only a defect in gluconeogenesis, but also a Krebs cycle defect. It is necessary for converting pyruvate to oxaloacetate, so the enzyme is important for anaplerosis of Krebs cycle intermediates (DeVivo et al., 1977). The hyperammonemia and hypercitrullinemia is caused by a deficiency of aspartate, as the latter is interconverted with oxaloacetate, and is an important urea cycle substrate for argininosuccinate synthetase. The increased lysine is caused by decreased concentrations of α-ketoglutarate, necessary for the mitochondrial catabolism of lysine. The increased proline is caused by inhibition of proline oxidase by lactic acid. The paradoxical ketosis is caused by increased availability of pyruvate for conversion into acetyl-CoA, a precursor to ketone body formation.

Treatment and outcomes

Sodium bicarbonate or dichloroacetate can be used to neutralize the lactic acid. Thiamine is frequently used in patients with PDH deficiency (Patel et al., 2012); responsiveness to thiamine (>400 mg/day) is more likely in those presenting after the first year of life, and with relapsing ataxia or possibly Leigh syndrome rather than with neonatal lactic acidosis or callosal anomalies (van Dongen et al., 2015). Ketogenic diet is used as a means of replenishing acetyl-CoA for citrate synthesis and is associated with clinical improvements in the areas of seizures, ataxia, sleep disturbance, and neurocognitive development (Sofou et al., 2017).

In pyruvate carboxylase deficiency, on the other hand, ketogenic diet is contraindicated, as it can worsen the ketoacidosis. One patient with the type B form was treated with high doses of citrate and aspartate, leading to some improvement in metabolic control—manifested by decreased lactate and ketone levels and near normalization of plasma amino acids—but the neurologic outcome still remained poor (Ahmad et al., 1999). Triheptanoin has also been used for the purpose of replenishing Krebs cycle intermediates; in one patient it led to marked metabolic improvement and even clinical improvement without evidence of neurodegeneration; however, the patient died during an episode of intercurrent illness (Mochel et al., 2005). In 2 other patients, it led to no clinical or biochemical improvement (Breen et al., 2014). One patient underwent orthotopic liver transplantation, which completely reversed the ketoacidosis and the renal tubular abnormalities, and it also decreased the lactic acidosis, but the preexisting brain damage remained unaltered (Nyhan et al., 2002).

NONKETOTIC HYPERGLYCINEMIA (GLYCINE ENCEPHALOPATHY)

Clinical symptoms

Patients with classic nonketotic hyperglycinemia (NKH) present with neonatal apnea, hypotonia, and seizures. Ninety percent of patients will have seizures, starting during the first month of life in 75% of cases (Hoover-Fong et al., 2004). About two-thirds of neonates will require ventilatory support during the first 10–20 days of life, and about one-third of all patients will die in the newborn period. Of those who survive, severe intellectual disability is the rule, with up to 20% eventually learning how to walk or how to say or sign words (Hoover-Fong et al., 2004).

Neuroimaging findings commonly include hypoplasia of corpus callosum and restricted diffusion of fibers that are myelinated at birth, such as the posterior limb of the internal capsule and the corticospinal tracts (Khong et al., 2003; Zubarioglu et al., 2016), although this latter finding disappears after infancy (Mourmans et al., 2006). A glycine peak at 3.5 ppm can also be detected by magnetic resonance spectroscopy (Heindel et al., 1993; Huisman et al., 2002).

Laboratory findings include an elevation of both plasma and CSF glycine concentrations. The CSF/plasma glycine ratio is higher than 0.08 in the severe classic form of the disease, while a cutoff of 0.04 is used for the attenuated classic form of the disease. A variant form of NKH also exists, which can be accompanied by an elevated concentration of lactate and certain organic acids such as α-ketoglutarate and aminoadipic acid. Other causes of hyperglycinemia include organic acidemias such as propionic acidemia, methylmalonic acidemia, isovaleric acidemia, and ß-ketothiolase deficiency (although these cause ketotic hyperglycinemia), valproate administration, PNPO deficiency, and perinatal hypoxic–ischemic injury due to breakdown of the blood–brain barrier leading to increased CSF glycine concentration (Van Hove et al., 1993).

Genes

Glycine is catabolized by the glycine cleavage system (GCS), composed of four proteins, and is fully expressed in the mitochondria of liver, kidney, and brain cells

(Kikuchi et al., 2008). The four components are: (1) the P-protein, a pyridoxal phosphate-dependent glycine decarboxylase, encoded by the *GLDC* gene; (2) the T-protein, a tetrahydrofolate-requiring aminomethyl transferase, encoded by the *AMT* gene; (3) the H-protein, a lipoic acid–containing carrier protein; and (4) the L-protein, or dihydrolipoamide dehydrogenase; the gene encoding this latter protein is still unknown, as controversy remains regarding the possibility of the E3-encoding *DLD* being the culprit gene. Mutations in *GLDC* account for 75%–80% of patients, while mutations in *AMT* account for 15%–20%, and mutations in *GCSH* explain less than 1% (Van Hove et al., 1993).

Variant NKH can be caused by mutations in: (1) *LIPT2*, due to impaired transfer of octanoic acid from an acyl carrier protein to the H-protein (Habarou et al., 2017); (2) *LIAS*, due to impaired lipoic acid synthesis from octanoic acid in the H-protein (Baker et al., 2014); and (3) mutations in *NFU1*, *IBA57*, *ISCA2*, *GLRX5*, and *BOLA3*, from deficient synthesis of the iron–sulfur cluster needed for the lipoic acid synthetase (Tort et al., 2016).

A form of glycine encephalopathy with normal serum glycine was recently described, caused by mutations in *SLC6A9*, encoding the glycine transporter 1 (Kurolap et al., 2016). This transporter is expressed mainly on astrocytes and is essential for clearance of glycine from the synaptic cleft. Mutations in *SLC6A5*, encoding the glycine transporter 2 expressed at glycinergic presynaptic terminals and needed for refilling presynaptic vesicles, are associated with hyperekplexia. The latter is characterized by generalized stiffness and exaggerated startle reflexes triggered by unexpected loud sounds or tactile stimulation and can also be caused by mutations in *GLRA1 or GLRB,* genes encoding glycine receptor subunits.

Biochemical defects and pathophysiology

Glycine is normally catabolized by the glycine cleavage system, the main activity of which is expressed in the liver. Patients with defects in the P-protein typically have no residual enzyme activity, while patients with defects in the T-protein can have activity up to 25% of normal values (Van Hove et al., 1993).

Glycine is a major neurotransmitter, which can be both inhibitory and excitatory, depending on the specific receptors to which it binds. By binding to glycine receptors, it acts as an inhibitory neurotransmitter, while it can also be a coagonist for excitatory glutamatergic NMDA receptors.

Variant NKH is caused by defects in the synthesis or incorporation of lipoic acid, needed for the function of the core H-protein. Since lipoic acid is also needed as a cofactor for PDH, α-ketoglutarate dehydrogenase, and α-ketoadipate dehydrogenase, patients with variant NKH can have increased levels of lactate and organic acids such as α-ketoglutarate and aminoadipic acid.

Treatment and outcomes

Benzoate is used with the purpose of decreasing plasma glycine concentrations between 120 and 300 μmol/L, as it conjugates to glycine to form hippuric acid, which is readily excreted in the urine. Benzoate is beneficial to decrease the number of seizures and increase alertness. Dextromethorphan and ketamine can be tried, given their effect as NMDA receptor antagonists. Regardless of treatment, neurologic outcomes remain poor for the classic severe form of the disease. Valproic acid should be avoided, as it inhibits the glycine cleavage system.

MOLYBDENUM COFACTOR DEFICIENCY AND ISOLATED SULFITE OXIDASE DEFICIENCY

Clinical symptoms

The presenting features of this condition include seizures in 72%, feeding difficulties in 26%, hypotonia in 11%, developmental delay in 9%, hemiplegia in 2%, and lens dislocation in 2%. Median age at onset is in the first day of life, with a median diagnostic delay of 89 days (Mechler et al., 2015). Seizures are typically intractable. Hyperekplexia can also be seen (Macaya et al., 2005; Holder et al., 2014), and, in fact, was seen in 5 of 9 patients in one series (Zaki et al., 2016).

The typical neuroimaging finding is that of T2-weighted hyperintensity, as well as hyperintense signal on DWI with hypointensity on apparent diffusion coefficient (i.e., restricted diffusion) in the cortex and subcortical white matter, suggestive of cytotoxic edema. Sometimes there is sparing of the frontal or temporal areas (Poretti et al., 2013). Subsequently, the edema decreases and cystic encephalomalacia appears (see Fig. 22.2, obtained from a 1-day-old patient with isolated sulfite oxidase deficiency) (Sass et al., 2010). Both the clinical and neuroradiologic changes can mimic those of hypoxic–ischemic encephalopathy (Topcu et al., 2001; Hobson et al., 2005), but they tend to be more severe (Hoffmann et al., 2007). Poor gyration and poor differentiation of cortical layers can be appreciated on fetal MRI as early as 21 weeks' gestation (Lee et al., 2017a).

Uric acid concentrations are low while xanthine levels are high in molybdenum cofactor deficiency, but normal in isolated sulfite oxidase deficiency. Elevated urine

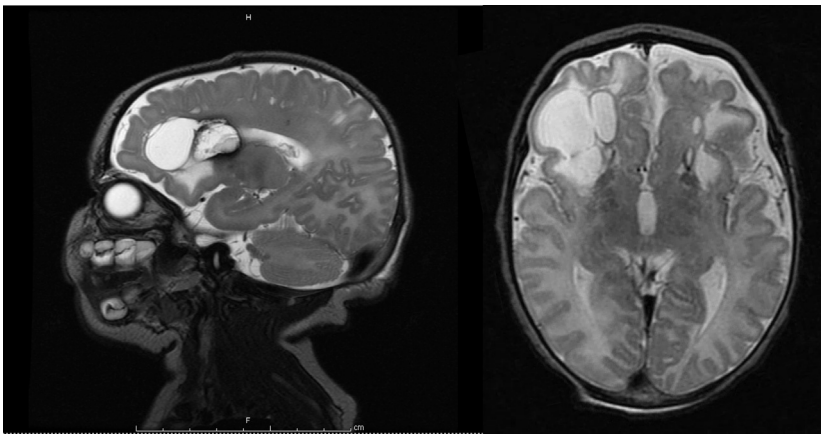

Fig. 22.2. Sagittal (*left*) and axial (*right*) T2-weighted imaging showing multiple cystic changes in a 3-day-old girl with isolated sulfite oxidase deficiency.

sulfite and *S*-sulfocysteine, as well as low cysteine concentrations, are seen in both conditions. The urinary levels of α-aminoadipic semialdehyde (AASA) are also elevated in both conditions (Mills et al., 2012).

Genes

MOCS1 is necessary for the synthesis of cyclic pyranopterin monophosphate (cPMP) from guanosine triphosphate (GTP), while *MOCS2* and *MOCS3* encode enzymes that convert cPMP into molybdopterin, and the latter is converted to molybdenum cofactor by gephyrin (encoded by *GPHN*). Mutations in *MOCS1* cause molybdenum cofactor deficiency type A; a mutation in *MOCS2* causes type B, while mutations in *GPHN* are associated with type C (Atwal and Scaglia, 2016). Around two-thirds of patients have mutations in *MOCS1*. Sulfite oxidase is encoded by *SUOX*.

Biochemical defects and pathophysiology

The enzymes requiring molybdenum cofactor include sulfite oxidase (which converts sulfite to sulfate), xanthine oxidase (catalyzing the conversion of xanthine to uric acid), aldehyde oxidase, and mitochondrial amidoxime reducing component (Atwal and Scaglia, 2016). Thus, an inability to synthesize molybdenum cofactor will lead not only to a deficiency of sulfite oxidase, but also to a deficiency of the other three enzymes. The accumulation of sulfite stems from the deficiency of sulfite oxidase, while the decrease in cysteine concentration is a result of the conjugation of sulfite with cysteine to form S-sulfocysteine, a diagnostic marker. The accumulation of sulfite also leads to inhibition of specific enzymes, such as AASA dehydrogenase (Mills et al., 2012). The increase in urinary xanthine and decrease in uric acid are a result of the decreased activity of xanthine oxidase in the absence of molybdenum cofactor; this also explains why both are normal in the setting of isolated sulfite oxidase deficiency.

Treatment and outcomes

Median survival is 36 months (Mechler et al., 2015). Biochemical and neurodevelopmental improvement can be seen in patients with molybdenum cofactor deficiency type A who are treated with cPMP infusions, as long as treatment is started as early as possible (Schwahn et al., 2015).

DISORDERS OF GABA METABOLISM

Clinical symptoms

GABA transaminase deficiency presents with symptoms of neonatal or infantile encephalopathy, including severe intellectual disability, hypotonia, hyperreflexia, a high-pitched cry, refractory epilepsy, and accelerated linear growth from increased growth hormone (GH) concentrations, the latter likely related to the GH-releasing effect of GABA (Medina-Kauwe et al., 1999). Hypersomnolence was found in all patients diagnosed to date (Besse et al., 2016; Koenig et al., 2017), and choreoathetosis has also been described (Koenig et al., 2017; Nagappa et al., 2017). Symptoms can start a few days after birth (Jaeken et al., 1984), and in fact neonatal onset was noted in 4 of 10 patients (Koenig et al., 2017). Brain MRS can identify elevated GABA (Tsuji et al., 2010), with a peak between 2.2 and 2.4 ppm (Nagappa et al., 2017). Characteristic laboratory findings include elevated GABA and beta-alanine levels in CSF and plasma (Medina-Kauwe et al., 1999).

Succinic semialdehyde dehydrogenase (SSADH) deficiency is associated with developmental delay and intellectual disability in all patients, hypotonia in 82%, ataxia in 77%, and seizures in 45% (Pearl et al., 2009). Mean age of onset is 11 months, but it can present in the neonatal period. Neuroimaging reveals pallidal, dentate, and subthalamic nucleus T2 hyperintensities (Ziyeh et al., 2002; Pearl et al., 2009). Urine organic analysis shows marked elevation of 4-hydroxybutyric acid (also known as gamma-hydroxybutyric acid or GHB). Other elevated organic acids include 4,5-dihydroxyhexanoic acid, 3-hydroxyproprionic acid, and dicarboxylic acids (Brown et al., 1987).

Genes

GABA transaminase is encoded by *ABAT*, while SSADH is encoded by *ALDH5A1*.

Biochemical defects and pathophysiology

GABA is metabolized to succinic semialdehyde by GABA transaminase, while SSADH metabolizes succinic semialdehyde to succinic acid. GABA is the main inhibitory neurotransmitter and is known to play a role in the pathogenesis of seizures in SSADH deficiency (Wu et al., 2006). In addition, GABA transaminase is also known to play a role in the mitochondrial nucleoside salvage pathway, as it converts dNDPs to dNTPs (Besse et al., 2015).

The 4-hydroxybutyric acid derives from succinic semialdehyde, while 4,5-dihydroxyhexanoic acid arises from condensation with a two-carbon intermediate in the PDH reaction, 3-hydroxyproprionic acid derives from alpha-oxidation of 4-hydroxybutyric acid, and the dicarboxylic aciduria results from secondary inhibition of mitochondrial beta-oxidation (Brown et al., 1987; Jakobs et al., 1993).

Treatment and outcomes

Flumazenil, a GABA-A receptor antagonist, has been used in two patients, leading to clinical and electrographical improvement in one, but no clinical benefit in another (Koenig et al., 2017). In theory, vigabatrin should be avoided, as it is an irreversible inhibitor of GABA transaminase (Besse et al., 2016).

Treatment of SSADH is symptomatic. A clinical trial of SGS-742, a GABA-B receptor antagonist, is currently taking place. It should be noted that valproic acid inhibits any residual SSADH enzyme activity, although it has been used in a few patients with improved seizure control (Vanadia et al., 2013).

PYRIDOXINE-DEPENDENT EPILEPSY

Clinical symptoms

Pyridoxine-dependent epilepsy (PDE) due to antiquitin (ATQ) deficiency typically presents with neonatal or early infantile seizures, which are refractory to pharmacologic anticonvulsive treatment but responsive to pyridoxine (vitamin B6) treatment. Seizures may occur in utero, with onset at the end of the last trimester.

The encephalopathy in neonates with ATQ deficiency may present as hyperalertness, motor hyperactivity, insomnia, and feeding refusal, resembling withdrawal from intrauterine substance exposure. Coexisting signs of birth asphyxia/perinatal stress are frequently encountered. Prolonged episodes of mixed multifocal myoclonic tonic symptoms, associated with grimacing and abnormal eye movements, are typical. Neonatal lactic acidosis, hypoglycemia, and electrolyte disturbances have been reported.

Milder variants with self-limited seizures (generalized, partial, atonic, myoclonic, infantile spasms), initial response to common anticonvulsants, and later childhood onset, (up to 3 years of age) may account for up to 30% of cases. Breakthrough seizures may occur during episodes of febrile illness or gastroenteritis, which reduces the bioavailability of pyridoxine.

Although there are no specific imaging findings in ATQ deficiency, mega cisterna magna, neuronal migration abnormalities, and progressive hydrocephalus requiring shunting have been reported in several patients, and varying degrees of cerebral atrophy have been described in late-diagnosed patients. White matter abnormalities are present in neonates and may resolve within the first year of life, while they can also be progressive over time. Intracerebral and retinal bleedings as well as intrauterine subependymal cysts add to the myriad of changes. ATQ is expressed within glial cells in the brain, and its dysfunction in PDE is associated with neuronal migration abnormalities and other structural brain defects, which might explain the limited developmental outcomes.

Gene

ALDH7A1 encodes for α-aminoadipic-semialdehyde dehydrogenase (AASAD) (also known as ATQ), the function of which lies in the catabolism of lysine.

Biochemical defects and pathophysiology

AASAD catalyzes the conversion of AASA and P6C into α-aminoadipic acid. Elevated concentration of α-aminoadipic semialdehyde (α-AASA) and P6C in

urine and plasma are a strong biomarker of the disorder; pipecolic acid may also be elevated in plasma and cerebrospinal fluid.

In ATQ deficiency, accumulating P6C results in a spontaneous chemical reaction with pyridoxal phosphate (PLP) and its inactivation via formation of a P6C–PLP complex. The accumulation of α-AASA, a reactive semialdehyde, might undergo multiple chemical reactions within the cell and thus interact with various metabolic pathways. Finally, the biochemical fate and potential toxicity of the PLP/P6C complex is unknown.

Treatment and outcomes

Treatment consists of the administration of 100 mg of pyridoxine intravenously, in a controlled setting, given that a sizable proportion of patients can develop apnea. Clinical seizures typically cease several minutes after administration of pyridoxine, while electrographic seizures can show a lag of several hours before resolution (Gospe, 1993). If there is no clinical response, the dose can be repeated up to a maximum of 500 mg. Alternatively, oral pyridoxine can be tried at a dose of 30 mg/kg/day, but in those cases, cessation of seizures might take up to 1 week. Chronic management also involves oral pyridoxine supplementation; during an acute illness, the daily dose of pyridoxine may be doubled for several days. It should be noted that pyridoxine overuse can cause a reversible sensory neuropathy that is seen typically with doses exceeding 900 mg/day but not with doses under 500 mg/day (Morris et al., 2017).

While treatment with pyridoxine compensates chemical PLP inactivation, it does not reduce the accumulation of lysine degradation products. These potentially neurotoxic compounds could explain the limited efficacy of pyridoxine, as 75%–80% of patients suffer intellectual disability despite excellent seizure control. Thus, a triple therapy was introduced consisting of pyridoxine, dietary lysine restriction to limit the neurotoxic metabolite accumulation, and L-arginine to compete for brain lysine influx and liver mitochondrial import (van Karnebeek et al., 2012a). Several studies report the effects of triple therapy, which reduced CSF, plasma, and urine biomarkers associated with neurotoxicity in PDE and appeared to improve neurodevelopmental outcomes (Coughlin et al., 2015). In such cases, residual symptoms might be related to early injury.

PYRIDOX(AM)INE-5′-PHOSPHATE OXIDASE DEFICIENCY

Clinical symptoms

The clinical presentation of PNPO deficiency is not distinguishable from PDE. Neonatal epileptic encephalopathy is frequently associated with prematurity. Seizure semiology may be tonic, clonic and myoclonic, focal or generalized, with burst suppression patterns and hypsarrhythmia on the EEG; onset is either in the neonatal period or within the first 6 months of life. Systemic comorbidities include anemia, coagulopathy, hypoglycemia, and lactic acidosis, giving rise to the suspicion of a primary mitochondrial disease.

Decreased pyridoxal-5′-phosphate (PLP) values in CSF of affected neonates have been reported. Because PLP is an essential cofactor of aromatic amino acid decarboxylase (AADC), reduced PLP synthesis in PNPO deficiency results in AADC-like neurotransmitter changes, including decreased serotonin (hydroxyindolacetic acid, HIAA) and dopamine (homovanillic acid, HVA) markers, and elevated 3-*O*-methydopa, vanillactic acid, and 5-hydroxytryptophan.

Gene

Biallelic mutations in *PNPO* cause this defect.

Biochemical defects and pathophysiology

PNPO catalyzes the synthesis of PLP from pyridoxine and pyridoxamine. It requires flavin mononucleotide (riboflavin-5′-phosphate) as a tightly bound (prosthetic) cofactor. Because of the inability to produce sufficient amounts of pyridoxal out of pyridoxine and pyridoxamine, patients with PNPO deficiency have reduced capacity to generate PLP, which is the active form of vitamin B6. There is no specific diagnostic marker for PNPO deficiency. Thus, in every patient at risk, molecular analysis of the *PNPO* gene is required to establish the diagnosis. Clinical responsiveness to pyridoxine does not exclude PNPO deficiency, and patients who are PDE negative for ATQ deficiency should be tested for PNPO deficiency. Because seizure exacerbation has been reported with high PLP dosages, PNPO mutation analysis might be considered in this type of patient as well.

Other genetic defects that may present as vitamin B6-responsive epilepsies include PROSC deficiency (Darin et al., 2016), hypophosphatasia (Baumgartner-Sigl et al., 2007), hyperprolinemia type 2 (Farrant et al., 2001), and GPI anchoring defects (Thompson et al., 2006).

Treatment and outcomes

Based on clinical responsiveness there seem to be at least three groups of patients: (1) patients who exclusively respond to PLP; (2) patients who respond to pyridoxine and PLP; and (3) patients who respond to pyridoxine but deteriorate upon PLP. Mutations affecting the binding

site of pyridoxine might explain why some patients respond to it. For PLP, the usual administered dosages vary between 30 and 60 mg/kg/day; liver function should be monitored during treatment, as abnormalities varying from elevated transaminases to fibrosis have been reported.

Because PNPO is a flavin mononucleotide-dependent enzyme, patients might benefit from riboflavin supplementation, particularly in the case of a mutation affecting the binding site to this cofactor. There are no reports about prenatal treatment of PNPO deficiency with PLP or pyridoxine.

There is limited information about long-term outcomes of treated PNPO deficiency. Compared to ATQ deficiency, outcomes seem to be less favorable. Seizure control is variable. Most children show marked developmental delay/intellectual disability, but there are also patients with minor or no cognitive impairments.

SERINE BIOSYNTHESIS DISORDERS

Clinical symptoms

The most common serine biosynthetic defect is 3-phosphoglycerate dehydrogenase (3-PGDH) deficiency. In the severe infantile form, patients present with congenital microcephaly, intractable seizures, and severe psychomotor retardation. Seizures can occur shortly after birth and show a limited response to standard antiepileptic drugs. Several seizure types have been observed in 3-PGDH deficiency; infants can present with classical West syndrome or can display a wide variation of clinical seizures such as tonic–clonic seizures, tonic seizures, atonic seizures, gelastic seizures, and myoclonic seizures. The EEG patterns also vary, as both hypsarrhythmia and multifocal seizure activity evolving toward Lennox–Gastaut syndrome have been observed in infants and children with 3-PGDH deficiency. On brain MRI, hypomyelination and severe white matter atrophy can be observed. The neurologic abnormalities arise before birth, given the congenital microcephaly. Milder presentations have been described, and this juvenile form presents with seizures of different types occurring during childhood and developmental delays that were mild to moderate with normocephaly.

Phosphoserine aminotransferase (PSAT) deficiency and phosphoserine phosphatase (PSPH) deficiency are rarer. The reported features include acquired microcephaly, treatment-resistant seizures, psychomotor delay, hypertonia, and feeding difficulties. All forms of serine biosynthesis defects can also present with extraneurologic features, particularly ichthyosis, while the more severe form of the disease is characterized by multiple congenital anomalies including IUGR, arthrogryposis, hypoplastic eyelids with ectropion, eclabion, micrognathia, lissencephaly, and premature death, a phenotype known as Neu–Laxova syndrome (Acuna-Hidalgo et al., 2014; Shaheen et al., 2014).

The diagnosis of serine deficiency can be made relatively easily with routine amino acids analyses of plasma and CSF, but one should bear in mind that plasma amino acid concentrations are influenced by the diet and therefore need to be taken after an overnight fast. Amino acids in CSF are not influenced by dietary absorption of amino acids and are, therefore, preferred. Additional biochemical markers in CSF are low concentrations of 5-methyltetrahydrofolate (5-MTHF) and D-serine.

Biochemical defects and pathophysiology

Three main enzymes are required to convert phosphoglycerate into L-serine, namely 3-PGDH, PSAT, and PSPH. The essential role of the de novo synthesis of the amino acid L-serine in the development and functioning of the CNS is illustrated by the severity of the phenotypes and the response to prenatal treatment. L-serine displays many metabolic functions during different developmental stages, including the provision of precursors for amino acids (in particular glycine), protein synthesis, nucleotide synthesis, neurotransmitter synthesis, and L-serine derived lipids.

Genes

Biallelic mutations in three genes cause the inborn errors of L-serine biosynthesis: 3-*PGDH*, *PSAT*, and *PSPH*.

Treatment and outcomes

Therapy is straightforward, i.e., oral or enteral administration of L-serine 200–600 mg/kg/day until normalization of L-serine in blood and ideally in CSF. If seizures persist, glycine should be added up to a maximal dose of 200 mg/kg/day. In cases with low 5-methyltetrahydrofolate (5-MTHF), additional treatment with folinic acid (10 mg/day) should be provided.

Oral L-serine supplementation has proven to be effective in the treatment of seizures in these patients, especially those with 3-PGDH deficiency; also, a remarkable increase of white matter volume on MRI has been noted. The effect of therapy on the patients' psychomotor development during long-term follow-up was much less. Prenatal treatment of a mother with L-serine has proven effective; 1 case with 3-PGDH deficiency born to a mother who was treated from week 27 onward did not develop any of the neurologic symptoms of the disorder (de Koning et al., 2004).

LYSOSOMAL STORAGE DISORDERS

Clinical symptoms

Type 2, or acute neuronopathic Gaucher disease, is a progressive neurodegenerative condition with death occurring within the first few years of life. Neurologic manifestations can include arthrogryposis, hypokinesia, microcephaly, rigidity, and neck retroflexion followed by frank opistothonus and brainstem involvement with convergent strabismus, poor suck and swallow reflexes, dysphagia, aspiration, and apnea (Gupta et al., 2011; Weiss et al., 2015). Myoclonus, seizures, and supranuclear gaze palsy can also occur. Extraneurologic involvement includes congenital splenomegaly and frequently hepatomegaly. Two characteristic findings that should raise suspicion for this disease include hydrops fetalis and neonatal ichthyosis, the latter sometimes leading to a collodion baby phenotype.

The neonatal form of Farber disease, also called type 4, presents with severe neurologic disease, such as joint contractures, and extraneurologic manifestations, such as hepatosplenomegaly, lymphadenopathy, and thrombocytopenia (Antonarakis et al., 1984; Nowaczyk et al., 1996). It can also be accompanied by hydrops fetalis (Alves et al., 2013), cholestasis (Willis et al., 2008), and macular cherry-red spots (Nowaczyk et al., 1996). The classic triad of arthropathy, subcutaneous nodules, and hoarseness is initially absent in this form of the disease, which is associated with death in the first year of life.

The deficiency of prosaposin—also known as combined saposin deficiency or Farber disease type 7—causes a neonatal form of neurodegeneration presenting immediately after birth with hyperkinetic movements, multifocal myoclonus, respiratory insufficiency, generalized seizures, and hepatosplenomegaly, gyration abnormalities on neuroimaging, and death within the first few months of life (Harzer et al., 1989; Schnabel et al., 1992; Elleder et al., 2005; Kuchar et al., 2009). It can present prenatally with joint contractures (Harzer et al., 1989). It can be confused with Gaucher disease type 2, particularly considering that both have decreased enzyme activity of glucocerebrosidase. However, clues aiding the clinician in making the correct diagnosis include lysosomal enzyme assays revealing deficiency not only of glucocerebrosidase but also ceramidase and galactocerebrosidase, and sphingolipid assays in tissues or urine showing increased concentrations of multiple sphingolipids.

The classic form of Krabbe disease, or globoid cell leukodystrophy, presents between 3 and 6 months of age, after a normal neonatal period, with irritability, spasticity, hypersensitivity to external stimuli, and severe mental and motor deterioration. Symptoms can, however, start in the neonatal period, as early as the first day of life (Clarke et al., 1981; Zafeiriou et al., 1997; Sahai et al., 2005), and hypotonia is not always preceded by spasticity in cases of neonatal onset. On neuroimaging, aside from the leukodystrophy seen on MRI, patients can also have intracranial calcifications (Livingston et al., 2012) or optic nerve enlargement (Castilha-Neto et al., 2012), but can be deceptively normal in the first few months of life (Zafeiriou et al., 1997; Kamate and Hattiholi, 2011).

Symptoms of the classic infantile-onset Pompe disease include cardiomegaly in 92%, hypotonia in 88%, muscle weakness in 63%, respiratory distress in 78%, feeding difficulties in 57%, and failure to thrive in 53% of patients (Kishnani et al., 2006). Median age at presentation was 2 months but patients can present in the neonatal period, while median age at initiation of ventilator support is 5.9 months and median age at death is 8.7 months. Pompe disease should always be considered in the differential diagnosis of floppy baby syndrome (Howell et al., 2006), especially since earlier treatment is associated with better outcomes (Yang et al., 2016).

Genes

Gaucher disease is caused by mutations in the *GBA* gene, Farber disease by mutations in *ASAH1*, prosaposin by mutations in *PSAP*, Krabbe disease by mutations in *GALC*, and Pompe disease by mutations in *GAA*.

Biochemical defects and pathophysiology

Gaucher disease is caused by a deficiency of glucocerebrosidase, which cleaves glucosylceramide into glucose plus ceramide. Krabbe disease is caused by the deficiency of galactocerebrosidase, which is responsible for the degradation of galactocerebroside to ceramide and galactose. Farber disease represents a deficiency of acid ceramidase, which cleaves ceramide into sphingosine and a fatty acid.

Four sphingolipid activator proteins, also known as SAPs or saposins, are derived from the same precursor protein, prosaposin. These four saposins are highly homologous, each about 80 amino acids long (Schuette et al., 2001). Sap-A and Sap-C are activators for galactocerebrosidase and glucocerebrosidase, Sap-B activates arylsulfatase A, α-galactosidase, β-galactosidase and sphingomyelinase, and Sap-D activates ceramidase and sphingomyelinase (Fürst and Sandhoff, 1992).

Pompe disease stems from a deficient enzymatic activity of α-glucosidase, also known as acid maltase.

Treatment and outcomes

Enzyme replacement therapy (ERT) does not facilitate neurologic improvement in the neuronopathic form of Gaucher disease, as it does not cross the blood–brain barrier; however, it has been used in some cases as a palliative agent in order to decrease visceral manifestations of the disease, such as splenomegaly (Weiss et al., 2015).

Although hematopoietic stem cell transplantation has been performed successfully in a few patients with Farber disease and without neurologic involvement (Vormoor et al., 2004; Ehlert et al., 2006), it did not prevent neurocognitive decline in 1 patient (Yeager et al., 2000).

Treatment with hematopoietic stem cell transplantation is controversial in Krabbe disease. In children who were transplanted postsymptomatically, there was minimal neurologic improvement (Escolar et al., 2005); however, it might be associated with improved survival (Langan et al., 2016). On the other hand, transplant performed in presymptomatic patients led to developmental progress and progression of myelination in one series (Escolar et al., 2005), while in another series, 2 of 4 patients who were diagnosed via newborn screening survived with moderate to severe disability, while the other 2 died from transplant-related complications (Orsini et al., 2016).

There is no treatment for prosaposin deficiency.

Pompe disease is treated by ERT with alglucosidase alfa. The enzyme is targeted to the lysosomes due to mannose 6-phosphate tags. ERT leads to a 79% decrease in risk of death and a 58% decrease in risk of invasive ventilation, while the left ventricular mass index improved or remained normal in all patients (Nicolino et al., 2009). The fact that the heart responds to ERT more favorably than skeletal muscle does is likely related to the fact that it has a higher number of mannose 6-phosphate receptors (Wenk et al., 1991). Patients who are negative for cross-reacting immunologic material (CRIM) develop higher titers of antibodies against the infused enzyme that lead to poorer outcomes (Kishnani et al., 2010), and they may need to undergo immune tolerance induction (Messinger et al., 2012). Despite ERT, long-term survivors commonly manifest residual motor weakness, hypernasal speech, dysphagia with aspiration risk, hearing loss, osteopenia, and risk for arrhythmias (Prater et al., 2012).

PEROXISOMAL DISORDERS

Clinical symptoms

Peroxisomal disorders can be classified into two groups: (1) those characterized by multiple defects in peroxisomal function (peroxisomal biogenesis disorders, or PBDs) and (2) those characterized by single-enzyme deficiencies. The PBDs can, in turn, be divided into the Zellweger spectrum and rhizomelic chondrodysplasia punctata (RCDP) type 1. Finally, PBD Zellweger spectrum is, in turn, subdivided into Zellweger syndrome (the most severe end of the spectrum), neonatal adrenoleukodystrophy (NALD, an intermediate phenotype), and infantile Refsum disease (the mildest end of the spectrum).

Zellweger syndrome, also known as cerebrohepatorenal syndrome, presents with severe hypotonia, neonatal seizures, severe developmental delay, failure to thrive, liver dysfunction with cholestasis, and coagulopathy. The kidneys can have multiple cysts, although these are often microscopic. Typical dysmorphic features include a tall forehead, enlarged anterior fontanel, hypoplastic supraorbital ridges, epicanthal folds, and flat facial profile. Sensorineural hearing loss and cataracts are common. Primary adrenal insufficiency is found in 29% of patients (Berendse et al., 2014). X-rays often reveal stippled calcifications, more common in the patella and Y-cartilage of the hip (Williams et al., 1972). Neuroimaging reveals perisylvian polymicrogyria, delayed myelination, germinolytic cysts, ventricular dilatation (Poll-The and Gärtner, 2012) and cerebellar hypoplasia in some. A lipid peak on brain MRS was found in the white matter in 4 of 5 patients (Rosewich et al., 2016).

Patients with the classic form of RCDP type 1 present with shortening of the humeri and, to a lesser extent, the femora, stippling of the epiphyses, coronal clefts of the vertebral bodies, joint contractures, and congenital cataracts. Growth parameters are at the lower limit of normal at birth, but progress to profound growth deficiency postnatally (Braverman et al., 1993). Congenital cardiac anomalies are seen in 40%–60% of patients (Huffnagel et al., 2013; Duker et al., 2016). Cervical spinal stenosis and cord compression are common (Abousamra et al., 2017). Seizures are seen in 84% of patients, and all have severe intellectual disability; in one series, no patient was ever able to lift their head when prone, sit without support, stand with limited support, feed themselves, or achieve toilet training (White et al., 2003).

Genes

PBD Zellweger spectrum is caused by mutations in one of 12 different peroxins necessary for the formation, proliferation, growth, or assembly of peroxisomes. *PEX1* accounts for 58% of cases, *PEX6* for 16%, and *PEX12* for 9%, while the rest are caused by mutations in *PEX2*, *PEX3*, *PEX5*, *PEXZ10*, *PEX13*, *PEX14*, *PEX16*, *PEX19*, and *PEX26* (Ebberink et al., 2011).

Enzymes are targeted to the peroxisomes by the presence of a peroxisomal targeting signal (PTS), of which there are two, PTS1 and PTS2. Most peroxisomal proteins contain the PTS1 sequence, while only three enzymes contain the PTS2 sequence: alkylglycerone phosphate synthase, phytanoyl-CoA hydroxylase, and 3-ketoacylthiolase (Wanders and Waterham, 2006). RCDP type 1 is caused by mutations in *PEX7*, the PTS2 receptor (Braverman et al., 1997), while a novel type of RCDP is caused by mutations resulting in the loss of only the long isoform of PEX5 (Barøy et al., 2015). *PEX5* encodes a long and a short isoform; while both isoforms recognize proteins that contain PTS1, only the long isoform acts as a PTS2 coreceptor.

Biochemical defects and pathophysiology

Some of the functions of the peroxisomes include the β-oxidation of straight very long-chain fatty acids and of a branched-chain fatty acid (i.e., pristanic acid), the β-oxidation of dicarboxylic fatty acids, α-oxidation of branched-chain fatty acids (i.e., phytanic acid), synthesis of plasmalogens and bile acid, and the catabolism of lysine. Patients with PBD Zellweger spectrum have abnormalities in all of these functions, and thus have increased concentrations of very long-chain fatty acids, dicarboxylic acids and phytanic acid, decreased concentrations of plasmalogens, and increased concentrations of bile acid intermediates (dihydroxycholestanoic and trihydroxycholestanoic acids) and pipecolic acid (a metabolite in the lysine degradation pathway), respectively. It should be noted that the accumulation of phytanic acid relies upon dietary intake and, since the amount of phytanic acid in breast milk is low, newborns can have normal phytanic acid concentrations.

RCDP type 1 is caused by a decreased import of peroxisomal proteins containing the PTS2 sequence, and thus patients only have decreased levels of plasmalogens (given deficient activity of alkylglycerone phosphate synthase) and increased levels of phytanic acid (given deficiency of phytanoyl-CoA hydroxylase); however, the concentrations of very long-chain fatty acids and pipecolic acid are normal. Other forms of RCDP exist, caused by deficiencies in single enzymes involved in the biosynthesis of plasmalogens, such as glyceronephosphate *O*-acyltransferase (encoded by *GNPAT* and associated with RCDP type 2) and alkylglycerone phosphate synthase (encoded by *AGPS*, associated with RCDP type 3).

Other single-enzyme deficiencies include D-bifunctional protein (encoded by *HSD17B4* and responsible for the second and third steps in β-oxidation of straight very long-chain and branched-chain fatty acids), and of acyl-CoA oxidase (encoded by *ACOX1* and required for the first step in the β-oxidation of straight very long-chain fatty acids). D-bifunctional protein deficiency is sometimes known as pseudo-Zellweger syndrome and is accompanied by elevation of very long-chain fatty acids and phytanic acid, while peroxisomal acyl-CoA oxidase deficiency is sometimes known as pseudo-NALD and is associated with elevated levels of very long-chain fatty acids only.

Treatment and outcomes

Supportive therapies include treatment of seizures, adrenal insufficiency, liposoluble vitamin deficiency, and hearing and vision loss (Klouwer et al., 2015). Supplementation with docosahexanoic acid (DHA) is sometimes recommended, based on its importance for brain and retinal function; however, its benefits remain controversial, as one group reported clinical benefits (Martínez et al., 2000; Noguer and Martinez, 2010) while another one did not (Paker et al., 2010). Cholic acid bypasses the block in bile acid synthesis and thus causes feedback inhibition of the bile acid synthetic pathway, leading to a decrease in the toxic bile acid intermediates. It was recently approved for patients with Zellweger spectrum who have liver disease or decreased liposoluble vitamin absorption. It is well tolerated and leads to improvement of liver disease (Heubi et al., 2017), although in a minority of patients with advanced liver disease it might lead to an increase in transaminases and worsening of cholestasis (Berendse et al., 2016).

CHOLESTEROL SYNTHESIS DISORDERS

Clinical symptoms

Mevalonate kinase deficiency is a disorder in the presqualene cholesterol biosynthetic pathway, characterized by recurrent inflammatory symptoms such as fever, lymphadenopathy, arthralgias, and abdominal pain, with each episode lasting typically 3–6 days (Ter Haar et al., 2016). Onset in the neonatal period is seen in about one-third of patients (Bader-Meunier et al., 2011). Neurologic symptoms include cerebellar ataxia in 3% of patients, seizures in 5%, and intellectual disability in 2%–4% (Zhang, 2016), although they are more common in the more severe form of the disease, known as mevalonic aciduria. Urine organic acid analysis reveals increased excretion of mevalonic acid, although this finding has a sensitivity of 92%; therefore absence of this finding does not exclude the disease (Jeyaratnam et al., 2016).

The prototypical disorder of the postsqualene cholesterol biosynthetic pathway is Smith–Lemli–Opitz syndrome, a condition with multiple congenital

anomalies and intellectual disability. Typical physical features include growth retardation, Y-shaped 2–3 toe syndactyly, hypospadias in 50% of affected males, cataracts in 20% of patients, and facial dysmorphic features including bitemporal narrowing, ptosis, anteverted nares, micrognathia, low-set posteriorly rotated ears, and a narrow high-arched palate, or even a cleft palate in 40%–50% of patients (Nowaczyk and Irons, 2012). Microcephaly is seen in 80%–84% of patients, while developmental delay and hypotonia are found in the vast majority. A characteristic behavior is that of opistokinesis, or sudden, rapid retropulsion of the head or torso. Neuroimaging reveals median or paramedian structural anomalies, such as abnormalities of the septum pellucidum in 76% of patients and abnormalities of the corpus callosum in 69% (Lee et al., 2013). A lipid peak was found on brain MRS in 2 of 16 patients (Caruso et al., 2004). The total cholesterol level is decreased in around 90% of patients, while 7-dehydrocholesterol and 8-dehydrocholesterol levels are increased. Low maternal estriol on second-trimester serum screening is a characteristic prenatal finding (Shinawi et al., 2005).

Genes

Mevalonate kinase deficiency is caused by mutations in the *MVK* gene, while Smith–Lemli–Opitz syndrome is caused by mutations in *DHCR7*. Other disorders in the postsqualene pathway that can be accompanied by multiple congenital anomalies and severe neurologic involvement include lathosterolosis, caused by mutations in *SC5D*, and desmosterolosis, caused by mutations in *DHCR24*.

Biochemical defects and pathophysiology

The inflammatory nature of mevalonate kinase deficiency results from a lack of posttranslational prenylation of certain proteins. In particular, the metabolic block leads to decreased synthesis of isoprenoids, such as farnesylpyrophosphate and geranylgeranylpyrophosphate. The decreased prenylation of Rab GTPases leads to increased release of interleukin 1 beta (van der Burgh et al., 2014; Jurczyluk et al., 2016).

Smith–Lemli–Opitz syndrome results from a defect in 7-dehydrocholesterol reductase, which converts 7-dehydrocholesterol to cholesterol. This leads to an accumulation of 7-dehydrocholesterol, which gets converted to 8-dehydrocholesterol by the action of 3β-hydroxysteroid-Δ8-Δ7-isomerase.

Treatment and outcomes

Mevalonate kinase deficiency is treated by antiinflammatory agents such as NSAIDs, corticosteroids, anti-TNF antagonists, and anti-IL1 antagonists; cases that are refractory to the aforementioned therapies might need hematopoietic stem cell transplantation (Favier and Schulert, 2016).

Cholesterol supplementation should be considered in every patient, as it has minimal adverse effects and is associated with improved growth and it improves photosensitivity (Azurdia et al., 2001; Starck et al., 2002). It does not, however, lead to improved developmental progress (Sikora et al., 2004) and probably does not significantly alter sterol levels in the brain, given the limited capacity for cholesterol to cross the blood–brain barrier, as the brain relies heavily on de novo cholesterol biosynthesis. Simvastatin leads to decreased levels of 7- and 8-dehydrocholesterol, but does not lead to improved growth or behavior (Haas et al., 2007).

CONGENITAL DISORDERS OF GLYCOSYLATION

Clinical symptoms

There are over 100 different types of congenital disorders of glycosylation, or CDGs (Jaeken and Péanne, 2017). The most common type of CDG, arising from phosphomannomutase deficiency, is a multisystemic disorder that can present in the newborn period with hydrops, pleural effusions, pericardial effusions, failure to thrive, hypotonia, microcephaly, developmental delay, strabismus, and roving eye movements (Grünewald, 2009; Freeze et al., 2012). Some neurologic complications of the disease include cerebellar atrophy, which can be present as early as the neonatal period, while seizures and stroke-like episodes typically start in early childhood. Peripheral neuropathy develops over time. Important clues toward the diagnosis are the presence of inverted nipples and abnormal fat distribution, including supragluteal and suprapubic fat pads; both findings, however, can disappear over the course of the first few years of life. Other organ systems that can be involved include the gastrointestinal (protein-losing enteropathy, hepatocellular liver disease), hematologic (coagulopathy, thrombosis), endocrine (hyperinsulinemic hypoglycemia, hypothyroidism), skeletal (kyphoscoliosis, pectus deformity), ocular (retinitis pigmentosa), renal (tubulopathy, proteinuria, cysts), and cardiac (hypertrophic cardiomyopathy) systems (Grünewald, 2009).

Genes

The most common type of CDG is caused by a deficiency of phosphomannomutase 2, encoded by *PMM2* (Matthijs et al., 1997). Most CDGs are inherited in a recessive manner, but other inheritance patterns such as X-linked are possible, as in ALG13-CDG (Timal et al., 2012),

SLC35A2-CDG (Ng et al., 2013), or PIGA-CDG (Johnston et al., 2012).

Biochemical defects and pathophysiology

It is estimated that half of all proteins are glycosylated (Apweiler et al., 1999) and that about 2% of the whole genome encodes proteins directly involved in glycosylation reactions (Freeze, 2013). In fact, the glycome, or the entire complement of sugars of an organism, is estimated to be several times larger than the proteome (Freeze, 2006). CDGs lead to human disease due to an inability to properly synthesize glycan chains. In particular, there can be a defect in protein N-linked glycosylation (a defect in attaching a glycan chain to the amino group of asparagine) or protein O-linked glycosylation (attaching the glycan to the hydroxyl group of serine or threonine), a defect in glycosphingolipid glycosylation, a defect in the synthesis of glycophosphatidylinositol (GPI) anchors, or a defect in vesicular trafficking.

Treatment and outcomes

There is no treatment for the most common type of CDG, PMM2-CDG. Some improvement can be seen with administration of mannose to patients with MPI-CDG (Niehues et al., 1998), fucose to patients with SLC35C1-CDG (Marquardt et al., 1999), or butyrate for PIGM-CDG (Almeida et al., 2007).

DISORDERS OF COPPER METABOLISM

Clinical symptoms

The disorders of copper metabolism include Menkes disease, Huppke–Brendel syndrome, and MEDNIK syndrome. The earliest manifestations of Menkes disease typically include hypothermia and prolonged hyperbilirubinemia (Tümer and Møller, 2010). A typical finding is that of sparse, coarse, brittle hair which, upon microscopic examination, represents pili torti. Connective tissue abnormalities include pudgy cheeks and cutis laxa on physical examination, arterial tortuosity on brain MRI, and bladder diverticula on pelvic ultrasound. By approximately 3 months of age, affected boys will start showing frank findings of neurologic involvement, including seizures and loss of developmental skills. The pattern of seizures in Menkes disease can be divided into three stages, with an early stage at around 3 months showing focal clonic status epilepticus, an intermediate stage at about 10 months showing intractable infantile spasms, and a late stage at about 25 months showing multifocal seizures, tonic spasms, and myoclonus (Bahi-Buisson et al., 2006). Progressive neurodegeneration leads to death in the first few years of life.

Neuroimaging reveals increased arterial tortuosity in 73% of patients, white matter tumefactive lesions in 27%–56%, focal nontumefactive white matter lesions in 35%, and abnormal myelination in 73% of patients (Manara et al., 2017a). Gray matter lesions, specifically basal ganglia abnormalities, are seen in 44%–75%, cerebral atrophy in 81%–88%, cerebellar atrophy in 70%–100%, and subdural collections are seen in about a quarter of patients (Manara et al., 2017b).

Skeletal radiographs can reveal metaphyseal lesions mimicking the corner fractures or bucket-handle fractures from child abuse. The combination of classic metaphyseal lesions and subdural hematomas can indeed lead to a diagnosis of nonaccidental trauma (Cronin et al., 2012).

Laboratory findings include low concentrations of serum copper and ceruloplasmin, although these are unreliable markers during the first several weeks of life, as infants under 6 months of age normally have low serum levels of both markers (Kaler, 1993). Instead, an early diagnosis can be established on biochemical grounds using concentrations of catecholamines, since the partial deficiency of dopamine hydroxylase leads to a characteristic pattern of plasma and cerebrospinal fluid neurochemical abnormalities (Kaler et al., 1993a, b). Thus, the ratio of a proximal metabolite in the pathway—the dopamine metabolite dyhydroxyphenylacetic acid, DOPAC—to a distal metabolite—dihydroxyphenylglycol, DHPG—or the ratio of dopamine to norepinephrine represent sensitive and specific markers in the diagnosis of Menkes disease during the neonatal period (Goldstein et al., 2009).

Huppke et al. described five patients with intellectual disability, congenital cataracts, nystagmus, hearing loss, hypomyelination, cerebral and cerebellar atrophy, early lethality, and low serum copper and ceruloplasmin levels (Huppke et al., 2012), and this novel metabolic condition is named after them.

MEDNIK syndrome is an acronym for Mental retardation, Enteropathy, Deafness, peripheral Neuropathy, Ichthyosis, and Keratodermia. Other findings include liver disease with cholestasis and elevated transaminases, decreased serum copper and ceruloplasmin, increased urine copper and increased liver copper concentration, and a mild increase in plasma very long-chain fatty acid levels (Martinelli et al., 2013). Neuroimaging can reveal bilateral T2-weighted hyperintensities of the basal ganglia.

Genes

Menkes syndrome is caused by mutations in *ATP7A*, encoding a copper transporter located in the trans-Golgi

network. The basic defect hinders transport of copper out of the enterocytes and into the circulation.

Huppke–Brendel syndrome is caused by mutations in the *SLC33A1* gene, encoding a transporter of acetyl-CoA into the ER lumen (Huppke et al., 2012).

MEDNIK syndrome is caused by mutations in *AP1S1*, encoding the σ1A subunit of the adaptor protein complex AP-1 (Montpetit et al., 2008).

Biochemical defects and pathophysiology

The underlying basis of Menkes disease is the defective transport and incorporation of copper into copper-containing enzymes, such as tyrosinase (the deficiency of which causes hypopigmentation of hair and skin), lysyl oxidase (the deficiency of which results in the connective tissue phenotype, due to defective elastin and collagen cross-linking), cytochrome *c* oxidase (associated with the hypothermia), and ascorbate oxidase, causative of the skeletal changes.

For Huppke–Brendel syndrome, the prevailing hypothesis is that reduced acetylation of ceruloplasmin leads to decreased secretion, which results in low serum copper concentrations, as ceruloplasmin carries 95% of serum copper (Huppke et al., 2012).

In MEDNIK syndrome, the normal recycling of copper ATPases between the trans-Golgi network and the plasma membrane is disrupted, as it is dependent on adaptor proteins (Montpetit et al., 2008). This leads to the characteristic phenotype of excess copper in the liver (reminiscent of Wilson disease), but lack of copper in other tissues such as the brain (reminiscent of Menkes disease).

Treatment and outcomes

In Menkes disease, the early administration of subcutaneous copper histidinate soon after birth can lead to some benefit, particularly if the mutation is associated with some residual ATP7A activity (Kaler et al., 2008).

For MEDNIK syndrome, treatment with zinc acetate has been associated with improved cholestasis and intellectual development (Martinelli et al., 2013).

GLUT1 DEFICIENCY SYNDROME

Clinical symptoms

The most common presenting symptom is seizures, reported in 61% of patients. The second most common form of presentation, found in 38% of patients, is eye movement abnormalities, such as eye rolling, eye fluttering, frequent eye blinks, or "opsoclonus" (Akman et al., 2016). Although these eye movements are indeed rapid and multidirectional, as in opsoclonus, they can be distinguished from it because a head movement in the same direction as the eye movement accompanies them, and because they are separated by clear intervals of fixation, 200–800 ms in length (Pearson et al., 2017). Eighteen of 133 patients (13.5%) experienced first symptoms during the neonatal period (Akman et al., 2016). The type of seizure is quite variable, being mixed in 68%, generalized tonic–clonic in 53%, absence in 49%, complex partial in 37%, myoclonic in 27%, drop attacks in 26%, tonic in 12%, simple partial in 3%, and spasms in 3% (Pong et al., 2012). About 1.4% of all cases of idiopathic generalized epilepsy are caused by GLUT1 deficiency (Arsov et al., 2012b), as are around 12% of cases of early-onset absence epilepsy presenting in patients before 4 years of age (Arsov et al., 2012a). The response to typical antiepileptic drugs should not dissuade the clinician from considering this condition, as some patients can remain seizure-free without a ketogenic diet (Pong et al., 2012).

Characteristic laboratory features include low CSF glucose concentration (≤10th centile), a low CSF to blood glucose ratio (≤25th centile), and a low CSF lactate concentration (≤10th centile); cut off values for different ages have been established (Leen et al., 2013). Some patients can have spontaneous ketosis as a means of cerebral metabolic compensation (Chenouard et al., 2015).

Genes

GLUT1 deficiency syndrome is caused by mutations in the *SLC2A1* gene. Most cases are the result of de novo heterozygous mutations in the gene and thus have a dominant pattern of inheritance, although rare cases carry biallelic mutations. Recently, a novel neurodevelopmental condition characterized by intellectual disability, epilepsy, and variable neuropsychiatric features was described, caused by biallelic mutations in *SLC45A1*, a cerebral glucose transporter expressed in neurons, unlike GLUT1 that is expressed at the blood–brain barrier (Srour et al., 2017).

Biochemical defects and pathophysiology

GLUT1 deficiency leads to an inability of glucose to cross the blood–brain barrier. Glucose represents the main source of energy for the brain, which consumes about 20% of the whole-body glucose-derived energy—approximately 5.6 mg glucose/100 g brain tissue/min (Mergenthaler et al., 2013).

Certain mutations lead not only to altered glucose transport with the consequent energy deficiency, but also to cation leak with osmotic instability, associated with periventricular calcifications, cataracts, hemolysis, and pseudohyperkalemia (Flatt et al., 2011; Bawazir et al., 2012; Shibata et al., 2017).

Treatment and outcomes

Treatment involves providing an alternative source of fuel for the brain. In particular, ketone bodies cross the blood–brain barrier via a monocarboxylate transporter (MCT1), and thus a ketogenic diet represents the treatment of choice (Klepper et al., 2004). Some patients can still show recurrence of seizures despite adequate ketosis (Klepper et al., 2005), and up to one-third of patients respond poorly to a ketogenic diet (Pascual et al., 2014). Triheptanoin has also been tried for anaplerosis, with encouraging results.

RECOMMENDED DIAGNOSTIC WORKUP

Signs and symptoms of IEMs can be rather nonspecific in the neonatal period. Newborns can present with feeding difficulty, emesis, dyspnea, lethargy, or frank encephalopathy, hypotonia, and/or seizures. In intoxication-type IEMs, there tends to be an asymptomatic period of at least several hours, since the placenta "dialyzes" the accumulated molecules, and it takes time for this intoxicating substance to accumulate after dietary exposure. IEMs should be considered when faced with unexplained neurologic symptoms, particularly if these happen to be progressive or if they follow an uneventful pregnancy and delivery. They should also be considered in the setting of specific laboratory findings, such as hypoglycemia, hyperammonemia, or high-anion gap metabolic acidosis. Fig. 22.3 provides a diagnostic algorithm for the different IEMs that can present with central or peripheral hypotonia in the neonate. Fig. 22.4 provides a diagnostic algorithm for IEMs that can present with encephalopathy and/or seizures. Fig. 22.5 provides a tiered algorithm providing guidance on which tests to obtain in order to reach the aforementioned diagnoses. Interactive online tools exist to facilitate diagnosis, such as http://www.treatable-id.org (van Karnebeek et al., 2012b) and http://iembase.org (Lee et al., 2017b).

NEWBORN SCREENING

Newborn population screening, pivotal for preventive health care for IEMs, was introduced in the 1960s for the detection of phenylketonuria. In the mid-1990s, MS/MS allowed for extended newborn screening and was consecutively incorporated into screening programs worldwide. MS/MS enables the diagnosis and treatment of a much larger number of metabolic disorders (fatty acid oxidation disorders, organic acidurias, some urea cycle defects, additional disorders of amino acid metabolism). Usually the bloodspot is taken on days 3–6 to allow for sufficient nutrient load. For the clinician, it is important to realize that great variability exists in the panel of disorders screened for in different countries and states, as there is no consensus on the basic decision criteria for inclusion. Also, false positives and false negatives exist, and thus biochemical confirmation and clinical evaluation are mandatory. A newborn may become sick before newborn screening results are available, as is often the case for maple syrup urine disease or male OTC deficiency. The consequences of positive screening

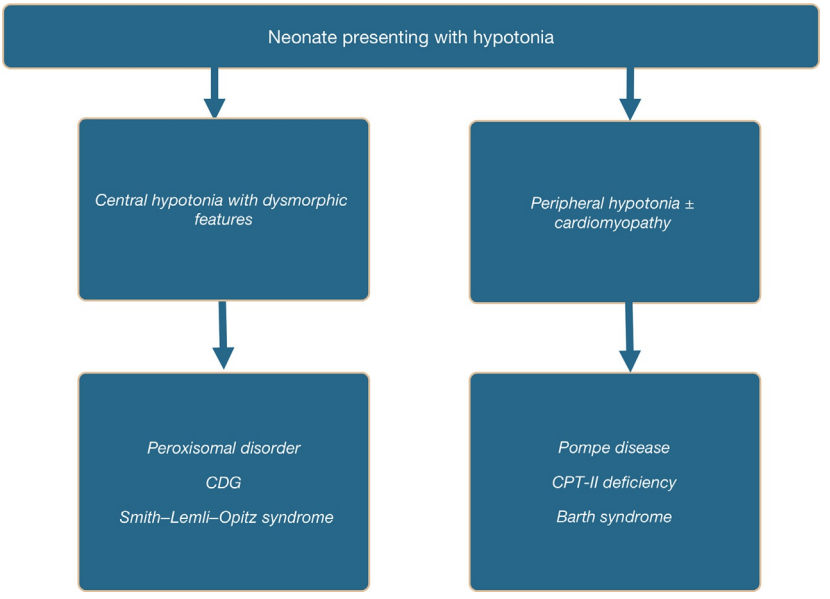

Fig. 22.3. Diagnostic algorithm for IEMs presenting with central or peripheral hypotonia in the neonate.

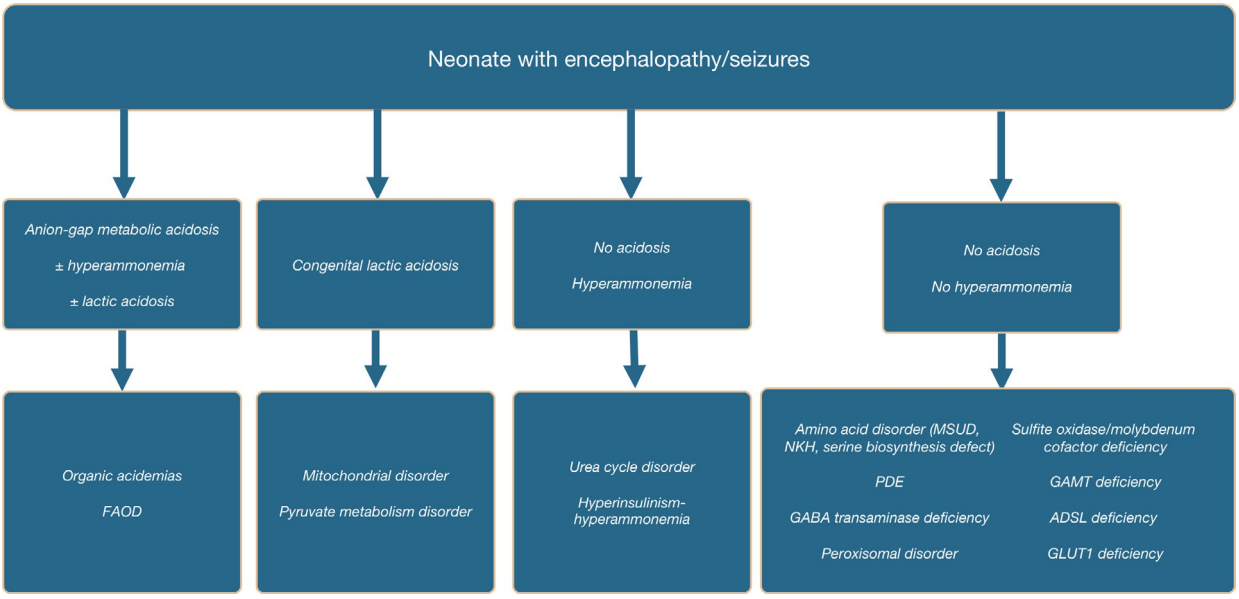

Fig. 22.4. Diagnostic algorithm for IEMs presenting with encephalopathy and/or seizures in the neonate.

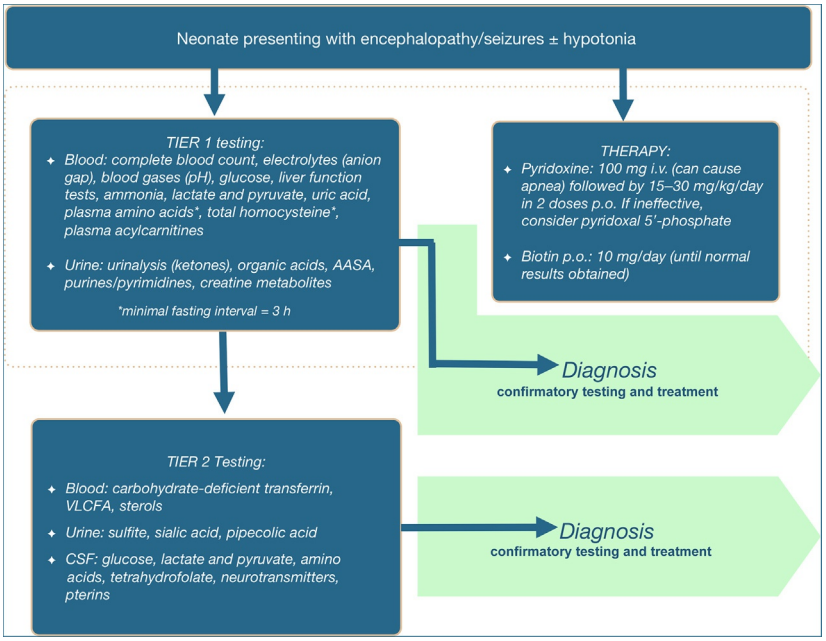

Fig. 22.5. Tiered diagnostic and therapeutic algorithm for neonatal-onset IEMs presenting with neurologic signs.

results differ between conditions. Sometimes only a repeat analysis from a second screening card is required. In other cases, immediate initiation of therapeutic measures is necessary and may require referral to a specialized metabolic center. Parents may need to understand that urgent intervention is necessary, even though newborn screening also detects asymptomatic variants of many conditions.

FUTURE DIRECTIONS

The number of recognized IEMs and insights into their varying phenotypes even during the neonatal period are expanding rapidly, through the use of genomic, metabolomic, and deep phenotyping technologies, such as high-resolution and functional neuroimaging. Prompt recognition of these conditions for treatment and best outcomes is essential but challenging; an awareness of their

existence and a structured diagnostic approach supported by digital tools aid the clinician. Understanding disease mechanisms and phenotypic modifiers is currently the big challenge; systems biology approaches and model organism studies pave the way. New therapies are not only under development but are also in clinical trials, and they vary from medical diets to pharmacotherapy and gene therapy. The potential to treat an increasing number of IEMs, however rare, motivates the expansion of newborn screening programs; however, the costs of therapy are sometimes prohibitive, such as enzyme replacement therapy in mucopolysaccharidoses. On the other hand, early identification of diseases that are asymptomatic during the newborn period, such as X-linked adrenoleukodystrophy, allow for the possible scrutiny of the disease course during early childhood years and aid in our pathophysiologic understanding and ability to provide timely interventions. Now, more than ever, in the age of big data, interdisciplinary collaboration is key to providing state-of-the-art care for neonates suffering IEMs. To diagnose and treat, the neonatal neurologist needs input from other clinicians (metabolic specialists, geneticists, radiologists, neonatologists) as well as laboratory specialists (biochemists, molecular geneticists, bioinformaticians) and researchers in the aforementioned fields.

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References

Abousamra O, Kandula V, Duker AL et al. (2017). Cervical spine deformities in children with rhizomelic chondrodysplasia punctata. J Pediatr Orthop. https://doi.org/10.1097/BPO.0000000000001014.

Acuna-Hidalgo R, Schanze D, Kariminejad A et al. (2014). Neu–Laxova syndrome is a heterogeneous metabolic disorder caused by defects in enzymes of the L-serine biosynthesis pathway. Am J Hum Genet 95: 285–293.

Ahmad A, Kahler SG, Kishnani PS et al. (1999). Treatment of pyruvate carboxylase deficiency with high doses of citrate and aspartate. Am J Med Genet 87: 331–338.

Akman CI, Yu J, Alter A et al. (2016). Diagnosing glucose transporter 1 deficiency at initial presentation facilitates early treatment. J Pediatr 171: 220–226.

Almeida AM, Murakami Y, Baker A et al. (2007). Targeted therapy for inherited GPI deficiency. N Engl J Med 356: 1641–1647. https://doi.org/10.1056/NEJMoa063369.

Alves MQ, Le Trionnaire E, Ribeiro I et al. (2013). Molecular basis of acid ceramidase deficiency in a neonatal form of Farber disease: identification of the first large deletion in ASAH1 gene. Mol Genet Metab 109: 276–281.

Amayreh W, Meyer U, Das AM (2014). Treatment of arginase deficiency revisited: guanidinoacetate as a therapeutic target and biomarker for therapeutic monitoring. Dev Med Child Neurol 56: 1021–1024.

Antonarakis SE, Valle D, Moser HW et al. (1984). Phenotypic variability in siblings with Farber disease. J Pediatr 104: 406–409.

Applegarth DA, Toone JR, Lowry RB (2000). Incidence of inborn errors of metabolism in British Columbia, 1969–1996. Pediatrics 105e10.

Apweiler R, Hermjakob H, Sharon N (1999). On the frequency of protein glycosylation, as deduced from analysis of the SWISS-PROT database. Biochim Biophys Acta 1473: 4–8.

Arbuckle HA, Morelli J (2006). Holocarboxylase synthetase deficiency presenting as ichthyosis. Pediatr Dermatol 23: 142–144.

Arsov T, Mullen SA, Damiano JA et al. (2012a). Early onset absence epilepsy: 1 in 10 cases is caused by GLUT1 deficiency. Epilepsia 53: e204–e207.

Arsov T, Mullen SA, Rogers S et al. (2012b). Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. Ann Neurol 72: 807–815.

Atwal PS, Scaglia F (2016). Molybdenum cofactor deficiency. Mol Genet Metab 117: 1–4.

Azurdia RM, Anstey AV, Rhodes LE (2001). Cholesterol supplementation objectively reduces photosensitivity in the Smith–Lemli–Opitz syndrome. Br J Dermatol 144: 143–145.

Bader-Meunier B, Florkin B, Sibilia J et al. (2011). Mevalonate kinase deficiency: a survey of 50 patients. Pediatrics 128: e152–e159.

Bahi-Buisson N, Kaminska A, Nabbout R et al. (2006). Epilepsy in Menkes disease: analysis of clinical stages. Epilepsia 47: 380–386.

Baker PR, Friederich MW, Swanson MA et al. (2014). Variant non ketotic hyperglycinemia is caused by mutations in LIAS, BOLA3 and the novel gene GLRX5. Brain J Neurol 137: 366–379.

Bandaralage SPS, Farnaghi S, Dulhunty JM et al. (2016). Antenatal and postnatal radiologic diagnosis of holocarboxylase synthetase deficiency: a systematic review. Pediatr Radiol 46: 357–364.

Barøy T, Koster J, Strømme P et al. (2015). A novel type of rhizomelic chondrodysplasia punctata, RCDP5, is caused by loss of the PEX5 long isoform. Hum Mol Genet 24: 5845–5854.

Baumgartner MR, Hörster F, Dionisi-Vici C et al. (2014). Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis 9: 130.

Baumgartner-Sigl S, Haberlandt E, Mumm S et al. (2007). Pyridoxine-responsive seizures as the first symptom of infantile hypophosphatasia caused by two novel missense mutations (c.677T>C, p.M226T; c.1112C>T, p.T371I) of the tissue-nonspecific alkaline phosphatase gene. Bone 40: 1655–1661.

Bawazir WM, Gevers EF, Flatt JF et al. (2012). An infant with pseudohyperkalemia, hemolysis, and seizures: cation-leaky GLUT1-deficiency syndrome due to a SLC2A1 mutation. J Clin Endocrinol Metab 97: E987–E993.

Berendse K, Engelen M, Linthorst GE et al. (2014). High prevalence of primary adrenal insufficiency in Zellweger spectrum disorders. Orphanet J Rare Dis 9: 133.

Berendse K, Klouwer FCC, Koot BGP et al. (2016). Cholic acid therapy in Zellweger spectrum disorders. J Inherit Metab Dis 39: 859–868.

Besse A, Wu P, Bruni F et al. (2015). The GABA transaminase, ABAT, is essential for mitochondrial nucleoside metabolism. Cell Metab 21: 417–427.

Besse A, Petersen AK, Hunter JV et al. (2016). Personalized medicine approach confirms a milder case of ABAT deficiency. Mol Brain 9: 93.

Braverman NE, Moser AB, Steinberg SJ (1993). Rhizomelic chondrodysplasia punctata type 1. In: MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJ Bean, HC Mefford, K Stephens, A Amemiya, N Ledbetter (Eds.), GeneReviews®. University of Washington, Seattle, WA.

Braverman N, Steel G, Obie C et al. (1997). Human PEX7 encodes the peroxisomal PTS2 receptor and is responsible for rhizomelic chondrodysplasia punctata. Nat Genet 15: 369–376.

Breen C, White FJ, Scott CAB et al. (2014). Unsuccessful treatment of severe pyruvate carboxylase deficiency with triheptanoin. Eur J Pediatr 173: 361–366.

Brivet M, Garcia-Cazorla A, Lyonnet S et al. (2003). Impaired mitochondrial pyruvate importation in a patient and a fetus at risk. Mol Genet Metab 78: 186–192.

Brown GK, Cromby CH, Manning NJ et al. (1987). Urinary organic acids in succinic semialdehyde dehydrogenase deficiency: evidence of alpha-oxidation of 4-hydroxybutyric acid, interaction of succinic semialdehyde with pyruvate dehydrogenase and possible secondary inhibition of mitochondrial beta-oxidation. J Inherit Metab Dis 10: 367–375.

Campeau PM, Scriver CR, Mitchell JJ (2008). A 25-year longitudinal analysis of treatment efficacy in inborn errors of metabolism. Mol Genet Metab 95: 11–16.

Carbone MA, MacKay N, Ling M et al. (1998). Amerindian pyruvate carboxylase deficiency is associated with two distinct missense mutations. Am J Hum Genet 62: 1312–1319.

Carleton SM, Peck DS, Grasela J et al. (2010). DNA carrier testing and newborn screening for maple syrup urine disease in Old Order Mennonite communities. Genet Test Mol Biomarkers 14: 205–208.

Carpente KH, Wilcken B, Christodoulou J et al. (2000). Holocarboxylase synthetase deficiency: urinary metabolites masked by gross ketosis. J Inherit Metab Dis 23: 845–846.

Caruso PA, Poussaint TY, Tzika AA et al. (2004). MRI and 1H MRS findings in Smith–Lemli–Opitz syndrome. Neuroradiology 46: 3–14.

Castilha-Neto D, Monteiro LF, Peruchi MM et al. (2012). Optic nerve enlargement in infantile form of Krabbe disease. Clin Pract 2e81.

Cavalleri F, Berardi A, Burlina AB et al. (2002). Diffusion-weighted MRI of maple syrup urine disease encephalopathy. Neuroradiology 44: 499–502.

Chenouard A, Vuillaumier-Barrot S, Seta N et al. (2015). A cause of permanent ketosis: GLUT-1 deficiency. JIMD Rep 18: 79–83.

Chuang DT, Chuang JL, Wynn RM (2006). Lessons from genetic disorders of branched-chain amino acid metabolism. J Nutr 136: 243S–249S.

Clarke JT, Ozere RL, Krause VW (1981). Early infantile variant of Krabbe globoid cell leucodystrophy with lung involvement. Arch Dis Child 56: 640–642.

Coughlin CR, van Karnebeek CDM, Al-Hertani W et al. (2015). Triple therapy with pyridoxine, arginine supplementation and dietary lysine restriction in pyridoxine-dependent epilepsy: neurodevelopmental outcome. Mol Genet Metab 116: 35–43.

Cronin H, Fussell JN, Pride H et al. (2012). Menkes syndrome presenting as possible child abuse. Cutis 90: 170–172.

Danhauser K, Herebian D, Haack TB et al. (2016). Fatal neonatal encephalopathy and lactic acidosis caused by a homozygous loss-of-function variant in COQ9. Eur J Hum Genet 24: 450–454.

Darin N, Reid E, Prunetti L et al. (2016). Mutations in PROSC disrupt cellular pyridoxal phosphate homeostasis and cause vitamin-B6-dependent epilepsy. Am J Hum Genet 99: 1325–1337.

De Castro M, Zand DJ, Lichter-Konecki U et al. (2015). Severe neonatal holocarboxylase synthetase deficiency in West African siblings. JIMD Rep 20: 1–4.

de Koning TJ, Klomp LWJ, van Oppen ACC et al. (2004). Prenatal and early postnatal treatment in 3-phosphoglycerate-dehydrogenase deficiency. Lancet 364: 2221–2222.

Debray F-G, Mitchell GA, Allard P et al. (2007). Diagnostic accuracy of blood lactate-to-pyruvate molar ratio in the differential diagnosis of congenital lactic acidosis. Clin Chem 53: 916–921.

DeVivo DC, Haymond MW, Leckie MP et al. (1977). The clinical and biochemical implications of pyruvate carboxylase deficiency. J Clin Endocrinol Metab 45: 1281–1296.

Dionisi-Vici C, Rizzo C, Burlina AB et al. (2002). Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J Pediatr 140: 321–327.

Donti TR, Blackburn PR, Atwal PS (2016). Holocarboxylase synthetase deficiency pre and post newborn screening. Mol Genet Metab Rep 7: 40–44.

Duker AL, Eldridge G, Braverman NE et al. (2016). Congenital heart defects common in rhizomelic chondrodysplasia punctata. Am J Med Genet A 170A: 270–272.

Ebberink MS, Mooijer PAW, Gootjes J et al. (2011). Genetic classification and mutational spectrum of more than 600 patients with a Zellweger syndrome spectrum disorder. Hum Mutat 32: 59–69.

Ehlert K, Roth J, Frosch M et al. (2006). Farber's disease without central nervous system involvement: bone-marrow transplantation provides a promising new approach. Ann Rheum Dis 65: 1665–1666.

Elleder M, Jerábková M, Befekadu A et al. (2005). Prosaposin deficiency—a rarely diagnosed, rapidly progressing, neonatal neurovisceral lipid storage disease. Report of a further patient. Neuropediatrics 36: 171–180.

Escolar ML, Poe MD, Provenzale JM et al. (2005). Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 352: 2069–2081.

Estivill E, Sanmarti FX, Vidal R et al. (1985). Comb-like rhythm: an EEG pattern peculiar to leucinosis. An Esp Pediatr 22: 123–127.

Farrant RD, Walker V, Mills GA et al. (2001). Pyridoxal phosphate de-activation by pyrroline-5-carboxylic acid. Increased risk of vitamin B6 deficiency and seizures in hyperprolinemia type II. J Biol Chem 276: 15107–15116.

Favier LA, Schulert GS (2016). Mevalonate kinase deficiency: current perspectives. Appl Clin Genet 9: 101–110.

Ferreira CR, Silber MH, Chang T et al. (2016). Cerebral lipid accumulation detected by MRS in a child with carnitine palmitoyltransferase 2 deficiency: a case report and review of the literature on genetic etiologies of lipid peaks on MRS. JIMD Rep 28: 69–74.

Flatt JF, Guizouarn H, Burton NM et al. (2011). Stomatin-deficient cryohydrocytosis results from mutations in SLC2A1: a novel form of GLUT1 deficiency syndrome. Blood 118: 5267–5277.

Freeze HH (2006). Genetic defects in the human glycome. Nat Rev Genet 7: 537–551.

Freeze HH (2013). Understanding human glycosylation disorders: biochemistry leads the charge. J Biol Chem 288: 6936–6945.

Freeze HH, Eklund EA, Ng BG et al. (2012). Neurology of inherited glycosylation disorders. Lancet Neurol 11: 453–466. https://doi.org/10.1016/S1474-4422(12)70040-6.

Fürst W, Sandhoff K (1992). Activator proteins and topology of lysosomal sphingolipid catabolism. Biochim Biophys Acta 1126: 1–16.

Ganetzky RD, Bloom K, Ahrens-Nicklas R et al. (2016). ECHS1 deficiency as a cause of severe neonatal lactic acidosis. JIMD Rep 30: 33–37.

García-Cazorla A, Rabier D, Touati G et al. (2006). Pyruvate carboxylase deficiency: metabolic characteristics and new neurological aspects. Ann Neurol 59: 121–127.

Garrod AE (1902). The incidence of alkaptonuria: a study in chemical individuality. Lancet 160: 1616–1620. Originally published as Vol. 2, Issue 4137.

Goldstein DS, Holmes CS, Kaler SG (2009). Relative efficiencies of plasma catechol levels and ratios for neonatal diagnosis of Menkes disease. Neurochem Res 34: 1464–1468.

Gospe SM (1993). Pyridoxine-dependent epilepsy. In: MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJ Bean, HC Mefford, K Stephens, A Amemiya, N Ledbetter (Eds.), GeneReviews®. University of Washington, Seattle, WA.

Grünewald S (2009). The clinical spectrum of phosphomannomutase 2 deficiency (CDG-Ia). Biochim Biophys Acta 1792: 827–834.

Gupta N, Oppenheim IM, Kauvar EF et al. (2011). Type 2 Gaucher disease: phenotypic variation and genotypic heterogeneity. Blood Cells Mol Dis 46: 75–84.

Ha JS, Kim T-K, Eun B-L et al. (2004). Maple syrup urine disease encephalopathy: a follow-up study in the acute stage using diffusion-weighted MRI. Pediatr Radiol 34: 163–166.

Haas D, Garbade SF, Vohwinkel C et al. (2007). Effects of cholesterol and simvastatin treatment in patients with Smith–Lemli–Opitz syndrome (SLOS). J Inherit Metab Dis 30: 375–387.

Habarou F, Hamel Y, Haack TB et al. (2017). Biallelic mutations in LIPT2 cause a mitochondrial lipoylation defect associated with severe neonatal encephalopathy. Am J Hum Genet 101: 283–290.

Häberle J, Boddaert N, Burlina A et al. (2012). Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis 7: 32.

Hard ML, Raha S, Spino M et al. (2001). Impairment of pyruvate dehydrogenase activity by acetaldehyde. Alcohol (Fayetteville, NY) 25: 1–8.

Harzer K, Paton BC, Poulos A et al. (1989). Sphingolipid activator protein deficiency in a 16-week-old atypical Gaucher disease patient and his fetal sibling: biochemical signs of combined sphingolipidoses. Eur J Pediatr 149: 31–39.

Heindel W, Kugel H, Roth B (1993). Noninvasive detection of increased glycine content by proton MR spectroscopy in the brains of two infants with nonketotic hyperglycinemia. Am J Neuroradiol 14: 629–635.

Heubi JE, Bove KE, Setchell KDR (2017). Oral cholic acid is efficacious and well tolerated in patients with bile acid synthesis and Zellweger spectrum disorders. J Pediatr Gastroenterol Nutr 65: 321–326.

Ho G, Ueda K, Houben RFA et al. (2016). Metabolic diet app suite for inborn errors of amino acid metabolism. Mol Genet Metab 117: 322–327.

Hobson EE, Thomas S, Crofton PM et al. (2005). Isolated sulphite oxidase deficiency mimics the features of hypoxic ischaemic encephalopathy. Eur J Pediatr 164: 655–659.

Hoffmann C, Ben-Zeev B, Anikster Y et al. (2007). Magnetic resonance imaging and magnetic resonance spectroscopy in isolated sulfite oxidase deficiency. J Child Neurol 22: 1214–1221.

Holder JL, Agadi S, Reese W et al. (2014). Infantile spasms and hyperekplexia associated with isolated sulfite oxidase deficiency. JAMA Neurol 71: 782–784.

Hoover-Fong JE, Shah S, Van Hove JLK et al. (2004). Natural history of nonketotic hyperglycinemia in 65 patients. Neurology 63: 1847–1853.

Howell RR, Byrne B, Darras BT et al. (2006). Diagnostic challenges for Pompe disease: an under-recognized cause of floppy baby syndrome. Genet Med 8: 289–296.

Huffnagel IC, Clur S-AB, Bams-Mengerink AM et al. (2013). Rhizomelic chondrodysplasia punctata and cardiac pathology. J Med Genet 50: 419–424.

Huisman TAGM, Thiel T, Steinmann B et al. (2002). Proton magnetic resonance spectroscopy of the brain of a neonate with nonketotic hyperglycinemia: in vivo–in vitro (ex vivo) correlation. Eur Radiol 12: 858–861.

Huppke P, Brendel C, Kalscheuer V et al. (2012). Mutations in SLC33A1 cause a lethal autosomal-recessive disorder with congenital cataracts, hearing loss, and low serum copper and ceruloplasmin. Am J Hum Genet 90: 61–68.

Illsinger S, Das AM (2010). Impact of selected inborn errors of metabolism on prenatal and neonatal development. IUBMB Life 62: 403–413.

Jaeken J, Péanne R (2017). What is new in CDG? J Inherit Metab Dis 40: 569–586. https://doi.org/10.1007/s10545-017-0050-6.

Jaeken J, Casaer P, de Cock P et al. (1984). Gamma-aminobutyric acid-transaminase deficiency: a newly recognized inborn error of neurotransmitter metabolism. Neuropediatrics 15: 165–169.

Jakobs C, Jaeken J, Gibson KM (1993). Inherited disorders of GABA metabolism. J Inherit Metab Dis 16: 704–715.

Jan W, Zimmerman RA, Wang ZJ et al. (2003). MR diffusion imaging and MR spectroscopy of maple syrup urine disease during acute metabolic decompensation. Neuroradiology 45: 393–399.

Jeyaratnam J, Ter Haar NM, de Sain- van der Velden MGM et al. (2016). Diagnostic value of urinary mevalonic acid excretion in patients with a clinical suspicion of mevalonate kinase deficiency (MKD). JIMD Rep 27: 33–38.

Johnston JJ, Gropman AL, Sapp JC et al. (2012). The phenotype of a germline mutation in PIGA: the gene somatically mutated in paroxysmal nocturnal hemoglobinuria. Am J Hum Genet 90: 295–300.

Jurczyluk J, Munoz MA, Skinner OP et al. (2016). Mevalonate kinase deficiency leads to decreased prenylation of Rab GTPases. Immunol Cell Biol 94: 994–999.

Kaler SG (1993). ATP7A-related copper transport disorders. In: MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJ Bean, K Stephens, A Amemiya (Eds.), GeneReviews®. University of Washington, Seattle, WA.

Kaler SG, Gahl WA, Berry SA et al. (1993a). Predictive value of plasma catecholamine levels in neonatal detection of Menkes disease. J Inherit Metab Dis 16: 907–908.

Kaler SG, Goldstein DS, Holmes C et al. (1993b). Plasma and cerebrospinal fluid neurochemical pattern in Menkes disease. Ann Neurol 33: 171–175.

Kaler SG, Holmes CS, Goldstein DS et al. (2008). Neonatal diagnosis and treatment of Menkes disease. N Engl J Med 358: 605–614.

Kamate M, Hattiholi V (2011). Normal neuroimaging in early-onset Krabbe disease. Pediatr Neurol 44: 374–376.

Khong P-L, Lam BCC, Chung BHY et al. (2003). Diffusion-weighted MR imaging in neonatal nonketotic hyperglycinemia. Am J Neuroradiol 24: 1181–1183.

Kikuchi G, Motokawa Y, Yoshida T et al. (2008). Glycine cleavage system: reaction mechanism, physiological significance, and hyperglycinemia. Proc Jpn Acad Ser B Phys Biol Sci 84: 246–263.

Kishnani PS, Hwu W-L, Mandel H et al. (2006). A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. J Pediatr 148: 671–676.

Kishnani PS, Goldenberg PC, DeArmey SL et al. (2010). Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. Mol Genet Metab 99: 26–33.

Klepper J, Diefenbach S, Kohlschütter A et al. (2004). Effects of the ketogenic diet in the glucose transporter 1 deficiency syndrome. Prostaglandins Leukot Essent Fatty Acids 70: 321–327.

Klepper J, Scheffer H, Leiendecker B et al. (2005). 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 36: 302–308.

Klouwer FCC, Berendse K, Ferdinandusse S et al. (2015). Zellweger spectrum disorders: clinical overview and management approach. Orphanet J Rare Dis 10: 151.

Koenig MK, Hodgeman R, Riviello JJ et al. (2017). Phenotype of GABA-transaminase deficiency. Neurology 88: 1919–1924.

Kuchar L, Ledvinová J, Hrebícek M et al. (2009). Prosaposin deficiency and saposin B deficiency (activator-deficient metachromatic leukodystrophy): report on two patients detected by analysis of urinary sphingolipids and carrying novel PSAP gene mutations. Am J Med Genet A 149A: 613–621.

Kültürsay N, Kütükçüler N, Büyükgebiz B et al. (1994). A case of maple syrup urine disease misdiagnosed as tetanus neonatorum on admission. Acta Paediatr Jpn 36: 284–286.

Kurolap A, Armbruster A, Hershkovitz T et al. (2016). Loss of glycine transporter 1 causes a subtype of glycine encephalopathy with arthrogryposis and mildly elevated cerebrospinal fluid glycine. Am J Hum Genet 99: 1172–1180.

Langan TJ, Barcykowski AL, Dare J et al. (2016). Evidence for improved survival in postsymptomatic stem cell-transplanted patients with Krabbe's disease. J Neurosci Res 94: 1189–1194.

Lanpher B, Brunetti-Pierri N, Lee B (2006). Inborn errors of metabolism: the flux from Mendelian to complex diseases. Nat Rev Genet 7: 449–460. https://doi.org/10.1038/nrg1880.

Leach EL, Shevell M, Bowden K et al. (2014). Treatable inborn errors of metabolism presenting as cerebral palsy mimics: systematic literature review. Orphanet J Rare Dis 9: 197.

Lee RWY, Conley SK, Gropman A et al. (2013). Brain magnetic resonance imaging findings in Smith–Lemli–Opitz syndrome. Am J Med Genet A 161A: 2407–2419.

Lee H-F, Chi C-S, Tsai C-R et al. (2017a). Prenatal brain disruption in isolated sulfite oxidase deficiency. Orphanet J Rare Dis 12: 115.

Lee JJY, Wasserman WW, Hoffmann GF et al. (2017b). Knowledge base and mini-expert platform for the diagnosis of inborn errors of metabolism. Genet Med 20: 151–158.

Leen WG, Wevers RA, Kamsteeg E-J et al. (2013). Cerebrospinal fluid analysis in the workup of GLUT1 deficiency syndrome: a systematic review. JAMA Neurol 70: 1440–1444.

León-Del-Río A, Valadez-Graham V, Gravel RA (2017). Holocarboxylase synthetase: a moonlighting transcriptional coregulator of gene expression and a cytosolic regulator of biotin utilization. Annu Rev Nutr 37: 207–223.

Livingston JH, Graziano C, Pysden K et al. (2012). Intracranial calcification in early infantile Krabbe disease: nothing new under the sun. Dev Med Child Neurol 54: 376–379.

Lund AM, Joensen F, Hougaard DM et al. (2007). Carnitine transporter and holocarboxylase synthetase deficiencies in The Faroe Islands. J Inherit Metab Dis 30: 341–349.

Macaya A, Brunso L, Fernández-Castillo N et al. (2005). Molybdenum cofactor deficiency presenting as neonatal hyperekplexia: a clinical, biochemical and genetic study. Neuropediatrics 36: 389–394.

Manara R, D'Agata L, Rocco MC et al. (2017a). Neuroimaging changes in Menkes disease, part 1. Am J Neuroradiol 38: 1850–1857.

Manara R, Rocco MC, D'agata L et al. (2017b). Neuroimaging changes in Menkes disease, part 2. Am J Neuroradiol 38: 1858–1865.

Marin-Valencia I, Roe CR, Pascual JM (2010). Pyruvate carboxylase deficiency: mechanisms, mimics and anaplerosis. Mol Genet Metab 101: 9–17.

Marquardt T, Lühn K, Srikrishna G et al. (1999). Correction of leukocyte adhesion deficiency type II with oral fucose. Blood 94: 3976–3985.

Martinelli D, Travaglini L, Drouin CA et al. (2013). MEDNIK syndrome: a novel defect of copper metabolism treatable by zinc acetate therapy. Brain J Neurol 136: 872–881.

Martínez M, Vázquez E, García-Silva MT et al. (2000). Therapeutic effects of docosahexaenoic acid ethyl ester in patients with generalized peroxisomal disorders. Am J Clin Nutr 71: 376S–385S.

Matthijs G, Schollen E, Pardon E et al. (1997). Mutations in PMM2, a phosphomannomutase gene on chromosome 16p13, in carbohydrate-deficient glycoprotein type I syndrome (Jaeken syndrome). Nat Genet 16: 88–92. https://doi.org/10.1038/ng0597-88.

Mayende L, Swift RD, Bailey LM et al. (2012). A novel molecular mechanism to explain biotin-unresponsive holocarboxylase synthetase deficiency. J Mol Med 90: 81–88.

Mayr JA, Haack TB, Graf E et al. (2012). Lack of the mitochondrial protein acylglycerol kinase causes Sengers syndrome. Am J Hum Genet 90: 314–320.

McAdams RM, Richards TL (2009). Detection of nonketotic hyperglycinemia in a neonate using proton magnetic resonance spectroscopy. Radiol Case Rep 4: 310.

Mechler K, Mountford WK, Hoffmann GF et al. (2015). Ultra-orphan diseases: a quantitative analysis of the natural history of molybdenum cofactor deficiency. Genet Med 17: 965–970.

Medina-Kauwe LK, Tobin AJ, De Meirleir L et al. (1999). 4-Aminobutyrate aminotransferase (GABA-transaminase) deficiency. J Inherit Metab Dis 22: 414–427.

Mergenthaler P, Lindauer U, Dienel GA et al. (2013). Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci 36: 587–597.

Messinger YH, Mendelsohn NJ, Rhead W et al. (2012). Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. Genet Med 14: 135–142.

Mills PB, Footitt EJ, Ceyhan S et al. (2012). Urinary AASA excretion is elevated in patients with molybdenum cofactor deficiency and isolated sulphite oxidase deficiency. J Inherit Metab Dis 35: 1031–1036.

Mochel F, DeLonlay P, Touati G et al. (2005). Pyruvate carboxylase deficiency: clinical and biochemical response to anaplerotic diet therapy. Mol Genet Metab 84: 305–312.

Montpetit A, Côté S, Brustein E et al. (2008). Disruption of AP1S1, causing a novel neurocutaneous syndrome, perturbs development of the skin and spinal cord. PLoS Genet 4: e1000296.

Morris AAM, Kožich V, Santra S et al. (2017). Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis 40: 49–74.

Mourmans J, Majoie CBLM, Barth PG et al. (2006). Sequential MR imaging changes in nonketotic hyperglycinemia. Am J Neuroradiol 27: 208–211.

Nagappa M, Bindu PS, Chiplunkar S et al. (2017). Hypersomnolence-hyperkinetic movement disorder in a child with compound heterozygous mutation in 4-aminobutyrate aminotransferase (ABAT) gene. Brain Dev 39: 161–165.

Narang MA, Dumas R, Ayer LM et al. (2004). Reduced histone biotinylation in multiple carboxylase deficiency patients: a nuclear role for holocarboxylase synthetase. Hum Mol Genet 13: 15–23.

Nellis MM, Danner DJ (2001). Gene preference in maple syrup urine disease. Am J Hum Genet 68: 232–237.

Ng BG, Buckingham KJ, Raymond K et al. (2013). Mosaicism of the UDP-galactose transporter SLC35A2 causes a congenital disorder of glycosylation. Am J Hum Genet 92: 632–636.

Nicolino M, Byrne B, Wraith JE et al. (2009). Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. Genet Med 11: 210–219.

Niehues R, Hasilik M, Alton G et al. (1998). Carbohydrate-deficient glycoprotein syndrome type Ib. Phosphomannose isomerase deficiency and mannose therapy. J Clin Invest 101: 1414–1420.

Nissenkorn A, Michelson M, Ben-Zeev B et al. (2001). Inborn errors of metabolism: a cause of abnormal brain development. Neurology 56: 1265–1272.

Noguer MT, Martinez M (2010). Visual follow-up in peroxisomal-disorder patients treated with docosahexaenoic acid ethyl ester. Invest Ophthalmol Vis Sci 51: 2277–2285.

Nowaczyk MJM, Irons MB (2012). Smith–Lemli–Opitz syndrome: phenotype, natural history, and epidemiology. Am J Med Genet C Semin Med Genet 160C: 250–262.

Nowaczyk MJ, Feigenbaum A, Silver MM et al. (1996). Bone marrow involvement and obstructive jaundice in Farber lipogranulomatosis: clinical and autopsy report of a new case. J Inherit Metab Dis 19: 655–660.

Nyhan WL, Khanna A, Barshop BA et al. (2002). Pyruvate carboxylase deficiency—insights from liver transplantation. Mol Genet Metab 77: 143–149.

Orsini JJ, Kay DM, Saavedra-Matiz CA et al. (2016). Newborn screening for Krabbe disease in New York State: the first eight years' experience. Genet Med 18: 239–248.

Oyarzabal A, Martínez-Pardo M, Merinero B et al. (2013). A novel regulatory defect in the branched-chain α-keto acid dehydrogenase complex due to a mutation in the PPM1K gene causes a mild variant phenotype of maple syrup urine disease. Hum Mutat 34: 355–362.

Paker AM, Sunness JS, Brereton NH et al. (2010). Docosahexaenoic acid therapy in peroxisomal diseases: results of a double-blind, randomized trial. Neurology 75: 826–830.

Parmar H, Sitoh YY, Ho L (2004). Maple syrup urine disease: diffusion-weighted and diffusion-tensor magnetic resonance imaging findings. J Comput Assist Tomogr 28: 93–97.

Pascual JM, Liu P, Mao D et al. (2014). Triheptanoin for glucose transporter type I deficiency (G1D): modulation of human ictogenesis, cerebral metabolic rate, and cognitive indices by a food supplement. JAMA Neurol 71: 1255–1265.

Patel KP, O'Brien TW, Subramony SH et al. (2012). The spectrum of pyruvate dehydrogenase complex deficiency: clinical, biochemical and genetic features in 371 patients. Mol Genet Metab 105: 34–43.

Pearl PL, Gibson KM, Cortez MA et al. (2009). Succinic semialdehyde dehydrogenase deficiency: lessons from mice and men. J Inherit Metab Dis 32: 343–352.

Pearson TS, Pons R, Engelstad K et al. (2017). Paroxysmal eye-head movements in Glut1 deficiency syndrome. Neurology 88: 1666–1673.

Peters H, Ferdinandusse S, Ruiter JP et al. (2015). Metabolite studies in HIBCH and ECHS1 defects: implications for screening. Mol Genet Metab 115: 168–173.

Pirot N, Crahes M, Adle-Biassette H et al. (2016). Phenotypic and neuropathological characterization of fetal pyruvate dehydrogenase deficiency. J Neuropathol Exp Neurol 75: 227–238.

Poll-The BT, Gärtner J (2012). Clinical diagnosis, biochemical findings and MRI spectrum of peroxisomal disorders. Biochim Biophys Acta 1822: 1421–1429.

Pong AW, Geary BR, Engelstad KM et al. (2012). Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes. Epilepsia 53: 1503–1510.

Poretti A, Blaser SI, Lequin MH et al. (2013). Neonatal neuroimaging findings in inborn errors of metabolism. J Magn Reson Imaging 37: 294–312.

Prater SN, Banugaria SG, DeArmey SM et al. (2012). The emerging phenotype of long-term survivors with infantile Pompe disease. Genet Med 14: 800–810.

Rahman S, Thorburn D (1993). Nuclear gene-encoded Leigh syndrome overview. In: MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJ Bean, HC Mefford, K Stephens, A Amemiya, N Ledbetter (Eds.), GeneReviews®. University of Washington, Seattle, WA.

Reuter MS, Sass JO, Leis T et al. (2014). HIBCH deficiency in a patient with phenotypic characteristics of mitochondrial disorders. Am J Med Genet A 164A: 3162–3169.

Rosewich H, Dechent P, Krause C et al. (2016). Diagnostic and prognostic value of in vivo proton MR spectroscopy for Zellweger syndrome spectrum patients. J Inherit Metab Dis 39: 869–876.

Ruhoy IS, Saneto RP (2014). The genetics of Leigh syndrome and its implications for clinical practice and risk management. Appl Clin Genet 7: 221–234.

Sahai I, Baris H, Kimonis V et al. (2005). Krabbe disease: severe neonatal presentation with a family history of multiple sclerosis. J Child Neurol 20: 826–828.

Sanderson S, Green A, Preece MA et al. (2006). The incidence of inherited metabolic disorders in the West Midlands, UK. Arch Dis Child 91: 896–899. https://doi.org/10.1136/adc.2005.091637.

Sass JO, Gunduz A, Araujo Rodrigues Funayama C et al. (2010). Functional deficiencies of sulfite oxidase: differential diagnoses in neonates presenting with intractable seizures and cystic encephalomalacia. Brain Dev 32: 544–549.

Sato T, Muroya K, Hanakawa J et al. (2014). Neonatal case of classic maple syrup urine disease: usefulness of (1) H-MRS in early diagnosis. Pediatr Int 56: 112–115.

Schnabel D, Schröder M, Fürst W et al. (1992). Simultaneous deficiency of sphingolipid activator proteins 1 and 2 is caused by a mutation in the initiation codon of their common gene. J Biol Chem 267: 3312–3315.

Schuette CG, Pierstorff B, Huettler S et al. (2001). Sphingolipid activator proteins: proteins with complex functions in lipid degradation and skin biogenesis. Glycobiology 11: 81R–90R.

Schwahn BC, Van Spronsen FJ, Belaidi AA et al. (2015). Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet 386: 1955–1963.

Shaheen R, Rahbeeni Z, Alhashem A et al. (2014). Neu–Laxova syndrome, an inborn error of serine metabolism, is caused by mutations in PHGDH. Am J Hum Genet 94: 898–904.

Shibata T, Kobayashi K, Yoshinaga H et al. (2017). Another case of glucose transporter 1 deficiency syndrome with periventricular calcification, cataracts, hemolysis, and pseudohyperkalemia. Neuropediatrics 48: 390–393.

Shinawi M, Szabo S, Popek E et al. (2005). Recognition of Smith-Lemli-Opitz syndrome (RSH) in the fetus: utility of ultrasonography and biochemical analysis in pregnancies with low maternal serum estriol. Am J Med Genet A 138: 56–60.

Sikora DM, Ruggiero M, Petit-Kekel K et al. (2004). Cholesterol supplementation does not improve developmental progress in Smith-Lemli-Opitz syndrome. J Pediatr 144: 783–791.

Sofou K, De Coo IFM, Isohanni P et al. (2014). A multicenter study on Leigh syndrome: disease course and predictors of survival. Orphanet J Rare Dis 9: 52.

Sofou K, Dahlin M, Hallböök T et al. (2017). Ketogenic diet in pyruvate dehydrogenase complex deficiency: short- and long-term outcomes. J Inherit Metab Dis 40: 237–245.

Srour M, Shimokawa N, Hamdan FF et al. (2017). Dysfunction of the cerebral glucose transporter SLC45A1 in individuals with intellectual disability and epilepsy. Am J Hum Genet 100: 824–830.

Starck L, Lövgren-Sandblom A, Björkhem I (2002). Cholesterol treatment forever? The first Scandinavian trial of cholesterol supplementation in the cholesterol-synthesis defect Smith-Lemli-Opitz syndrome. J Intern Med 252: 314–321.

Staufner C, Haack TB, Feyh P et al. (2016). Genetic cause and prevalence of hydroxyprolinemia. J Inherit Metab Dis 39: 625–632.

Strauss KA, Puffenberger EG, Morton DH (1993). Maple syrup urine disease. In: MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJ Bean, HC Mefford, K Stephens, A Amemiya, N Ledbetter (Eds.), GeneReviews®. University of Washington, Seattle, WA.

Strauss KA, Mazariegos GV, Sindhi R et al. (2006). Elective liver transplantation for the treatment of classical maple syrup urine disease. Am J Transplant 6: 557–564.

Strauss KA, Wardley B, Robinson D et al. (2010). Classical maple syrup urine disease and brain development: principles of management and formula design. Mol Genet Metab 99: 333–345.

Subramanian VS, Constantinescu AR, Benke PJ et al. (2017). Mutations in SLC5A6 associated with brain, immune, bone, and intestinal dysfunction in a young child. Hum Genet 136: 253–261.

Suryawan A, Hawes JW, Harris RA et al. (1998). A molecular model of human branched-chain amino acid metabolism. Am J Clin Nutr 68: 72–81.

Ter Haar NM, Jeyaratnam J, Lachmann HJ et al. (2016). The phenotype and genotype of mevalonate kinase deficiency: a series of 114 cases from the eurofever registry. Arthritis Rheumatol 68: 2795–2805.

Tharp BR (1992). Unique EEG pattern (comb-like rhythm) in neonatal maple syrup urine disease. Pediatr Neurol 8: 65–68.

Thompson MD, Killoran A, Percy ME et al. (2006). Hyperphosphatasia with neurologic deficit: a pyridoxine-responsive seizure disorder? Pediatr Neurol 34: 303–307.

Thorburn DR, Rahman J, Rahman S (1993). Mitochondrial DNA-associated Leigh syndrome and NARP. In: MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJ Bean, HC Mefford, K Stephens, A Amemiya, N Ledbetter (Eds.), GeneReviews®. University of Washington, Seattle, WA.

Timal S, Hoischen A, Lehle L et al. (2012). Gene identification in the congenital disorders of glycosylation type I by whole-exome sequencing. Hum Mol Genet 21: 4151–4161. https://doi.org/10.1093/hmg/dds123.

Topcu M, Coskun T, Haliloglu G et al. (2001). Molybdenum cofactor deficiency: report of three cases presenting as hypoxic–ischemic encephalopathy. J Child Neurol 16: 264–270.

Tort F, Ferrer-Cortes X, Ribes A (2016). Differential diagnosis of lipoic acid synthesis defects. J Inherit Metab Dis 39: 781–793.

Tsuji M, Aida N, Obata T et al. (2010). A new case of GABA transaminase deficiency facilitated by proton MR spectroscopy. J Inherit Metab Dis 33: 85–90.

Tümer Z, Møller LB (2010). Menkes disease. Eur J Hum Genet 18: 511–518.

Unal O, Orhan D, Ostergaard E et al. (2013). A patient with pyruvate carboxylase deficiency and nemaline rods on muscle biopsy. J Child Neurol 28: 1505–1508.

van der Burgh R, Pervolaraki K, Turkenburg M et al. (2014). Unprenylated RhoA contributes to IL-1β hypersecretion in mevalonate kinase deficiency model through stimulation of Rac1 activity. J Biol Chem 289: 27757–27765.

van Dongen S, Brown RM, Brown GK et al. (2015). Thiamine-responsive and non-responsive patients with PDHC-E1 deficiency: a retrospective assessment. JIMD Rep 15: 13–27.

Van Hove J, Coughlin C, Scharer G (1993). Glycine encephalopathy. In: MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJ Bean, HC Mefford, K Stephens, A Amemiya, N Ledbetter (Eds.), GeneReviews®. University of Washington, Seattle, WA.

Van Hove JLK, Josefsberg S, Freehauf C et al. (2008). Management of a patient with holocarboxylase synthetase deficiency. Mol Genet Metab 95: 201–205.

van Karnebeek CDM, Stockler S (2012). Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. Mol Genet Metab 105: 368–381.

van Karnebeek CDM, Hartmann H, Jaggumantri S et al. (2012a). Lysine restricted diet for pyridoxine-dependent epilepsy: first evidence and future trials. Mol Genet Metab 107: 335–344.

van Karnebeek CDM, Houben RFA, Lafek M et al. (2012b). The treatable intellectual disability APP www.treatable-id.org: a digital tool to enhance diagnosis & care for rare diseases. Orphanet J Rare Dis 7: 47.

van Karnebeek CD, Sly WS, Ross CJ et al. (2014). Mitochondrial carbonic anhydrase VA deficiency resulting from CA5A alterations presents with hyperammonemia in early childhood. Am J Hum Genet 94: 453–461.

van Karnebeek CDM, Sayson B, Lee JJY et al. (2018). Metabolic evaluation of epilepsy: a diagnostic algorithm with focus on treatable conditions. Front Neurol 9: 1016. https://doi.org/10.3389/fneur.2018.01016.

Vanadia E, Gibson KM, Pearl PL et al. (2013). Therapeutic efficacy of magnesium valproate in succinic semialdehyde dehydrogenase deficiency. JIMD Rep 8: 133–137.

Vormoor J, Ehlert K, Groll AH et al. (2004). Successful hematopoietic stem cell transplantation in Farber disease. J Pediatr 144: 132–134.

Wanders RJA, Waterham HR (2006). Biochemistry of mammalian peroxisomes revisited. Annu Rev Biochem 75: 295–332.

Weiss K, Gonzalez A, Lopez G et al. (2015). The clinical management of Type 2 Gaucher disease. Mol Genet Metab 114: 110–122.

Wenk J, Hille A, von Figura K (1991). Quantitation of Mr 46000 and Mr 300000 mannose 6-phosphate receptors in human cells and tissues. Biochem Int 23: 723–731.

White AL, Modaff P, Holland-Morris F et al. (2003). Natural history of rhizomelic chondrodysplasia punctata. Am J Med Genet A 118A: 332–342.

Williams JP, Secrist L, Fowler GW et al. (1972). Roentgenographic features of the cerebrohepatorenal syndrome of Zellweger. Am J Roentgenol Radium Ther Nucl Med 115: 607–610.

Willis A, Vanhuse C, Newton KP et al. (2008). Farber's disease type IV presenting with cholestasis and neonatal liver failure: report of two cases. Pediatr Dev Pathol 11: 305–308.

Wilson CJ, Myer M, Darlow BA et al. (2005). Severe holocarboxylase synthetase deficiency with incomplete biotin responsiveness resulting in antenatal insult in Samoan neonates. J Pediatr 147: 115–118.

Wu Y, Buzzi A, Frantseva M et al. (2006). Status epilepticus in mice deficient for succinate semialdehyde dehydrogenase: GABAA receptor-mediated mechanisms. Ann Neurol 59: 42–52.

Yang C-F, Yang CC, Liao H-C et al. (2016). Very early treatment for infantile-onset Pompe disease contributes to better outcomes. J Pediatr 169: 174–180.e1.

Yeager AM, Uhas KA, Coles CD et al. (2000). Bone marrow transplantation for infantile ceramidase deficiency (Farber disease). Bone Marrow Transplant 26: 357–363.

Yokoi K, Ito T, Maeda Y et al. (2009). A case of holocarboxylase synthetase deficiency with insufficient response to prenatal biotin therapy. Brain Dev 31: 775–778.

Zafeiriou DI, Anastasiou AL, Michelakaki EM et al. (1997). Early infantile Krabbe disease: deceptively normal magnetic resonance imaging and serial neurophysiological studies. Brain Dev 19: 488–491.

Zaki MS, Selim L, El-Bassyouni HT et al. (2016). Molybdenum cofactor and isolated sulphite oxidase deficiencies: clinical and molecular spectrum among Egyptian patients. Eur J Paediatr Neurol 20: 714–722.

Zhang S (2016). Natural history of mevalonate kinase deficiency: a literature review. Pediatr Rheumatol Online J 14: 30.

Zinnanti WJ, Lazovic J, Griffin K et al. (2009). Dual mechanism of brain injury and novel treatment strategy in maple syrup urine disease. Brain J Neurol 132: 903–918.

Ziyeh S, Berlis A, Korinthenberg R et al. (2002). Selective involvement of the globus pallidus and dentate nucleus in succinic semialdehyde dehydrogenase deficiency. Pediatr Radiol 32: 598–600.

Zubarioglu T, Kiykim E, Cansever MS et al. (2016). Neonatal nonketotic hyperglycinemia: diffusion-weighted magnetic resonance imaging and diagnostic clues. Acta Neurol Belg 116: 671–673.