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Objectives

After completing this article, readers should be able to:

1. Describe the neurodegenerative disorders that present at various ages and their clinical phenotypes.
2. Characterize the lipidoses and associated effects on lysosomal enzymes.
3. Describe the effects of peroxisomal disorders on catabolic and synthetic metabolic functions.
4. Delineate how mitochondrial disorders affect oxidative metabolism and defects of the respiratory chain.
5. Name the disorders that can be identified by their specific enzyme defect or by specific DNA deletion or duplication.

Introduction

A child's development generally proceeds along expected pathways, with anticipated levels of function for specific ages. When these levels are not met, the treating physician must determine whether the child has a static or a progressive process. If the child achieves certain levels of development, then loses these skills, the chance is greater that the process is progressive. The technological revolution and progress in molecular genetics in the past 20 to 30 years provide greater avenues for the diagnosis of many of the progressive disorders affecting neurons and central nervous system (CNS) function. Many disorders can be diagnosed in utero, and treatments are available for some. It has become increasingly evident that many of the inherited neurodegenerative disorders have varied clinical phenotypes, and clinical phenotypes may overlap between some of the disorders. This article provides a framework for the primary physician to consider some of these disorders and a rational approach to the evaluation of a child suspected of having a progressive neurodegenerative disorder.

Neurodegenerative disorders can present at any age, with manifestations varying with the age of presentation. Tables 1 and 2 provide some of the clinical and laboratory features that may be seen in a neonate or child who has a progressive disorder. Certain historical and physical findings may indicate such disorders. Some of these disorders are referred to as lysosomal disorders because of the tendency to store breakdown products of normal substrates within the lysozyme. Categories of lysosomal disorders include the storage of mucopolysaccharides, lipids, glycogen, and oligosaccharides. Recent enzyme determinations show that the infantile and childhood forms of neuronal ceroid lipofucinoses also fit into this broad category. Clinical symptoms involve a variety of organ systems that may be reflected by bone abnormalities, organomegaly, CNS abnormalities, and coarseness of face and hair. A recent study from Australia reports the prevalence of lysosomal storage disorders for that continent as 1 per 7,700 live births (Meikle et al 1999).

Lipidoses

These disorders are the result of inherited abnormalities of lipid metabolism and involve those lipids containing sphingosine, which is a primary component of the myelin and comprises about 16% of white matter. Lysosomal enzymes, frequently hydrolases, may be decreased, absent, or nonfunctional. This allows abnormal accumulation of the specific

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Table 1. Features of Neonatal Encephalopathy

Presentation
• Lethargy/hypotonia with or without seizures
Physical Examination
• Evaluate for organomegaly, skin rashes
Laboratory Evaluation
• Complete blood count with differential count • Glucose, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, ammonia, serum lactate and pyruvate, arterial blood gases • Cultures of blood, urine, cerebrospinal fluid • Urine reducing substances
Findings and Potential Diagnoses
• Hypoglycemia —Disorders of carbohydrate metabolism —Fatty acid oxidation defects —Gluconeogenesis defects —Disorders of branched-chain amino acids —Urea cycle defects Measure insulin levels, aspartate aminotransferase (AST)/alanine aminotransferase (ALT), serum/urine amino acids, urine organic acids
• Hyperammonemia —Urea cycle defects —Organic acidopathies without lactic acidosis (not lactate)—urea cycle defects —Organic acidopathies with metabolic acidosis—organic acid defect Measure urine/serum amino acids, urine organic acids, AST/ALT
• Metabolic and Lactic Acidosis —Disorders of oxidative metabolism —Respiratory chain defects Obtain possible muscle biopsy, investigation of respiratory chain enzymes, evaluation of mitochondria

lipids within the CNS white matter. Enzyme levels down to 10% of normal may still result in a phenotypically normal individual. The lipidoses include: Niemann-Pick disease (disorder of sphingomyelin), Gaucher disease (disorder of glucosylceramide), Krabbe disease (disorder of galactosylceramide), metachromatic leukodystrophy (disorder of sulfatide), Tay-Sachs Disease (GM_2 gangliosidosis), and generalized gangliosidosis (GM_1 gangliosidosis) (Table 3). Within each one of these disorders are many phenotypes and ages of presentation.

Niemann-Pick Disease (Sphingomyelin Lipidosis)

This disease has four clinical types: A, B, C, and D. A recently described form in adults (type E) has storage of sphingomyelin, but no neurologic symptons. The lysosomal enzyme deficiency is sphingomyelinase. About 85% of the cases fall into the classic infantile form (type A). Types A, B, and C are associated with hepatosplenomegaly and "foam cells" (Niemann-Pick cells) in the liver and bone marrow. Type C presents in early childhood, between 2 to 4 years of age, and type D presents in later childhood. Types A, C, and D progress to death within 2 to 5 years of presentation. All have an autosomal recessive inheritance pattern.

The primary clinical features are hepatosplenomegaly, cognitive regression, macular degeneration with cherry-red spot in about 25% of cases, hypotonia, areflexia, and delayed nerve conduction velocities. Type B has visceral but no CNS involvement. Brain imaging with both computed tomography (CT) and magnetic resonance imaging (MRI) reveal brain atrophy with volume loss. The diagnosis is made by assay of the bone marrow or liver for foam cells and determination of sphingomyelinase levels in white blood cells for types A and B and fibroblasts for type C. Treatment is primarily supportive. Bone marrow transplant has been tried in a few cases, but without success.

Gaucher Disease (Glucosylceramide Lipidosis)

All three forms of Gaucher disease present with hepatosplenomegaly. The infantile and juvenile forms progress to an early death following regression in psychomotor skills and cognitive functioning. This disease is one of the most frequent lysosomal disorders and the most common among Ashkenazi Jews, in whom the prevalence is 1 per 855 (Meikle, 1999). The enzyme defect is beta-glucocerebrosidase; the defect leads to an accumulation of glucosylceramide in brain, liver, spleen, and bone marrow.

The infantile form of this disease presents within the first year of life, usually by 6 months of age. The infant is hyperextended, seemingly opisthotonic, and has an enlarged spleen and liver. Death occurs by 2 years in the infantile form and by early adolescence in the juvenile form. The adult form, which presents in the teen years, consists of visceromegaly and is associated with a long

Table 2. Clinical Features of Childhood Encephalopathy

Visual Changes/Loss	
• Lipidoses • Neuronal ceroid lipofucinosis • Mucopolysaccharidosis (Hurler syndrome) • Peroxisomal disorders • Mitochondrial disorders	Obtain urine for mucopolysaccharides, white blood cell count or fibroblasts for lysosomal enzymes, very long-chain fatty acids, phytanic acid, pipecolic acid
Gait Disturbances	
• Ataxia—metachromatic leukodystrophy • Hemiparesis—Krabbe disease	Measure lysosomal enzymes
Cognitive Loss With or Without Seizures	
• Adrenoleukodystrophy • Metachromatic dystrophy • Neuronal ceroid lipofucinosis	Obtain lysosomal enzymes in white blood cells/fibroblasts, electroretinogram for neuronal ceroid lipofucinosis, urine dolichols
Stroke	
• Mitochondrial homocystinuria	Measure serum/urine amino acids, serum lactate/pyruvate, cerebrospinal fluid lactate

survival. Radiographs of the bones may demonstrate rarefactions from the storage material. Brain imaging with either CT or MRI shows nonspecific atrophy without white matter changes. The diagnosis can be made by assaying for beta-glucocerebrosidase in white blood cells or fibroblasts. Inheritance is autosomal recessive, and in utero diagnosis is possible. Treatment options include splenectomy (reverses symptoms of hypersplenism), bone marrow transplantation, and replacement with alpha-glucerase to specific macrophages. The replacement therapy has improved both hematologic and visceral symptoms.

Krabbe Disease (Galactosylceramide Lipidosis)

This also has been called globoid cell leukodystrophy. There are two phenotypic forms of this lipidosis. One presents within the first 3 to 6 months of life and the other later in infancy or childhood. Inheritance is autosomal recessive, and the lysosomal enzyme defect is galactocerebrosidase. White blood cells, serum, and amniotic fluid are all sources for enzyme determination. Typically, affected infants present within the first 3 to 4 months of life with extreme irritability, fevers of unknown origin, and rigidity leading to feeding problems. Muscle stretch reflexes initially may be increased, but as the course progresses, they are lost. With disease progression, vision and hearing are lost. The child usually dies of intercurrent illnesses within the first 2 years of life. Brain imaging with both CT and MRI reveal significant white matter changes, primarily in the occipital and parietal lobes. T_2 changes in the centrum semiovale also have been reported.

Metachromatic Leukodystrophy (Sulfatide Lipidosis)

This lipidosis occurs because of deficiency of the lysosomal enzyme arylsulfatase A, a cerebroside sulfatase. There are three isoenzymes for arylsulfatase: A, B, and C. The A isoenzyme is decreased in the infantile, juvenile, and adult forms of metachromatic leukodystrophy. The genes for this enzyme have been mapped to chromosome 22, 22q13.31.

Clinical features typically develop within the first 2 years of life, but presentation may occur as late as 4 to 5 years. The initial presentation is a gait dysfunction, usually ataxia with or without weakness. There also is a prominent neuropathy, and the muscle stretch reflexes typically are decreased or absent. The course progresses rapidly over the next 1 to 2 years, with the development of spasticity, loss of intellectual skills, optic atrophy, and seizures. Some patients may have a cherry-red spot in the macula. The juvenile form develops around 5 to 10 years of age. The progression of the illness is similar to that of the infantile form. Affected children may live into their late teens or early 20s compared with death before the age of 10 years among those who have infantile-onset disease. An adult form can present in the third to fourth decade with psychosis, dementia, and progressive clinical signs of the spinocerebellar, corticospinal, and cerebellar systems. A motor neuron disease presentation has been described.

Pertinent laboratory studies include demonstration of absent or decreased enzyme in urine or leukocytes; ab-

Table 3. Selected Clinical Features of Degenerative Disorders

Lipidoses

- Neimann-Pick Disease (sphingomyelin lipidosis)
  - —Hypotonia/areflexia
  - —Hepatosplenomegaly
  - —Macular degeneration with cherry-red spot
  - —Cognitive regression
  - —(Type B visceral, but no CNS involvement)
- Gaucher Disease (glucosylceramide lipidosis)
  - —Hepatosplenomegaly
  - —Cognitive and psychomotor regression
  - —Bone rarefactions
- Krabbe Disease (galactosylceramide lipidosis)
  - —Onset of irritability in first 3 to 4 months of life
  - —Fevers of unknown origin
  - —Rigidity
  - —Feeding problems
- Metachromatic Leukodystrophy (sulfatide lipidosis)
  - —Typical onset first 2 to 5 years of life
  - —Gait problems, often ataxia
  - —Neuropathy with decreased or absent muscle stretch reflexes
  - —Cognitive regression
  - —Optic atrophy
  - —Seizures
- Tay-Sachs Disease (GM_2 gangliosidosis)
  - —Onset in early infancy
  - —Increased sensitivity to noise (hyperacusis)
  - —Increased startle response
  - —Myoclonic seizures
  - —Optic: "cherry-red spot"
- Generalized Gangliosidosis
  - —Three clinical forms: infantile, juvenile, and chronic
  - —Coarse facial features
  - —Edema of face, hands, and feet
  - —Hepatosplenomegaly
  - —Bony abnormalities

Neuronal Ceroid Lipidoses

Six clinical groups, all with similar clinical features

- Infantile (Santavouri-Haltia)
- Late Infantile (Jansky-Bielchowsky)
- Juvenile (Spielmeyer-Vogt-Sjögren or Batten)
- Adult (Kufs)
- Finnish Late Infantile
- Finnish Early Luvenile
  - —Myoclonic seizures
  - —Visual impairment with optic atrophy and macular changes
  - —Psychomotor regression
  - —Dementia

Carbohydrate-deficient Glycoprotein Syndromes

One common phenotype of phosphomutase deficiency

- —History of life-threatening illnesses in infancy
- —Cerebellar hypoplasia
- —Cataracts
- —History of hypoglycemic episodes
- —Protein-losing enteropathy
- —Stroke-like episodes
- —Retinopathy
- —Recurrent infections

Peroxisomal Disorders

- Zellweger Syndrome
- Neonatal Adrenoleukodystrophy
- Refsun Disease
  - —Hypotonia
  - —Hepatomegaly
  - —Retinal pigmentation or absent electroretinogram
  - —Sensorineural hearing loss
  - —Renal cysts
  - —Aberrant calcific stippling
  - —Adrenal insufficiency
  - —Psychomotor retardation

Mitochondrial Disorders (see Table 5)

- Disorders of oxidative metabolism
- Disorders of pyruvate metabolism
- Defects of the respiratory chain

sent gallbladder function on a cholecystography; abnormal brainstem auditory, visual, and somatosensory evoked potentials; elevated cerebrospinal fluid protein levels; and brain imaging showing white matter abnormalities.

Like the other lysosomal disorders, metachromatic leukodystrophy is inherited as an autosomal recessive trait. Treatment to date has been primarily supportive. Some have reported a delay in disease progression after bone marrow transplantation. Recent research reveals

that enzyme activity can be restored to normal in human fibroblasts via retroviral vector-mediated gene transfer.

Tay–Sachs Disease (GM_2 Gangliosidosis)

Tay-Sachs disease results from deficiency of the enzyme hexosaminidase A and subsequent storage of ganglioside within neurons of the CNS and autonomic and peripheral nervous systems. Children present in early infancy with increased sensitivity to noise (hyperacusis) and an increased startle response to noise. Development is delayed, as is vision; children who have developed some vision lose it and are usually blind by 1 year of age. The other characteristic feature is the cherry-red spot that represents loss of ganglion cells in the foveal area with the remaining ones filled with the ganglioside. Most infants also develop myoclonic seizures during the first year of life. Brain CT and MRI findings are abnormal. CT findings include areas of low density in the basal ganglia and cerebral white matter, and MRI changes include an increased signal in these same regions on T_2-weighted images. Death occurs at 2 to 3 years of age, with some affected children living to 4 years.

This disease is transmitted as an autosomal recessive trait, primarily in those of Ashkenazi Jewish descent. The carrier state for this population is 1 in 27. The gene locus for the enzyme is 15q23-q24. Prenatal screening can identify affected fetuses using amniotic fluid and chorionic villi for assay of the enzyme. Treatment to date has been primarily supportive. There has been some research using enzyme replacement therapy and bone marrow transplantation.

Sandoff disease is a variant of GM_2 gangliosidosis that results from deficiencies of both hexosaminidase A and B. Clinical symptoms are very similar to those of Tay-Sachs disease, including the cherry-red spot. Affected infants die within the first 2 to 3 years of life. It is possible to diagnose carriers and fetuses. Treatment options are similar to those for Tay-Sachs disease.

Generalized Gangliosidosis (GM_1 Gangliosidosis)

Brain and other organs are involved with this lipidosis. Neurons store GM_1 ganglioside because of deficiencies in beta-galactosidase and asialoganglioside (neuraminic acid). Mucopolysaccharides, in the form of keratan sulfates, also are stored in the liver and spleen. Three clinical forms are recognized: infantile, juvenile, and chronic. Clinically, affected infants demonstrate coarse facial features at birth; edema of the face, hands, and feet; frontal bossing; a dull look; and prominent hepatosplenomegaly. They often are misdiagnosed as having a mucopolysaccharidosis. Bony abnormalities of dyostosis multiplex, with kyphoscoliosis, beaking of vertebrae, and shortened fingers and toes, become more evident as the children age. Disease progression is characterized by the development of seizures, blindness, deafness, and death by 2 years of age. The progression is slower in the juvenile and adult forms. In the latter, visceral and bone storage does not occur. Brain imaging abnormalities have been noted on both CT and MRI. These changes are often nonspecific, with diffuse atrophy, although high-intensity signals have been reported in the basal ganglia on T_2-weighted MRI. Inheritance is autosomal recessive. Diagnosis can be established by identifying the absence of the enzyme beta-galactosidase in white blood cells, fibroblasts, and cultured amniocytes. Treatment is supportive.

Neuronal Ceroid Lipidoses

This group of disorders has been grouped with the lipid storage diseases because storage material was found in neurons that absorbed lipid stains and resembled lipofuscin. Earlier classification systems identified four main types, based on age at presentation and the ultrastructure of the stored material. However, there was not always a clear-cut association between these two features. Current classification recognizes six different clinical syndromes. Chromosomal linkage is known for five of the syndromes, and specific genes have been mapped for four. The six clinical groups are: infantile (Santavuori-Haltia), late infantile (Jansky-Bielschowsky), juvenile (Spielmeyer-Vogt-Sjögren or Batten), adult (Kufs), Finnish late infantile, and Finnish early juvenile.

The infantile form presents between 8 and 18 months of age. Affected infants often exhibit microcephaly and myoclonic seizures. There is visual impairment, with optic atrophy, narrowing of the retinal vessels, and some macular changes. The children progressively lose developmental skills, reaching a vegetative state and death by about 10 years of age. Inclusions of autofluorescent lipofuscin (saposin) are found not only in neurons but in other organs of the body, including thyroid, pancreas, kidneys, testes, and smooth and skeletal muscle. The ultrastructure of the lipopigment on skin biopsy shows granular osmophilic deposits.

The late infantile form (Jansky-Bielschowsky) presents between 2 and 4 years of age with seizures (both myoclonic and convulsive), ataxia, basal ganglia dysfunction, progressive mental and motor deterioration, and visual loss. The visual impairment occurs late in the disease course. The disease is progressive, with death occurring between 8 and 15 years of age. The electro-

retinogram (ERG) is unusually small or absent later in the course of the disease. Electroencephalography demonstrates an exaggerated response to photic stimulation, and background patterns become increasingly slow and less well-regulated. Inclusions of the lipofuscin pigment are detected as curvilinear bodies in various tissues, including neurons, hepatocytes, and bone marrow. The gene for this form (LINCL) has been mapped to a lysosomal pepstatin-insensitive peptidase on chromosome 11p15. Prenatal detection of this gene has been reported using DNA and enzyme-based methods on amniocytes. Treatment remains supportive. Seizures are difficult to treat and often unresponsive to antiepileptic medications.

. . . psychomotor retardation, dysmorphia, hypotonia, hepatomegaly, seizures, retinal pigmentation or absent ERG, sensorineural hearing loss, renal cysts, aberrant calcific stippling, and adrenal insufficiency are indicative of Group I peroxisomal disorders . . .

The juvenile form (Spielmeyer-Vogt-Sjögren) presents with early visual loss and later seizures and dementia. Onset usually is between 5 and 10 years of age. As with the earlier forms, the disease is progressive, with death occurring in the teens and 20s. The gene for this disorder (LINCL3) codes for the lysomal enzyme adenosine triphosphate synthase on chromosome 16p12. The ultrastructure of the stored lipofuscin is that of a fingerprint.

There are adult forms of this disorder and other variants referred to as the Finnish type. The chromosome for the adult variant is not yet known, and the Finnish forms code to chromosome 13q31–32. Laboratory results that may be helpful include the ERG if decreased or absent, presence of dolichols in the urine, and retinal deterioration with small vessels. Inheritance is autosomal recessive.

Carbohydrate-deficient Glycoprotein Syndromes

Diseases in this category (Table 3) occur as deficiencies involving the endoplasmic reticulum and the Golgi apparatus. These cellular structures are involved in protein translation and modification with sugar molecules (endoplasmic reticulum) and importation of the proteins with further modification (Golgi apparatus). It is here that oligosaccharides are added to some of the glycoproteins. A number of different phenotypes are recognized, but the most frequently recognized is type 1a (phosphomannomutase deficiency). Clinically, affected children may present with life-threatening illnesses in infancy that could include heart, liver, or other organ failure. There is cerebellar hypoplasia, cataracts, history of hypoglycemia, protein-losing enteropathy, stroke-like episodes, seizures, retinopathy, and recurrent infections. Measurement of glycoproteins antithrombin III and thyroid-binding globulin may indicate deficiencies in this group of glycoproteins. A reliable laboratory test is the measurement of the abnormal transferrin isoform by immunoisoelectric focusing. Many affected children die in early childhood from intercurrent illnesses. The disease may stabilize in later childhood; a severe peripheral neuropathy then may develop. Some children survive to adulthood with disproportionately long limbs and short trunk, ataxia, and mental retardation.

Peroxisomal Disorders

Peroxisomes are membrane-bound organelles that play important roles in multiple catabolic and synthetic metabolic functions. Some of these include beta-oxidation of fatty acids, alpha-oxidation of branched-chain fatty acids, pipecolic acid degradation, and plasmalogen ether lipid and bile acid synthesis. Diseases related to the dysfunction of these organelles were first noted in 1973 when they were found to be missing in Zellweger syndrome. Diseases occurring as a result of peroxisome dysfunction fit into one of three categories: 1) disorder of biogenesis with decreased numbers of peroxisomes or misshapen peroxisomes; 2) multiple syndromes with single enzyme defects; and 3) impaired peroxisomal function with intact peroxisomes. These organelles play significant roles in neuronal migration, the metabolism of cholesterol and polyunsaturated fats, and prostaglandins.

Examples of Group I peroxisomal disorders include Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease (Table 4). Naidu and associates have noted the phenotypic and genotypic variabil-

Table 4. Peroxisomal Disorders: Laboratory Assessments

Disorder	Assay	Value
Group I Examples		
Zellweger syndrome	Plasma VLCFAs	Increased
Neonatal adrenoleukodystrophy	Pipecolic acid	Increased
Infantile Refsum disease	Phytanic acid	Increased
	Bile acid intermediates	Decreased or absent
	RBCs: plasmalogen	Decreased
Group II Examples		
X-linked adrenoleukodystrophy	Plasma/RBC/fibroblast VLCFAs	Increased
Refsum disease	Plasma phytanic acid	Increased
Group III Examples		
Rhizomelic chondrodysplasia punctata	Plasma phytanic acid	Increased
	RBCs: plasmalogen	Decreased

VLCFAs = very long-chain fatty acids, RBCs = red blood cells

ity of this group. Certain physical findings suggest this group of disorders, including psychomotor retardation, dysmorphic features, hypotonia, hepatomegaly, seizures, retinal pigmentation or absent ERG, sensorineural hearing loss, renal cysts, aberrant calcific stippling, and adrenal insufficiency (Table 3). Theil reported that more than 75% of patients have at least three major features.

Group II peroxisomal disorders include childhood X-linked adrenoleukodystrophy, adrenomyeloleukodystrophy, and classic Refsum disease. Most patients who have disorders in this group have elevations in plasma very long-chain fatty acids (VLCFAs). Some also may have elevated bile acid intermediates. The most common form of this group is the X-linked adrenoleukodystrophy that presents in males during childhood (4 to 8 years). Affected children often present with progressive deterioration in schoolwork, auditory discrimination and speech problems, and sometimes seizures. Brain MRI shows distinctive white matter changes in the parieto-occipital region in about 85% of cases and in the frontal regions in 15% of cases. A common presentation is Addison disease without a CNS abnormality.

Rhizomelic chondroplasia punctata is the major disorder in Group III peroxisomal disorders. Peroxisomes are intact, but there is dysfunction of more than one peroxisomal enzyme. Typical clinical features include shortening of the proximal portion of upper and lower extremities, microcephaly, ichthyosis, cataracts, and severe mental retardation. The striking feature is the radiographic appearance of epiphyseal stippling in the knees, hips, elbows, and shoulders.

The biochemical defects common to the disorders of peroxisomal biogenesis include elevation of VLCFAs, increased plasma phytanic acid, decreased plasma erythrocyte plasmalogen lipids, increased abnormal bile acid intermediates, and deficient docosahexaenoic acid (Table 4). Measurements of these chemicals usually cannot distinguish the different forms of peroxisomal disorders.

Prenatal screening is possible for several of the disorders. All of the Group I disorders can be diagnosed by measuring VLCFAs and plasmalogen synthesis in cultured amniocytes and chorionic villus cells. Peroxisomal structure also can be assessed using cultured amniocytes and chorionic villus samples. Isolated acyl-CoA oxidase deficiency with elevated VLCFAs and normal bile acid intermediates have been reported in amniotic fluid; deficient alanine cyloxylate aminotransferase in fetal liver biopsy; classic Refsum disease via elevations in phytanic acid in cultured amniocytes or chorionic villus samples; and rhizomelic chondrodysplasia punctata on fetal ultrasonography.

Therapies for these disorders are much less precise and effective. For the group I disorders, treatment is primarily supportive, with referral to programs for occupational, physical, and speech therapy. Medical therapies include treatment of liver dysfunction with vitamin K. Dietary manipulation of the VLCFAs has not been shown to alter the disease course. Use of ursodeoxycholic acid may decrease some of the bile acid intermediates, thereby preventing some liver damage. There has been much more publicity about the treatment for the group II disorders (eg, X-linked adrenoleukodystropy). Trials of dietary restriction of VLCFAs have not documented alterations in their plasma levels or the clinical course of the disease. Bone marrow transplantation has been performed in individuals who are diagnosed early in the disease course and who do not yet have significant involvement. Treatment for group III disorders (rhizomelic chondrodysplasia punctata) is primarily supportive, with the addition of dietary restriction of phytanic acid.

Mitochondrial Disorders

Disorders involving the mitochondrion have many phenotypes. These diseases involve disorders of oxidative

metabolism, including fatty acid oxidation, pyruvate metabolism, and defects of the respiratory chain. Multiple classifications systems have been used, but a useful one involves categorization of the site of the molecular lesion and includes the two broad categories of inherited and acquired conditions. There are two categories within the inherited group: nuclear DNA defects and mitochondrial DNA defects. The oxidative metabolism complexes may be derived from either nuclear or mitochondrial DNA. Inheritance patterns differ, with nuclear DNA following mendelian inheritance patterns and mitochondrial DNA following nonmendelian patterns. Mitochondrial DNA controls only the respiratory chain. All mitochondrial DNA comes from the unfertilized ovum and, therefore, is maternal in origin. The human cell has thousands of mitochondrial DNAs, each with a high rate of replication and mutation. Thus, the mitochondrial genome may be a mixture of wild and mutant types of DNA. These mixtures lead to the various phenotypes for the disorders. More than 50 point mutations, plus deletions and duplications of mitochondrial DNA, have been identified. Acquired disorders of oxidative metabolism can occur secondary to a viral illness or varicella such as in Reye syndrome or arise from toxins, drugs, or aging. Inherited metabolic disorders may produce a Reye-like syndrome.

Specific mitochondrial syndromes are mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS); myoclonus epilepsy with ragged-red fibers (MERRF); Kearns-Sayre syndrome (KSS), characterized by progressive external ophthalmoplegia, pigmentary degeneration of the retina, and heart block, cerebellar syndrome, or elevated CSF protein; and Leigh syndrome (LS).

Symptoms of mitochondrial disorders involve many systems of the body because multiple tissues are affected by these disorders of oxidative metabolism (Table 5). These include apnea or other respiratory abnormalities, cardiomyopathy, hypotonia, ophthalmoplegia, acute life-threatening event, myoclonic seizures, paroxysmal vomiting, sensorineural hearing loss, thyroid disease, migraine, and pancreatitis.

When the clinical history suggests a mitochondrial disorder, certain laboratory studies may be helpful in the diagnosis, including serum lactate and pyruvate (blood should be free-flowing, placed on ice, and sent to the laboratory) and CSF lactate and pyruvate. The latter may be more accurate than serum values and frequently is abnormal when the corresponding serum value is normal. Other important studies include measurement of serum glucose; a serum carnitine profile that includes total, free, and acylcarnitine levels; and evaluation of urine organic acids, serum amino acids, and serum ammonia. Biopsies of liver and muscle may be necessary in some instances. In some disorders of lactic acidemia, examination of muscle tissue using a Gomori trichome stain may show a pattern referred to as "ragged red fibers," which represent aggregates of mitochondria. Electron microscopic examination of muscle tissue also may reveal other abnormalities of mitochondrial structure, size, and number. Certain laboratories throughout the United States can assay frozen muscle tissue for some of the specific respiratory enzyme complexes I to IV, but

Table 5. Symptoms of Mitochondrial Disorders

Auditory
• Sensorineural hearing loss
Brain
• Myoclonic seizures • Ataxia • Progressive mental retardation • Stroke-like episodes • Movement disorders: choreoathetosis and/or dystonia • Migraine headaches
Endocrine
• Diabetes mellitus • Hypothyroidism • Hypoparathyroidism • Growth hormone deficiency • Delayed puberty • Infertility
Heart
• Cardiomyopathy • Conduction disturbances
Neuromuscular
• Hypotonia • Weakness • Muscle atrophy • Peripheral neuropathy
Ophthalmologic
• Optic atrophy • Retinal changes • External ophthalmoplegia • Ptosis
Pulmonary
• Central hypoventilation or apnea
Renal
• Renal tubular dysfunction: generalized aminoaciduria

freshly isolated mitochondria provide better material for study. Liver biopsies are useful in diagnosing disorders of beta-oxidation.

Neuroimaging with MRI is an important and useful tool in the diagnosis of mitochondrial disorders. One acute change during a metabolic crisis may be diffuse cerebral edema. Bilaterally increased signals in the putamen, caudate nucleus, and globus pallidus are often seen in LS. Calcification of the basal ganglia is seen in MELAS and KSS. Patients who have MELAS may have lesions in the posterior cerebrum that appear as strokes. Agenesis of the corpus callosum has been reported with pyruvate dehyrogenase deficiency.

Genetic testing for some of the most common mutations of the mitochondrion (MELAS, MERRF, Leber optic atrophy, KSS) can be performed using blood samples. In some of the other disorders involving a single deletion, muscle tissue may be better for the DNA analysis.

Treatment

Therapy to date for these degenerative disorders has been limited and not very successful. The goals have been to correct the metabolic abnormalities such as lactic acidosis, remove toxic metabolites, and treat cardiac irregularities and other life-threatening conditions. Specific treatment regimens include the use of biotin in biotinidase deficiency; folic acid supplementation in Kearn-Sayre syndrome; L-carnitine in carnitine deficient syndromes; coenzyme Q and B complex multivitains in mitochondrial disorders; and the ketogenic diet with medium-chain triglyceride oil, thiamine, and lipoic acid in disorders of the pyruvate dehydrogenase complex. Treatment of lactic acidosis has not been successful; the use of sodium bicarbonate sometimes worsens the associated cerebral edema. Dichloroacetate may be more effective, but its use is still experimental. Other therapies include cardiac pacemakers for those who have cardiac rhythm disorders as in Kearn-Sayre syndrome and adequate caloric supplementation.

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PIR Quiz

Quiz also available online at *www.pedsinreview.org.*

5. You have been asked to evaluate an 8-month-old infant girl who has hepatosplenomegaly, macular degeneration with a cherry-red spot, hypotonia, and areflexia. Although she had been able to roll over, bat at objects, and babble, she has become increasingly apathetic and has lost these skills over the past 2 months. Imaging reveals brain atrophy. Foam cells were identified in a bone marrow biopsy. The *most* likely diagnosis for this patient is:

   A. Gaucher disease.
   B. Krabbe disease.
   C. Metachromatic leukodystrophy.
   D. Neimann-Pick disease.
   E. Tay-Sachs disease.

6. The parents of a 6-week-old infant report that she seems especially sensitive to noise. They were particularly concerned yesterday when she startled very vigorously to the sound of a champagne bottle being opened in the next room. They also report that she has stopped gazing at her mother when breastfeeding. The *most* likely diagnosis for this patient is:

   A. Gaucher disease.
   B. Krabbe disease.
   C. Metachromatic leukodystrophy.
   D. Neimann-Pick disease.
   E. Tay-Sachs disease.

7. You have been asked to consult on a 6-year-old boy in the first grade who had a progressively difficult time in kindergarten and now has lost many of his social and early reading skills. According to his teacher, he does not pay attention in class and seldom completes tasks. Although his kindergarten teacher had not been concerned about any speech problems, the first grade teacher has asked for an evaluation. His skin has become tanned, and a deceased uncle had similar findings. Among the following, the *most* likely diagnosis for this patient is:

   A. Kearns-Sayre syndrome.
   B. Leigh syndrome.
   C. Rhizomelic chondrodysplasia punctata.
   D. X-linked adrenoleukodystrophy.
   E. Zellweger syndrome.

8. Among the following, the brain imaging finding *most* supportive of the suspected diagnosis in the previously described boy is:

   A. Agenesis of the corpus callosum.
   B. Calcification of the basal ganglia.
   C. Diffuse cortical atrophy.
   D. Parieto-occipital white matter changes.
   E. Ventricular dilatation

Degenerative Disorders of the Central Nervous System

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