INTRODUCTION

This manual reviews metabolic diseases that affect the nervous system, focusing on the usual presentations from the perspective of a pediatric neurologist. Many of these disorders will also have milder presentations in later life; these are not discussed. This review presents sufficient information to begin a workup and to institute initial interventions. A beginning neurologist will need to learn more about each disorder as he or she closes in on the definitive diagnosis. If a diagnosis is not readily apparent by clinical presentation, one must resort to a more systematic approach.

In this review, disorders are generally grouped according to defects of the various biochemical pathways. Metabolic disorders caused by defects in the mobilization of glycogen (ie, glycogen storage diseases) or fats (ie, fatty acid oxidation defects) or defects in the citric acid cycle or respiratory chain (ie, mitochondrial disorders). These disorders tend to present as decompensations with stress or increased energy demand. Metabolic disorders caused by defects in amino acid metabolism include the organic acidemias, aminoacidopathies, and urea cycle defects. These disorders tend to present in infancy as increasing lethargy and vomiting with initiation of feeds. Lysosomal disorders result in the accumulation of large carbohydrate–lipid complexes and present as dysmorphism with organomegaly, psychiatric symptoms, or white matter disease. Aside from the glycogen storage disorders, the disorders of carbohydrate metabolism are rather heterogeneous. Finally, some primarily white matter disorders are suggested by clinical presentation, such as increasing spasticity and abnormalities in white matter on magnetic resonance imaging (MRI), whereas primarily gray matter disorders present as seizures and cognitive decline.

In the United States, most states screen newborns for phenylketonuria, galactosemia, hypothyroidism, congenital adrenal hyperplasia, hemoglobinopathies, and maple syrup urine disease. Some states employ tandem mass spectroscopy, which gives amino acid and acylcarnitine profiles. These tests are useful for diagnosing many metabolic disorders, as described below.

DISORDERS CAUSED BY ENERGY FAILURE

GLYCOCEN STORAGE DISORDERS (GSD)

Glycogen is an important source of stored glucose found primarily in liver and muscle. Defects in glycogen mobilization can lead to energy failure during times of fasting and exercise.

GSD TYPE II

GSD type II (Pompe disease) is caused by deficiency of the lysosomal enzyme acid maltase (α-1,4-glucosidase). The infantile form presents as severe hypotonia and cardiomyopathy and is usually fatal before 12 months of age. The childhood form affects only skeletal muscle and presents as progressive weakness. Creatine kinase (CK) levels are markedly elevated, and muscle biopsy demonstrates glycogen storage in muscle fibers and absence of acid maltase. Hypoglycemia is not seen in GSD II.

GSD TYPE V

GSD type V (McArdle disease) is caused by deficiency of myophosphorylase and presents in adolescents as cramps and muscle fatigue shortly after initiating exercise. A “second wind” effect can occur (ie, renewed ability to continue exercising if patients rest briefly after the onset of fatigue). Laboratory studies show elevated CK levels, post-exertional myoglobinuria, and a failure of normal rise in lactate levels with exercise. The forearm ischemic test is the classic exercise test but is difficult to perform reliably. Muscle biopsy shows glycogen storage in muscle and absence of myophosphorylase. Moderate exercise with careful warmup is advisable. Dietary treatments have been disappointing.

FATTY ACID OXIDATION DISORDERS

Fatty acid oxidation disorders consist of autosomal recessive defects in either the transport of fatty acids into mitochondria or in the intramitochondrial β-oxidation of fatty acids. A prolonged fast or significant stress (eg, illness, surgery) may deplete liver stores of glycogen. If fatty stores fail to be mobilized for fuel, the result is the classic laboratory finding of hypoketotic hypoglycemia. A mild to
moderate hyperammonemia may also be seen. Organs especially sensitive to fatty acid oxidation defects include the brain (which depends on ketones for fuel in the fasted state), the heart and muscles (due to high metabolic demand and because fatty fuels spare proteolysis), and the liver (which relies on energy derived from fatty acid oxidation for gluconeogenesis and ureagenesis). Management for all fatty acid oxidation disorders includes avoiding prolonged fasts and aggressive use of dextrose-containing fluids during decompensations.

Carnitine must bind to long-chain fatty acids for fatty acid transport across the mitochondrial double membrane. Carnitine enters the cell through a carnitine transporter. It is bound to the fatty acyl group by carnitine palmitoyl transferase 1 (CPT1) at the outer mitochondrial membrane. Acylcarnitine is then transported to the inner mitochondrial membrane by acylcarnitine translocase. At the inner mitochondrial membrane, acylcarnitine is disassembled into acyl coenzyme A (CoA) and free carnitine by carnitine palmitoyl transferase 2 (CPT2). Acyl CoA then enters β-oxidation while free carnitine is recirculated to the cell cytoplasm. The first
step in \( \beta \)-oxidation is performed by acyl CoA dehydrogenases, which are distinct depending on the acyl-group chain length.

Carnitine also acts as a scavenger of potentially toxic acyl CoA metabolites, forming acylcarnitine esters that are excreted in the urine. A secondary carnitine deficiency results when urinary acylcarnitine loss is excessive. Blood carnitine levels then show an elevated acylcarnitine ester-to-free carnitine ratio (ie, > 0.4). Valproic acid therapy can cause secondary carnitine deficiency in this way by forming valproyl carnitine ester.

Screening laboratory tests include plasma free and total carnitines, plasma acylcarnitine profile, and urine acylglycines. Laboratory findings are summarized in Table 2. Interpretation of urine acylglycines is complex and is omitted in this review.

Carnitine Disorders

Carnitine transporter deficiency leads to total body carnitine depletion secondary to increased renal loss. Symptoms include muscle weakness and cardiomyopathy. Carnitine given in high doses reverses symptoms and can be lifesaving.

CPT1 deficiency presents as a Reye-like syndrome, with progressive encephalopathy, seizures secondary to hypoglycemia, hepatomegaly, moderate hyperammonemia, and elevated liver enzymes. Skeletal and cardiac muscle are not involved. Acylcarnitine profile shows decreased long-chain acylcarnitines (C16, C18). Chronic treatment with medium-chain fatty acids may be of benefit.

CPT2 deficiency has an infantile (liver) and adult (muscle) form. The infantile form presents as hepatomegaly, liver failure, cardiomegaly, arrhythmias, and seizures, with hypoketotic hypoglycemia. The adult form presents in the teens to twenties as episodic rhabdomyolysis and myoglobinuria following prolonged exercise, cold exposure, infection, or fasting, with elevated CK levels and myoglobinuria.

Disorders of \( \beta \)-Oxidation and Ketogenesis

Medium-chain acyl CoA dehydrogenase (MCAD) deficiency is the most common of the fatty acid oxidation disorders. MCAD helps metabolize medium-chain fatty acids to ketones, which are used as fuel during times of stress and fasting. Acute presentation consists of lethargy, vomiting, seizure, and progressive encephalopathy after fasting or physical stress. An initial attack may result in sudden infant death. Management includes moderate dietary fat restriction and carnitine supplementation.

Very-long-chain acyl CoA dehydrogenase (VLCAD) deficiency and long-chain 3-hydroxy acyl CoA dehydrogenase (LCHAD) deficiency are associated with cardiomyopathy, skeletal myopathy, post-exertional rhabdomyolysis, and hypoketotic hypoglycemia with decompensations. Children with VLCAD deficiency can present with a Reye-like syndrome, which can be fatal. Mothers carrying a fetus with LCHAD deficiency can present with hemolysis, elevated liver function tests, and low platelet counts (HELLP syndrome). Diagnosis is by acylcarnitine profile, which shows elevated long-chain acylcarnitines and hydroxy-acylcarnitines, respectively, in patients with VLCAD deficiency and LCHAD deficiency. Medium-chain triglycerides (MCT oil) are supplemented.

Glutaric acidemia type II (multiple acyl CoA-dehydrogenase deficiency) involves defects in the flavin adenine dinucleotide (FAD)–dependent electron transfer from dehydrogenase enzymes to the electron transport chain. This disorder affects both fatty acid

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Total</th>
<th>Free (F)</th>
<th>Esters (E)</th>
<th>E:F Ratio</th>
<th>Serum Acylcarnitine Profile</th>
<th>Age of Onset</th>
<th>Tissue Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transporter</td>
<td>↓↓</td>
<td>↓</td>
<td>↓↓</td>
<td>&lt; 0.3 (nl)</td>
<td>↓All esters</td>
<td>I/C</td>
<td>H/M/L</td>
</tr>
<tr>
<td>CPT1</td>
<td>↑↑</td>
<td>↓</td>
<td>↓↓</td>
<td>&lt; 0.2</td>
<td>↓C16, C18</td>
<td>I/C</td>
<td>L</td>
</tr>
<tr>
<td>Translocase</td>
<td>↓↓</td>
<td>↑</td>
<td>↓↓</td>
<td>&gt; 0.4</td>
<td>↑C16, C18</td>
<td>N</td>
<td>H/L</td>
</tr>
<tr>
<td>CPT2 (liver)</td>
<td>↓↓</td>
<td>↓</td>
<td>↑</td>
<td>&gt; 0.4</td>
<td>↑C16, C18</td>
<td>N/I</td>
<td>H/L</td>
</tr>
<tr>
<td>CPT2 (muscle)</td>
<td>↓↓</td>
<td>↓</td>
<td>↑</td>
<td>&gt; 0.4</td>
<td>↑C16, C18</td>
<td>C/A</td>
<td>H/M</td>
</tr>
<tr>
<td>MCAD</td>
<td>↓↓</td>
<td>↑</td>
<td>↑↑</td>
<td>&gt; 0.4</td>
<td>↑C6, C8, C10:1</td>
<td>I/C</td>
<td>L</td>
</tr>
<tr>
<td>LCHAD</td>
<td>↓</td>
<td>↓</td>
<td>↑↑</td>
<td>&gt; 0.4</td>
<td>↑C16-OH, C18-OH</td>
<td>I/C</td>
<td>H/M/L</td>
</tr>
</tbody>
</table>

A = adult; C = child; CPT = carnitine palmitoyl transferase; H = heart; I = infant; L = liver/Reye syndrome; LCHAD = long-chain hydroxyacyl CoA dehydrogenase; M = skeletal muscle; MCAD = medium-chain acyl CoA dehydrogenase; N = neonate; nl = normal. (Adapted from Nyhan WL, Ozand PT. Atlas of metabolic diseases. New York: Chapman and Hall; 1998.)

Table 2. Carnitine-Associated and Fatty Acid Disorders
oxidation and amino acid metabolism. The classic neonatal form is severe and presents as a Reye-like syndrome, followed by seizures and progressive neurodegeneration. Dysmorphism and cystic kidneys may be present. Diagnosis is by recognizing a complex pattern in plasma acylcarnitines, urine organic acids, and urine acylglycines, including urine glutaric acid.

MITOCHONDRIAL DISORDERS

Mitochondrial disorders are caused by a genetic defect in either nuclear or mitochondrial DNA. Many mitochondrial syndromes have been defined, but there is significant overlap with a complex relationship between identified genetic defects and classic mitochondrial syndromes4 (Table 3).4–9

Clinical Features

Mitochondrial disorders are highly variable in presentation. Suspicion for a mitochondrial defect increases if there is multisystem involvement of high energy systems3,10 (Table 4). Diagnosis of mitochondrial disorders begins with analysis of serum lactate, pyruvate, and CK levels. Classically, lactate is elevated even at rest, with a lactate-to-pyruvate ratio greater than 25 (more commonly, from 50 to 250). However, 40% of patients have normal lactate levels at rest. Furthermore, mitochondrial DNA panels are abnormal in only 10% of patients.11 Thus muscle biopsy remains a key to diagnosis. Muscle biopsy may show ragged red fibers on Gomori trichrome stain, succinate dehydrogenase stains the same fibers blue, and cytochrome c oxidase stains reveal deficient mitochondrial respiratory chain protein synthesis.

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Table 3. Mitochondrial Disorders

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Characteristic Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELAS4</td>
<td>Recurrent stroke-like events, migrating lesions on MRI, episodic encephalopathy, migraines, seizures</td>
<td>Leucine tRNA mtDNA mutation in 80%</td>
</tr>
<tr>
<td>MERRF5</td>
<td>Myoclonic epilepsy, ataxia, optic atrophy, hearing loss</td>
<td>Lysine tRNA mtDNA mutation in 80%</td>
</tr>
<tr>
<td>CPEO6</td>
<td>CPEO, ptosis, variable skeletal muscle weakness</td>
<td>Multiple mtDNA deletion; only skeletal muscle affected</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome 4</td>
<td>CPEO, retinitis pigmentosa, and one of following: cerebellar ataxia, conduction block, CSF protein &gt; 100 mg/dL</td>
<td>Multiple mtDNA deletion; all tissues affected; check serial ECGs</td>
</tr>
<tr>
<td>Leigh syndrome, or subacute necrotizing encephalomyelopathy7</td>
<td>Ataxia, hypotonia, ophthalmoplegia, dysphagia, dystonia</td>
<td>Severe neurodegenerative disease; most die by 3 years of age</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy8</td>
<td>Acute: optic nerve hyperemia, vascular tortuosity Chronic: optic atrophy Uncommon: cardiac conduction abnormalities</td>
<td>Painless; initially asymmetric; progresses over weeks to months</td>
</tr>
<tr>
<td>Neurogenic muscle weakness, ataxia, and retinitis pigmentosa7</td>
<td>Neuropathy, ataxia, retinitis pigmentosa, proximal weakness, mental retardation</td>
<td>Can go years without exacerbation; mtATPase affected</td>
</tr>
<tr>
<td>Friedreich ataxia9</td>
<td>Ataxia, areflexia, loss of vibration and proprioceptive sense, with onset before age 25 years Associated: diabetes, cardiomyopathy, scoliosis, optic atrophy, deafness</td>
<td>Trinucleotide expansion in Frataxin gene; autosomal recessive (nuclear gene) Causes intramitochondrial iron accumulation; most die in mid-30s. Milder variant exists with retained reflexes</td>
</tr>
</tbody>
</table>

CPEO = chronic progressive external ophthalmoplegia; CSF = cerebrospinal fluid; ECG = electrocardiogram; MELAS = mitochondrial myopathy, encephalopathy, and lactic acidosis with stroke-like episodes; MERRF = myoclonic epilepsy with ragged red fibers; MRI = magnetic resonance imaging; mt = mitochondrial.

Table 4. Clinical Features of Mitochondrial Disorders

| Brain: | Psychiatric disorder, seizures, ataxia, myoclonus, migraine, stroke-like events |
| Eyes: | Optic neuropathy, retinitis pigmentosa, ptosis, external ophthalmoplegia |
| Ears: | Sensorineural hearing loss |
| Nerve: | Neuropathic pain, areflexia, gastrointestinal pseudo-obstruction, dysautonomia |
| Muscle: | Hypotonia, weakness, exercise intolerance, cramping |
| Heart: | Conduction block, cardiomyopathy, arrhythmia |
| Liver: | Hypoglycemia, liver failure |
| Kidneys: | Proximal renal tubular dysfunction (Fanconi syndrome) |
| Endocrine: | Diabetes, hypoparathyroidism |


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Biochemical analysis of muscle can reveal decreases in activity of the respiratory chain complexes I to IV. Electron microscopy shows overabundant, enlarged, and bizarrely shaped mitochondria with paracrystalline inclusions. Brain MRI may show lesions of the basal ganglia, thalamus, midbrain, or cerebral white matter. In the cerebral white matter, recurrent stroke-like events may occur, with transitory migrating lesions that cross vascular territories (Figure 2). Magnetic resonance spectroscopy may show elevated lactate peaks in these lesions. Impaired autoregulation of cerebral vasculature has been suggested as the etiology of stroke-like events.

**Treatment**

Treatment is with L-carnitine, B vitamins (riboflavin and thiamine), and coenzyme Q or idebenone. Biotin, antioxidants (vitamins A and C), folate, and lipoic acid are also used. Dichloroacetic acid may lower lactate levels in some patients. Response to treatment is variable, with some patients experiencing improvement in energy and function but many experiencing no discernible improvement.

**PYRUVATE DEHYDROGENASE COMPLEX DEFICIENCY**

Pyruvate dehydrogenase complex (PDHC) deficiency blocks entry of pyruvate into the citric acid cycle, resulting in elevated lactate and pyruvate levels. PDHC deficiency presents similar to the mitochondrial disorders. The severe neonatal form is fatal in infancy. Leigh disease can develop later in infancy. Diagnosis is based on finding elevated lactate and pyruvate levels with preservation of the lactate-to-pyruvate ratio (ie, < 20).

Treatment involves supplementation with thiamine, which is a cofactor for PDHC, and a high fat, low carbohydrate diet. Acetazolamide may abort attacks.

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**DISORDERS OF AMINO ACID METABOLISM**

**ORGANIC ACIDEMIAS**

Organic acidemias are caused by autosomal recessive disorders of amino acid metabolism. The usual presentation is that of nonspecific poor feeding, lethargy, and vomiting in the neonatal period, eventually progressing to coma. Symptoms are often initially mistaken for sepsis. Laboratory findings include metabolic acidosis with an elevated anion gap, sometimes with ketosis and hyperammonemia (Table 5). Diagnosis during the acute illness depends on plasma amino acids, plasma acylcarnitine profile, urine organic acids, and urine acylglycine profile. The detailed analysis of these profiles is often complex and is not discussed here. Acute treatment involves withholding protein feeds and aggressively pushing dextrose-containing fluids, to induce an anabolic state. Chronic treatment consists of specific dietary protein restriction. Carnitine supplementation can be helpful.

**Propionic Acidemia**

Propionic acidemia is caused by a deficiency in propionyl CoA carboxylase. Most children have some cognitive disability even with optimal therapy. Cardiomyopathy, pancreatitis, osteoporosis, and movement disorders are late complications.
Methylmalonic Acidemia

Methylmalonic acidemia is caused by a defect in methylmalonyl CoA mutase. Acidosis and hyperammonemia can be severe, and a single attack can cause permanent cognitive disability. Seizures, spasticity, behavioral problems, and ataxia are common. Metabolic stroke with an acute decompensation can occur. Many patients will develop renal failure and require renal transplantation. Methylmalonic acid can also be elevated in disorders of cobalamin (vitamin B12) metabolism, and megaloblastic anemia can be seen. Brain MRI may show bilateral globus pallidus infarction. Management of methylmalonic acidemia consists of vitamin B12 supplementation and dietary protein restriction.

Glutaric Acidemia Type I

Glutaric acidemia type I is caused by a deficiency in glutaryl CoA dehydrogenase, which results in dystonia, ataxia, cognitive disability, and spasticity. Metabolic acidosis is not a prominent feature even with acute decompensation. Diagnostic studies are often normal when affected individuals are healthy. Neuroimaging shows frontotemporal atrophy with basal ganglia lesions. Basal ganglia injury can appear even with a first attack. Macrocephaly is common. Chronic management consists of carnitine supplementation and protein restriction.18

Aminoacidopathies

Classic Phenylketonuria

Classic phenylketonuria (PKU) is caused by a deficiency in the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine. Neurotoxic phenylketones then accumulate. Testing shows elevated levels of blood phenylalanine and urine phenylketones. Infants are normal at birth but in the first year of life manifest progressive cognitive delay, microcephaly, spasticity, recurrent eczematous rash, and a musty odor. Seizures occur in 25% of untreated PKU patients.19 Newborn screening and early treatment can prevent these symptoms. Treatment in classic PKU consists of dietary restriction of phenylalanine and close monitoring of blood phenylalanine levels. Women with PKU should have phenylalanine levels under control before attempting to conceive. Fetuses exposed to high levels of phenylalanine are at risk for congenital heart disease, intrauterine growth restriction, mental retardation, and microcephaly. Approximately 2% of PKU patients have normal phenylalanine hydroxylase activity but are deficient in the cofactor tetrahydrobiopterin.20 These patients require biopterin supplementation.

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) is caused by a deficiency in branched-chain α-ketoacid dehydrogenase, which is responsible for the metabolism of leucine, isoleucine, and valine. The classic form presents in the first week of life with poor feeding, lethargy, and vomiting, quickly progressing to coma, seizures and death if untreated. An intermittent form may present later in life with attacks of transient ataxia, sometimes accompanied by cerebral edema.21 These attacks are triggered by intercurrent illness or stresses. Urine, sweat, and cerumen often smell like maple syrup. Acidosis and hyperammonemia are uncommon.

In the United States, many states screen newborns for MSUD. Testing during an attack shows elevated leucine, isoleucine, and valine in blood as well as branched-chain metabolites in urine, but these levels may be normal in the immediate neonatal period before branched-chain amino acids have accumulated and in the intermittent form between attacks. Acute management includes aggressive high calorie intravenous or nasogastric feeds, sometimes with intravenous insulin to help induce an anabolic state. Special MSUD total parenteral nutrition is available with the proper mixture of amino acids. Chronic management relies on dietary restriction of branched-chain amino acids. With early diagnosis and tight metabolic control, the prognosis is for normal development.

Classic Homocystinuria

Classic homocystinuria is an autosomal recessive disorder caused by a defect in the enzyme cystathionine β-synthetase, resulting in elevations of homocystine and methionine. Infants are usually asymptomatic, but mental retardation can develop in untreated patients. Adults are often tall and thin, and most have significant myopia. Lens dislocation (ectopia lentis) may develop later in life, but the lens is usually dislocated inferiorly, which is the opposite of what is seen in Marfan syndrome. Untreated

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patients are at risk for seizures, psychiatric disorders, and thromboembolic events including stroke, myocardial infarction, and pulmonary emboli. Treatment involves protein restriction, supplementation with vitamin B\textsubscript{12} and folate, and stroke prophylaxis with aspirin.

Nonketotic Hyperglycinemia

Nonketotic hyperglycinemia (glycine encephalopathy) is caused by a defect in glycine cleavage.\textsuperscript{23} This defect results in elevated glycine levels in the blood, urine, and cerebrospinal fluid (CSF). The neonatal form presents as lethargy and poor feeding after the initiation of protein feeds, quickly progressing to persistent seizures, encephalopathy, and coma. Apnea is common and persistent hiccups have also been seen. Diagnosis depends on simultaneous measurement of CSF and plasma glycine levels. A CSF-to-plasma glycine ratio greater than 0.06 supports this diagnosis.\textsuperscript{24} Acute management includes use of sodium benzoate to help normalize plasma glycine level. Dextromethorphan, an NMDA (N-methyl-D-aspartate) receptor antagonist, may be beneficial. Valproic acid, which inhibits metabolism of glycine, is contraindicated. The prognosis for the neonatal form is poor. Survivors often have spastic quadriplegia, intractable seizures, and severe mental retardation. Infantile, childhood, and adult-onset forms exist but are uncommon; these forms have milder outcomes.

UREA CYCLE DISORDERS

The urea cycle converts ammonia, which is a toxic byproduct of protein metabolism, into urea (Figure 3). All urea cycle disorders are autosomal recessive with the exception of ornithine transcarbamylase deficiency, which is X-linked.

Clinical Features

Similar to the organic acidemias, urea cycle disorders classically present in neonates as lethargy, poor feeding, and vomiting soon after initiating protein feeds.\textsuperscript{25} What distinguishes the urea cycle disorders from the organic acidemias, however, is hyperammonemia without acidosis (Table 5). In an acute crisis, encephalopathy quickly progresses to coma, seizures, and death if left untreated. Cerebral edema (with a bulging fontanelle and tachypnea) can occur early and progresses rapidly. Metabolic strokes may also occur. All urea cycle disorders with the exception of argininemia are accompanied by hyperammonemia. Ammonia levels exceeding 200 µg/dL cause lethargy and vomiting, levels greater than 300 µg/dL result in coma, and levels exceeding 500 µg/dL cause seizures.\textsuperscript{17} Any catabolic state, including the immediate postnatal period before initiation of feeding, can provoke a crisis because of associated proteolysis. Permanent neurologic sequelae can occur after a single crisis. Ammonia levels greater than 350 µg/dL\textsuperscript{26} and coma for longer than 24 hours\textsuperscript{27} are correlated with death or profound mental retardation. Ammonia levels less than 180 µg/dL usually result in normal development or only mild mental retardation.\textsuperscript{26} Milder forms including female carriers of ornithine transcarbamylase deficiency can have a more subtle presentation.

Treatment

Hyperammonemia in an encephalopathic infant is a medical emergency. In addition to determining ammonia levels and acid-base status, laboratory studies should be ordered for electrolytes, calcium, glucose, lactate, liver enzymes, free and total carnitine, quantitative plasma amino acids, and urine organic acids. Acute management for all urea cycle disorders consists of (1) stopping all protein intake; (2) starting an intravenous infusion of 10% glucose plus lipid to promote the anabolic state; and (3) starting arginine HCl, sodium benzoate, and sodium phenylacetate with intravenous loading doses followed by maintenance infusions. Peritoneal dialysis or hemodialysis should be considered if there is clinical deterioration and ammonia levels are not responding. Chronic management typically includes protein restriction, and oral sodium benzoate and sodium phenylacetate supplementation.\textsuperscript{28} Because the urea...
cycle takes place in the liver, liver transplantation is curative for the metabolic disorder but does not reverse accumulated neurologic injury. In the severe forms of the urea cycle disorders (eg, carbamyl phosphate synthetase I [CPS1] deficiency, ornithine transcarbamylase [OTC] deficiency), liver transplantation before 1 year of age is associated with better survival into the childhood years with mild (rather than profound) mental retardation.\(^{28}\)

### Specific Disorders

**CPS1 deficiency** blocks formation of carbamyl phosphate and has the classic presentation described above. Orotic acid is a metabolite of carbamyl phosphate. Thus, CPS1 deficiency is the only urea cycle disorder without elevated urine orotic acid. Plasma amino acids show decreased citrulline and arginine. Chronic management is as described above plus arginine supplementation. Prognosis is poor with neonatal presentations. Recurrent exacerbations occur even with optimal therapy. Survivors are generally profoundly mentally retarded. Initial presentation is usually in the neonatal period but can be delayed into childhood. The outcome in later onset cases can be milder but still includes mental retardation, motor deficits, and death.

**OTC deficiency** is identical to CPS1 deficiency in presentation except that urine orotic acids are elevated. Plasma amino acids show decreased citrulline and arginine. Due to skewed X-inactivation, 15% of females will develop hyperammonemia.\(^{29}\) Many of these females learn to avoid meat. A protein load can induce symptoms. The catabolic postpartum state can also provoke a crisis. Chronic management involves protein restriction and oral sodium benzoate, phenylacetate, and citrulline supplementation. Prognosis is the same as for CPS1 deficiency.

**Citrullinemia** is caused by a defect in arginosuccinic acid synthetase. The presentation is similar to that of CPS1 deficiency, but prognosis for survivors of the initial episode is somewhat better, with future exacerbations becoming easier to manage with age. A milder, late-onset form of citrullinemia exists. Plasma amino acids show increased citrulline and reduced arginine. Chronic management is as described above plus arginine supplementation. Prognosis is the same as for CPS1 deficiency.

**Argininemia** is caused by a defect in arginase. Argininemia is unique among the urea cycle disorders in that it rarely causes acute hyperammonemic crisis. Ammonias may chronically be mildly elevated. Spasticity and developmental regression develop early in childhood, often with cyclic vomiting, seizures, and failure to thrive. Children are often misdiagnosed as having cerebral palsy. Diagnosis is based on elevated arginine in plasma, although levels can be normal in the immediate newborn period. Treatment involves an arginine-restricted diet. The prognosis includes mental retardation, seizures, and spastic diparesis.

### DISORDERS OF CARBOHYDRATE METABOLISM

**GALACTOSEMIA**

Galactosemia results from a deficiency in galactose-1-phosphate uridylyltransferase.\(^{30}\) Neonates present with vomiting, poor feeding, and lethargy following the initiation of breast or bottle feeding. Jaundice and hepatomegaly are seen, and simultaneous *Escherichia coli* sepsis is associated. Untreated infants develop profound mental retardation and often renal failure. Lenticular cataracts develop after only 1 month if untreated. Those with suboptimal control are at risk for behavioral and learning problems. Even with good dietary control, patients may have subtle cognitive delays or learning disabilities. Action tremor may become a prominent complaint, refractory to medical therapy. Females are at risk for premature ovarian failure, even if treated. The diagnosis is suggested by finding reducing substances in urine and confirmed by elevations in serum galactose-1-phosphate. Treatment is based on dietary restriction of galactose.

**CONGENITAL DISORDERS OF GLYCOXYLATION**

Congenital disorders of glycosylation (CDG, formerly called carbohydrate-deficient glycoprotein syndrome) are a heterogenous group of mostly autosomal recessive disorders with deficient glycosylation of glycoproteins.\(^{31}\) **CDG Ia** is the most common type and involves deficiency of phosphomannomutase. **CDG Ib** is unique in presenting as hypoglycemia and protein-losing enteropathy, without neurologic features. CDG as a group is suggested in an infant or a child with some combination of failure to thrive, stroke-like episodes, a clotting or bleeding tendency, hypotonia, psychomotor
retardation, strabismus, retinitis pigmentosa, hypogonadism, ataxia, and cerebellar hypoplasia. There may be inverted nipples and unusual fat deposits in the suprapubic and supragluteal regions. Peripheral neuropathy may occur. Severity of symptoms is highly variable. Most adults are wheelchair bound. Diagnosis and separation into subtypes is by transferrin electrophoresis. Coagulation studies may show deficiencies of factor XI, proteins C and S, and antithrombin. Oral mannose is effective in CDG Ib, but no treatment exists for the other types of CDG.31

LA FORA BODY DISEASE

Lafora body disease is an autosomal recessive polyglucosan storage disorder that presents as myoclonic seizures in the mid-teens, with rapid neurocognitive deterioration. Neurons show Lafora bodies with a core that stains very dark with periodic acid Schiff, with a lighter outer “halo.” Skin, liver, or muscle biopsy can also be diagnostic.32

LYSOSOMAL STORAGE DISORDERS

Lysosomes are involved in the degradation of large molecules, including mucopolysaccharides, sphingolipids, sphingomyelin, and several others. Progressive organomegaly, dysmorphism, and neurodegeneration are typical.

MUCOPOLYSACCHARIDOSES

In the mucopolysaccharidoses (MPS), impaired degradation of various mucopolysaccharides (also known as glycosaminoglycans) cause variable combinations of coarse facies, short stature, bony defects, stiff joints, mental retardation, hepatosplenomegaly, and corneal clouding. All forms of MPS are autosomal recessive except MPS type II (Hunter syndrome), which is X-linked recessive. Neonates appear normal. Onset of disease is insidious. Other features are listed in Table 6. Urinary testing for MPS suggests the diagnosis, which is confirmed by enzyme assays from leukocytes or fibroblasts.

SPHINGOLIPIDOSES

The sphingolipidoses involve abnormal metabolism and accumulation of sphingolipids. Deficiency of hexosaminidase A alone results in GM2 gangliosidosis, the classic form of which is Tay-Sachs disease. Tay-Sachs disease is more common in Ashkenazi Jews than in the general population and is autosomal recessive. Onset of symptoms is between 3 and 6 months of age. The initial sign is an excessive startle reflex. A macular cherry red spot (see Table 1) almost always is present at this stage, and psychomotor regression then begins. By age 1 year, the child is unresponsive and spastic. Seizures and macrocephaly soon follow, and most children die by 4 to 5 years of age. Late-onset GM2 gangliosidosis, also more common in Ashkenazi Jews, presents in childhood and adulthood. Symptoms include weakness, personality change, tongue atrophy and fasciculations, tremor, and mixed upper and lower motor neuron signs. Dysarthria, ataxia, and progressive spasticity and dementia follow. A cherry red macula is not present in late-onset disease. Diagnosis of both forms of GM2 gangliosidosis is by assays of hexosaminidase A activity in serum, leukocytes, or cultured fibroblasts. No treatment is available.

SANDHOFF DISEASE

Sandhoff disease is a rare autosomal recessive disorder caused by deficiencies in both hexosaminidase A and B. It is not more prevalent in Ashkenazi Jews. Clinical features are identical to those of Tay-Sachs
disease, with additional findings of hepatosplenomegaly and bony deformities. Diagnosis is by enzyme assays of hexosaminidase. Foamy histiocytes are sometimes seen in bone marrow. No treatment is available.

FABRY DISEASE

Fabry disease is an X-linked recessive disorder caused by α-galactosidase deficiency. Presentation is usually during adolescence or early adulthood with painful crises in the extremities and paresthesias. Angiokeratomas and gastrointestinal complaints are often present. There is an increased risk for stroke, heart disease, renal failure, pulmonary complications, and hearing loss. Intelligence is normal. Diagnosis is by enzyme assay showing decreased activity. α-Galactosidase replacement therapy is available and appears promising.33

NIEMANN-PICK DISEASE

Niemann-Pick Type A

Niemann-Pick type A is caused by sphingomyelinase deficiency, which results in accumulation of lipids, mainly sphingomyelin. Infants are normal at birth but develop feeding problems, hepatomegaly, and psychomotor regression in the first several months of life. In half of cases, children have cherry red spots. Opisthotonus and hyperreflexia are common, whereas seizure is uncommon. Death occurs between ages 2 and 4 years. Diagnosis is based on enzyme assay. Foamy cells are observed in bone marrow and blood.

Niemann-Pick Type C

Niemann-Pick type C is an autosomal recessive disorder that may present in neonates as severe liver or lung disease or in children as upgaze palsy or apraxia, ataxia, seizures, dementia, dystarthritis, dysphagia, and dystonia. Adults present with psychiatric symptoms. Diagnosis is suggested by finding impaired cholesterol esterification and is confirmed by genetic testing for the NPC1 and NPC2 genes. Foamy cells are observed in liver, spleen, and marrow. Sea-blue histocyes are seen in marrow in advanced disease. Cholesterol-lowering drugs reduce cholesterol levels, but no treatment improves neurologic symptoms.34

PEROXISOMAL BIOGENESIS DISORDERS

Peroxisomes degrade very-long-chain fatty acids (C24, C26). The classic peroxisomal biogenesis disorder is Zellweger syndrome (cerebrohepatorenal syndrome), an autosomal recessive disorder caused by deficiency of multiple proteins responsible for peroxisomal assembly.

Zellweger syndrome presents at birth as severe hypotonia, high forehead, wide-open fontanelles, hepatomegaly, and hyporeflexia. Intractable seizures, liver dysfunction, renal cysts, cardiac defects, retinal dystrophy, and sensorineural hearing loss are common. Brain MRI demonstrates severe hypomyelination of the hemispheres, with neuronal migrational defects (eg, polymicrogyria, pachygryria, periventricular heterotopias). Plasma very-long-chain fatty acids (C26:0 and C26:1) are elevated. After the neonatal period, phytanic acid also is elevated. Specific genetic testing is available for 6 known mutations, the most common affecting the PEX1 gene. The majority of affected infants die in the first year. Severe psychomotor retardation develops in survivors.35

Milder presentations of peroxisomal biogenesis...
disorders include neonatal adrenoleukodystrophy (not related to X-linked adrenoleukodystrophy, which is discussed below) and Refsum disease. Both conditions can present in infancy or childhood as hypotonia, developmental delay, vitamin K-responsive bleeding tendency (due to liver dysfunction), sensorineural hearing loss, retinitis pigmentosa, neuropathy, and ataxia. The spectrum is continuous with no simple phenotype-genotype correlations, and diagnosis can be delayed into late adulthood.35

**WHITE MATTER DISORDERS**

White matter disorders classically present as progressive spasticity and neurocognitive regression. Hypotonia is characteristic in the neonatal period, whereas psychiatric disturbance is typical in children and adults. Discussed below are vanishing white matter disorder, Alexander disease, metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, X-linked adrenoleukodystrophy, Canavan disease, and Krabbe disease.36,37 A useful mnemonic for recalling these disorders is VAMPACK.

**VANISHING WHITE MATTER DISEASE**

Vanishing white matter disease (childhood ataxia with central hypomyelination) is an autosomal recessive disorder that usually presents in children aged 2 to 6 years as slowly progressive cerebellar ataxia, spasticity, variable optic atrophy, and relatively preserved cognitive abilities.38 Infections and minor head trauma may lead to altered level of consciousness leading into coma. Brain MRI shows progressive loss of white matter diffusely with cystic degeneration. CSF may show elevated glycine. Later-onset (including adult-onset) disease has been described and is associated with a milder clinical course. Mutations have been found in genes that encode eukaryotic initiation factor 2B (eIF2B) subunits, which in turn may affect the regulation of protein synthesis during cellular stress.39

**ALEXANDER DISEASE**

Alexander disease classically presents at approximately 6 months of age as megalencephaly, progressive spasticity, seizures, and developmental regression. Death is common in infancy and usually occurs before age 10 years. Brain MRI shows frontally dominant demyelination involving the subcortical U fibers and contrast enhancement in the deep frontal white matter, basal ganglia, and periventricular rim. Pathology shows astrocytic intracytoplasmic inclusion bodies called Rosenthal fibers (Figure 4). More than 30 mutations of genes encoding the glial fibrillary acidic protein (GFAP) have been identified in association with Alexander disease. GFAP is a major component of Rosenthal fibers. Juvenile- and adult-onset forms of Alexander disease have a milder course, with no macrocephaly or cognitive decline but with a higher incidence of bulbar signs, ataxia, and positive family history. Demyelination in late-onset disease is seen posteriorly rather than anteriorly.40,41

**METACHROMATIC LEUKODYSTROPHY**

Metachromatic leukodystrophy (sulfatide lipidosis) is an autosomal recessive disorder usually caused by deficiency of arylsulfatase A and, less commonly, by deficiency of the sphingolipid activator protein, saposin B. Sulfatides then accumulate, leading to myelin destabilization. The late infantile form is most common, with onset after 1 year of age. This form is characterized by ataxia, hypotonia, and peripheral neuropathy followed later by progressive spasticity and cognitive decline. In the juvenile and adult forms, central nervous system (CNS) symptoms are more prominent, with behavioral disturbances, spasticity, and cognitive decline. Brain MRI shows demyelination of periventricular white matter symmetrically, with involvement of the corpus callosum, early sparing of the subcortical U fibers, and late atrophy. There is no enhancement with contrast. A tigroid pattern with patchy white matter sparing (formerly thought pathognomonic for Pelizaeus-Merzbacher disease) and a leopard skin pattern have been described. In this case, the islands of normal-appearing white matter may enhance with contrast, but the demyelinated patches do not (Figure 5). Diagnosis is by testing for arylsulfatase A activity. Bone marrow transplantation may be beneficial in mildly affected patients with late-onset disease.

**PELIZAEUS-MERZBACHER DISEASE**

Pelizaeus-Merzbacher disease classically presents as neonatal nystagmus, choreoathetosis, progressive ataxia, spasticity, and developmental regression, with death often by 5 to 7 years of age. The spasticity may affect the legs preferentially. The nystagmus can sometimes resolve. Milder cases present later, and children who present after 1 year of age may live into adulthood. Brain MRI shows diffusely deficient myelination of the cerebral hemispheres, with a thin corpus callosum and atrophy of white matter. Histopathology of early disease shows patches or stripes of perivascular white matter sparing, resulting in a tigroid pattern, sometimes also visible on MRI (see Figure 5). The etiology is duplication or mutation of the proteolipid protein gene (PLP1) on the X chromosome, resulting in over- or underproduction of proteolipid protein. Diagnosis is by detecting duplication or mutation of the PLP1 gene.
X-LINKED ADRENOLEUKODYSTROPHY

X-Linked adrenoleukodystrophy presents at 5 to 8 years of age as a subacute onset of behavioral problems, visual loss, hyperpigmented skin, and adrenal insufficiency, leading to progressive spasticity, optic atrophy, late seizures, and eventual vegetative state. Death is typical by 3 years after diagnosis. Brain MRI shows demyelination, which begins in the splenium of the corpus callosum and spreads in a posterior to anterior pattern. The leading edge of demyelination enhances with contrast (Figure 6). The defect is in the ABCD1 gene, which codes for a peroxisomal membrane ATP-binding cassette protein transporter. As a result, very-long-chain fatty acids are not degraded and, thus, accumulate. Diagnosis is suggested by MRI findings and by elevated very-long-chain fatty acids in blood, especially C26:0 but not C26:1 (elevated C26:0 plus C26:1 suggests Zellweger syndrome).

CANAVAN DISEASE

Canavan disease (spongiform leukodystrophy) is an autosomal recessive disorder that presents at 2 to 4 months of age as megalencephaly and hypotonia, leading to developmental regression, progressive spasticity, and seizures. Brain MRI shows diffuse demyelination that begins in subcortical and cerebellar white matter, later involving central white matter (Figure 7). The globus pallidi and thalami are involved, but the caudate is spared. MR spectroscopy shows a large N-acetylaspartic acid (NAA) peak. The deficiency is in aspartoacylase. Diagnosis is by finding large quantities of NAA in urine.

KRABBE DISEASE

Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder that presents at 1 to 7 months of age as irritability and hyperreactive startle.
Developmental regression, spasticity, areflexia, startle myoclonus, seizures, and blindness follow. Most affected infants die by 1 year of age. Brain MRI shows diffuse demyelination beginning in deep white matter, later involving subcortical white matter. Computed tomography shows calcification in basal ganglia, thalami, and corona radiata. CSF shows elevated proteins. Motor nerve conduction velocities are prolonged. Diagnosis is by demonstrating deficient galactocerebroside \( \beta \)-galactosidase activity in leukocytes or cultured fibroblasts.

**GRAY MATTER DISORDERS**

Gray matter diseases classically present as seizures and loss of function of affected cortex. Prototypical gray matter diseases include Tay-Sachs disease (discussed previously) and the neuronal ceroid lipofuscinoses.

The neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of inherited neurodegenerative lysosomal storage disorders presenting as some combination of visual loss, behavioral change, movement disorder, and seizures, especially myoclonic seizures. The infantile, late infantile, and juvenile forms are more likely to be accompanied by retinal blindness. The adult form is usually not associated with visual loss. Those affected by the infantile form are normal at birth. Onset of seizures and visual loss occurs within 2 years and death is typical by age 10 years. In the late infantile form, initial symptoms are seizures between ages 2 and 4 years, followed by developmental regression, dementia, pyramidal and extrapyramidal signs, and visual loss; death occurs between ages 6 and 30 years. The juvenile form presents between ages 4 and 10 years as rapidly progressive visual loss leading to total blindness within 2 to 4 years; seizures begin between ages 5 and 18 years and death occurs in the teens to thirties. The adult-onset form presents in the thirties, resulting in death within 10 years later. All of the NCLs are autosomal recessive except the adult form, which is autosomal dominant. The genes involved are PPT1 (at locus CLN1), CLN2 through CLN6, and CLN 8. PPT1 defects can present at any age, whereas CLN3 and CLN4 present in children and adults. Electron microscopy of white blood cells, skin, conjunctiva, or anal mucosa shows fingerprint, curvilinear, or granular osmiophilic deposits. More specific enzyme assays and genetic testing are available. Treatment is supportive. Seizures may be worsened by phenytoin and carbamazepine. Lamotrigine may be the most efficacious and best-tolerated anticonvulsant. Trihexyphenidyl improves dystonia and sialorrhea.

**OTHER METABOLIC DISORDERS**

**SMITH-LEMLI-OPITZ SYNDROME**

Smith-Lemli-Opitz syndrome is caused by deficiency of 7-dehydrocholesterol reductase, which leads to impaired cholesterol synthesis. Patients have ptosis, anteverted nares, micrognathia, microcephaly, hypospadias, and cardiac defects. Syndactyly of the second and third toes is almost always present. Presentation is that of poor growth and developmental delay. Diagnosis is based on elevations of 7-dehydrocholesterol and decreased serum cholesterol. Management is with cholesterol supplementation.

**LESCH-NYHAN SYNDROME**

Lesch-Nyhan syndrome is an X-linked recessive disorder caused by deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT), an enzyme involved in the metabolism of purines. This defect leads to hyperuricemia and increased urinary excretion of uric acid. Most neonates are normal until 3 months of age, when they demonstrate hypotonia and global developmental delay. By age 1 to 2 years, choreoathetosis and dystonia are apparent, and by age 2 to 3 years, the characteristic severe self-mutilating behavior is apparent. Most children never learn to walk. Renal failure due to urate deposition and gouty arthritis occur.
MENKES DISEASE

Menkes (kinky hair) disease is an X-linked recessive disorder of copper transport resulting in low serum copper levels, decreased intestinal copper absorption, and reduced activity of copper-dependent enzymes. Affected males develop normally during the first months of life, but development then slows and regression occurs. Myoclonic seizures in response to stimulation are an early and almost constant feature. Dysautonomia occurs. The hair takes on a brittle, steel wool appearance. Other findings on examination include skin laxity, sagging jowls, and hypotonia. Cerebral vessels are often tortuous and narrowed. Ischemic infarcts and subdural hematomas can occur. Death usually occurs before age 3 years. Laboratory evaluation shows low serum copper and ceruloplasmin. CSF and plasma catecholamines are abnormal. Molecular testing is available. Treatment involves subcutaneous or intravenous copper administration. Results are variable, possibly because of poor CNS penetration.44

WILSON’S DISEASE

Wilson’s disease is an autosomal recessive disorder with defective copper transporting ATPase that results in impaired binding of copper to ceruloplasmin and impaired excretion of copper into bile. Copper accumulates in the liver, and patients present with liver or CNS disease. CNS symptoms include tremor, chorea, dystonia, dysarthria, psychiatric disturbance, and cognitive impairment. Liver disease is more common in children, with fulminant liver failure described in preschool-age children.45 CNS disease with mild liver disease more typically is seen in teens and adults. Laboratory studies show low serum copper and ceruloplasmin and elevated urinary copper. Copper deposition in Descemet’s membrane is seen on slit-lamp examination (Kayser-Fleischer rings). Kayser-Fleischer rings and low serum ceruloplasmin are found in more than 90% of those presenting with CNS disease but may be absent in those with liver disease. MRI shows symmetric lesions in basal ganglia, thalamus, and brainstem that are bright on T2-weighted sequences. Asymmetric lesions may be seen in white matter.46 Genetic testing is available. Traditional treatment is with a copper chelator (ie, penicillamine or trientine). Trientine plus zinc, which impairs copper absorption from the gut, may work as well as penicillamine and is better tolerated.47 Tetrahydroxymolybdate, a promising investigational drug that impairs copper absorption in the gut and binds copper in blood, works faster than zinc and is also better tolerated than penicillamine.49

OTHER

Pyridoxine-dependent epilepsy presents as neonatal seizures that respond only to pyridoxine.50 Biotinidase deficiency presents as seizures later in infancy to early childhood, which respond to biotin.51 Glucose transporter 1 (GLUT-1) deficiency syndrome presents as refractory seizures, acquired microcephaly, ataxia, and low CSF glucose between 1 and 4 months of age. Symptoms are due to defective transport of glucose across the blood-brain barrier. Seizures respond to the ketogenic diet.52,53

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