Inborn Errors of Metabolism : Part 2: Specific Disorders

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Part 2: Specific Disorders

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Amino Acid Disorders

There is no one prototypical disorder of amino acid metabolism; each disorder has its own unique collection of symptoms. Four well-described amino acid disorders have been chosen as examples of this group.

Phenylketonuria, a disorder of phenylalanine metabolism, leads to intellectual disability if untreated.

Maple syrup urine disease involves an enzyme common to the degradation of the branched-chain amino acids (leucine, isoleucine, and valine). Although there are five subtypes of maple syrup urine disease, the classic form has a neonatal onset and generally progresses from poor feeding to coma and death if not treated.

Tyrosinemia also has multiple subtypes. Hepatorenal tyrosinemia (type I) may present with liver failure (elevated transaminase concentrations, hyperbilirubinemia, coagulopathy, ascites, and gastrointestinal bleeding) as well as kidney involvement (tubular dysfunction) and peripheral nerve involvement (painful crises, weakness or paralysis). Type II tyrosinemia is an oculocutaneous form of the disease that has corneal lesions and skin findings.

Homocystinuria, most commonly caused by cystathionine beta-synthase deficiency, presents with ocular (ectopia lentis), skeletal (marfanoid features such as dolichostenomelia and arachnodactyly), vascular (thromboembolic), and central nervous system (intellectual disability, stroke, and seizures) abnormalities.

When an amino acid disorder is suspected, measurement of plasma amino acids generally is sufficient to make the diagnosis. Assessment of urine amino acids can be helpful for homocystinuria and some abnormalities of amino acid transport (cystinuria, dicarboxylic amino aciduria) that affect the kidneys and for detecting generalized amino aciduria found with some kidney disease and mitochondrial disorders.

Urea Cycle Disorders

The degradation of amino acids results in their deamination, generating ammonia as the waste nitrogen. The urea cycle removes the excess ammonia by generating urea, which is eliminated in the urine. Six disorders of the urea cycle are known. Classic forms of urea cycle defects present in the first few days after birth with poor feeding, vomiting, tachypnea (sometimes with respiratory alkalosis), and lethargy that progresses to coma. There also are later-onset forms of many of the urea cycle disorders. Ornithine transcarbamylase (OTC) deficiency is an X-linked disorder, so it occurs more commonly in males, although carrier females may become symptomatic sometime during their lifetimes. Only

Abbreviations

ALD:	adrenoleukodystrophy
AMN:	adrenomyeloneuropathy
CACT:	carnitine acylcarnitine translocase
CNS:	central nervous system
CPK:	creatine phosphokinase
CPS:	carbamyl phosphate synthetase
CPT:	carnitine palmitoyltransferase
CSF:	cerebrospinal fluid
GSD:	glycogen storage disease
LCAD:	long-chain acyl-coA dehydrogenase
LCFA:	long-chain fatty acid
MCAD:	medium-chain acyl-coA dehydrogenase
MLD:	metachromatic leukodystrophy
MPS:	mucopolysaccharidosis
mtDNA:	mitochondrial DNA
NAGS:	N-acetyl glutamate synthetase
nDNA:	nuclear DNA
OTC:	ornithine transcarbamylase
OXPHOS:	oxidative phosphorylation
RCDP:	rhizomelic chondroplasia punctuate
SCAD:	short-chain acyl-coA dehydrogenase
VLCAD:	very long-chain acyl-coA dehydrogenase
VLCFA:	very long-chain fatty acids

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arginase deficiency, a defect of the last step of the urea cycle, does not present with the hyperammonemia common to the other urea cycle disorders. Instead, it presents with neurologic manifestations (progressive spastic quadriplegia, tremor, choreoathetosis, ataxia, seizures, and slowing of cognitive development).

The difficulty with diagnosing the urea cycle disorders is their lack of biochemical abnormality on routine testing; electrolytes and liver enzyme values usually are normal. Many infants who have urea cycle defects initially are believed to have sepsis. Only if ammonia is measured in a sick neonate can the suggestion of a defect in the urea cycle be seen. Assessment of plasma amino acid concentrations often makes the diagnosis. Determination of the orotic acid value may be necessary to distinguish between OTC or carbamyl phosphate synthetase (CPS) deficiency and the rarer N-acetyl glutamate synthetase (NAGS) deficiency (OTC deficiency causes an elevated orotic acid concentration, whereas CPS and NAGS deficiencies are associated with normal or low orotic acid values).

Organic Acid Disorders

This group of disorders results from enzyme deficiencies in pathways of amino acid degradation. Defects in the metabolism of the branched-chain amino acids (leucine, isoleucine, valine) as well as tyrosine, homocysteine, methionine, threonine, lysine, hydroxylysine, and tryptophan are responsible for most of the 25 organic acid disorders. Some of these conditions have been described in only a few patients. The distinction between organic acid disorders and amino acid disorders, however artificial, generally stems from how the disorders are detected. Amino acid disorders are diagnosed by high-performance liquid chromatography amino acid analysis and organic acid disorders by urine organic acid analysis, usually by gas chromatography mass spectrometry.

Many disorders in this group present with acidosis, due to the nature of the accumulating metabolite. Hypoglycemia, lactic acidosis, and ketosis also may occur, either separately or in combination. Analysis of urine for organic acids is the mainstay of diagnosis, and an acylcarnitine profile often is helpful. This test can be performed on blood spotted on newborn screening filter paper.

Carbohydrate Disorders

Glycogen Storage Diseases (GSDs)

These disorders can be subdivided into those that present primarily with liver disease, those that can affect muscle and liver, and those that primarily affect muscle. Because the disorders were numbered in the order of their discovery, the numbers are not useful in separating the disorders by clinical symptoms. GSD I, III, VI, and IX present with hepatomegaly and hypoglycemia. GSD III is subdivided into patients who have no muscle involvement (IIIb) and those who develop muscle weakness by their teenage years (IIIa). GSD IV leads to the formation of an abnormal glycogen that appears to be exceedingly noxious to the liver. Severe liver disease develops in the first few months after birth, leading to cirrhosis. Unlike the other primarily liver disorders, GSD IV often causes severe liver failure before the hypoglycemia is evident. GSD V, VII, and II primarily involve muscle. GSD II is unique in that it is a lysosomal storage disorder that presents in early childhood with progressive cardiomyopathy and hypotonia. GSD V and VII often present in adolescence with exercise intolerance and myoglobinuria.

Hypoglycemia and hepatomegaly suggest a GSD. Measuring concentrations of glucose, uric acid, lactic acid, liver transaminases, and lipids (cholesterol and triglycerides) generally is helpful. GSD I is distinguished from the other disorders that primarily affect liver by markedly elevated lactic acid as well as elevated uric acid and cholesterol concentrations. GSD III is characterized by normal or slightly increased concentrations of lactic acid, normal uric acid, but a greater elevation of triglycerides and cholesterol than GSD I. Creatinine phosphokinase (CPK) may be elevated in older children and adolescents if there is muscle involvement. GSD VI and IX have more benign courses than GSD I and III. Hypoglycemia is less severe, and hepatomegaly often resolves after puberty. Liver failure with portal hypertension suggests GSD IV. A liver biopsy usually is necessary to confirm the diagnosis of the liver GSDs, but DNA testing is increasingly available.

Myoglobinuria after exertion, with exercise intolerance that appears in adolescence, is highly suggestive of GSD V and VII. A muscle biopsy may be necessary to confirm the diagnosis. DNA testing now offers an alternative. DNA testing should help distinguish between type V and type VII.

Galactosemia

There are three disorders of galactose metabolism, but it is a deficiency of the second step of the pathway that is referred to as galactosemia. Infants who have classic galactosemia present with poor weight gain, poor feeding, vomiting, lethargy, jaundice, and hepatomegaly. They also are prone to sepsis from *Escherichia coli*. If the jaundice does not bring them to medical attention, it may resolve and the infants subsequently develop cirrho-

sis with portal hypertension and ascites. The diagnosis is confirmed by enzyme assay, usually on red blood cells

Hereditary Fructose Intolerance

The first exposure to fructose, usually from the disaccharide sucrose (fructose and glucose), results in vomiting and poor feeding. Continued exposure to fructose results in failure to thrive, hepatomegaly, hypoglycemia, jaundice, and renal dysfunction, followed by liver failure with clotting abnormalities, elevated liver transaminases, and ascites. Removal of fructose from the diet usually leads to rapid improvement, but this action requires suspicion of a problem with fructose. Elimination of other causes of hepatomegaly and hypoglycemia often suggest hereditary fructose intolerance. The diagnosis is confirmed by enzyme assay on a liver biopsy. DNA analysis is available for the common mutations.

Fructose-1,6-bisphosphatase Deficiency

Deficiency of this enzyme leads to hypoglycemia resulting from disruption of glucose production by gluconeogenesis. Hypoglycemia, lactic acidosis, and ketosis with hepatomegaly often are presenting signs. Generally, other disorders that cause both hypoglycemia and lactic acidosis need to be excluded. Improvement should be seen with removal of fructose from the diet. Confirmation is by enzyme assay on a liver biopsy.

Protein Glycosylation Disorders

This group of disorders is based on the relatively recent discovery of defects in protein glycosylation. As much as 50% of the body's proteins are modified with sugar (glycan) side chains. The glycan side chains modulate protein function, regulate protein half-life, provide structure (collagen and proteoglycans), and are involved in antibody recognition. Three types of linkage are used to modify proteins. N-linkage occurs with asparagine; O-linkage with serine, threonine, or hydroxylysine; and C-linkage with tryptophan. Defects with the formation of the N- and O-linkage have been reported, but not, as yet, for the C-linkage group.

N-linked glycosylation defects are referred to as congenital disorders of glycosylation. A characteristic of these disorders is the varied involvement of many organ systems. Intellectual disability, hypotonia, seizures, hepatic dysfunction, failure to thrive, vomiting, recurrent infections, and cerebellar hypoplasia are all features of this group.

O-linked glycoproteins are subdivided by the bridging sugar between the glycan side chain and the serine, threonine, or hydroxylysine amino acid in the protein. Bridging sugars include N-acetylgalactosamine, galactosamine (O-galactosyl glycans), xylose (O-xylosyl glycans), mannose (O-mannosyl glycans), and fucose (O-fucosyl glycans).

Two disorders associated with xylose as the bridging sugar include a progeroid variant of Ehlers-Danlos syndrome and a multiple exostosis syndrome. Mannose sometimes is a bridge for glycoproteins found in brain, muscle, and nerves. Walker-Warburg syndrome, muscle-eye-brain disease, a limb girdle muscular dystrophy, and several other congenital muscular dystrophies have been reported to have defects of O-linked glycosylation.

The N-linked disorders can be diagnosed by transferrin electrophoresis. This glycosylated protein found in blood helps to identify the N-linked glycosylation defect. Diagnosis of the O-linked disorders is more difficult, and transferrin testing is not helpful. For this mannose-bridged group, immunostaining of muscle biopsy specimens can look for dystroglycan abnormalities. Electrophoresis of apolipoprotein C-III is useful for diagnosing mucin type proteoglycans (those with N-acetylgalactosamine as a bridge).

Lysosomal Disorders

Lysosomes are cellular organelles that contain more than 30 acid hydrolases that degrade complex cellular molecules to their building blocks. A deficient enzyme results in the accumulation or storage of an intermediate compound. Over time, this stored material leads to cellular damage and disease symptoms. Three groups of lysosomal storage disorders are discussed, and all involve complex organic molecules called glycoproteins. These molecules have a protein backbone to which a polysaccharide side chain (glycan) is attached.

The first group of disorders has deficiencies of lysosomal enzymes that degrade the polysaccharide chain (glycosaminoglycan) and lead to the mucopolysaccharidoses (MPSs). The second group has deficiencies of the enzymes that degrade glycoproteins with a less complex polysaccharide than the glycan involved in the MPSs. Molecules that have this simpler polysaccharide are termed oligosaccharides. The oligosaccharidoses include mannosidosis, sialidosis, fucosidosis, and aspartylglucosaminuria. The third group is the sphingolipidoses. This group involves glycoproteins with a backbone comprised of sphingosine and a long-chain fatty acid (LCFA) to produce ceramide. These sphingolipidoses include Fabry, Farber, Gaucher, Krabbe, and Niemann-Pick diseases, as well as G_{M1} and G_{M2} gangliosidoses and metachromatic leukodystrophy (MLD).

Mucopolysaccharidoses (MPSs)

Children who have an MPS disorder are normal at birth. The disorders are progressive, with most having neurologic involvement that leads to characteristic regression and loss of milestones. Most affected patients have intellectual disability. Hepatosplenomegaly is found in most of the disorders. Bone involvement leads to short stature and the characteristic radiologic findings (dysostosis multiplex). Many children who have MPS disorders have frequent bouts of otitis media.

The seven MPS disorders include three that have both central nervous system (CNS) and somatic involvement (MPS I: Hunter/Scheie syndrome, MPS II: Hunter syndrome, and MPS VII: Sly syndrome), one disorder that has somatic involvement but minimal CNS involvement (MPS VI: Maroteaux-Lamy syndrome), one disorder that has CNS involvement and minimal somatic involvement (MPS III: Sanfilippo syndrome), and two disorders that have bone or joint involvement (MPS IV: Morquio syndrome and MPS IX).

Coarsened facial features, hepatosplenomegaly, joint involvement, and developmental delay followed by regression are presenting features in children who have an MPS. Radiographs looking for evidence of bony involvement (dysostosis multiplex) often are helpful. A screening test may bolster the suspicion if the glycosaminoglycans are increased in the urine, but the diagnosis generally is confirmed by enzyme assay.

Oligosaccharidoses

This group is similar to the MPSs, with many disorders associated with coarsened facial features, hepatosplenomegaly, and retinal (cherry red spot) or corneal involvement. Regression also is found with this group of lysosomal storage disorders.

Urine tested for glycosaminoglycans is negative, despite the concern for an MPS disorder. Urine for oligosaccharides may suggest one of the disorders in this group. Radiographs show dysostosis multiplex for many of the oligosaccharidoses. In addition, alpha mannosidosis should be considered in the presence of severe dysostosis multiplex, hepatosplenomegaly, and intellectual disability. Beta-mannosidosis may be distinguished by hearing loss, sialidosis by cherry red spots and myoclonus, and fucosidosis by recurrent respiratory infections and angiokeratoma (similar to Fabry disease). An enzyme assay is used to confirm the suspected diagnosis in most cases.

Sphingolipidoses

The prominent features of this group include hepatosplenomegaly (Niemann-Pick disease, G_{M1} gangliosidosis, Gaucher disease), demyelination (Krabbe disease, MLD, G_{M1} and G_{M2} gangliosidoses), and neuronal storage (G_{M1} and G_{M2} gangliosidoses). Most of these disorders are characterized by neurologic regression.

Initial normal development followed by neurologic regression suggests a lysosomal storage disorder. Although a negative test for glycosaminoglycans and oligosaccharides in urine does not completely rule out an MPS or oligosaccharidosis, this finding does suggest consideration of a sphingolipidosis (which does not have any abnormality of glycosaminoglycans or oligosaccharides). Magnetic resonance imaging may show demyelination, and an ophthalmologic examination may reveal a cherry red spot. Diagnosis and confirmation generally are by enzyme assay.

Peroxisomal Disorders

Peroxisomes are cellular organelles involved in beta-oxidation of very long-chain fatty acids (VLCFAs), the degradation of phytanic acid by alpha-oxidation, and the synthesis of plasmalogens. Peroxisomal disorders can be divided into two groups: peroxisomal biogenesis disorders, typified by Zellweger syndrome, and disorders involving mutations of individual peroxisomal enzymes.

Zellweger Syndrome Spectrum Group

Peroxisomal biogenesis disorders fall into a spectrum, with Zellweger syndrome being the most severe, infantile Refsum disease being less severe, and neonatal adrenoleukodystrophy (ALD) being somewhat milder. Zellweger syndrome is the prototypical biogenesis disorder. It is characterized by dysmorphic features (high forehead, flat occiput, large anterior fontanelle, hypoplastic superior orbital ridges, epicanthal folds, broad nasal bridge, anteverted nostrils, and micrognathia), brain defects (migrational brain defects with microgyria, pachygyria, and dysmyelination) and seizures, liver disease (dysfunction and cirrhosis), adrenal insufficiency, and often, renal abnormalities (microcysts). Children suffer severe intellectual disability (little, if any, development) and die from multiple problems, often in the first postnatal year.

Due to the biogenesis defect, all of the peroxisomal enzymes are deficient. Patients generally accumulate VLCFAs and develop abnormalities in phytanic acid (high) and plasmalogens (low).

Rhizomelic Chondrodysplasia Punctata (RCDP)

The peroxisomal biogenesis disorders are due to defects in the importation of proteins produced in the cytosol into the peroxisomes. Another peroxisomal biogenesis disorder, RCDP, is due to an importation defect of a subset of peroxisomal enzymes that use a different recognition marker. Most of the peroxisomal enzymes normally are imported, with only a few that use the different recognition marker failing to reach their place within the peroxisome. B-oxidation of LCFAs and VLCFAs is unaffected, but phytanic acid alpha oxidation and plasmalogen synthesis are affected. Clinical features of the three types of RCDP are similar, but type 1 is a peroxisomal biogenesis defect, while types 2 and 3 are single-enzyme defects of peroxisomal enzymes. Patients have rhizomelic shortening of the limbs (humerus more than femur), joint contractures, congenital cataracts, calcific stippling of epiphyses of long bones, growth failure, and profound developmental delay.

VLCFA concentrations are normal. Red blood cell plasmalogens are low, and phytanic acid concentrations are elevated. For types 2 and 3 RCDP, only the red blood cell plasmalogens are low; phytanic acid values are normal. Care should be taken not to draw conclusions about normal phytanic acid values because, with the diet as the only source of phytanic acid, concentrations in young patients may be normal, only becoming elevated over time. Enzyme assays on fibroblasts or DNA analysis may be necessary to distinguish the different types of RCDP.

Peroxisomal B-oxidation of LCFAs and VLCFAs

A few deficiencies of the enzymes involved in the B-oxidation of VLCFA have been described. They generally present similarly to the Zellweger spectrum disorders. One disorder even has been reported to have a neuronal migration defect similar to the Zellweger spectrum disorders, which suggests that this abnormality in the Zellweger spectrum may be due to abnormal B-oxidation of LCFA and VLCFA.

Another disorder of peroxisomal B-oxidation, racemase deficiency, presents with a late-onset neuropathy, rather than a picture similar to the Zellweger spectrum disorders.

X-linked ALD

This disorder is presumed to involve a peroxisomal membrane protein that transports VLCFA into the peroxisomes. Although not an enzyme defect of the VLCFA pathway, failure of such transport leads to accumulation of VLCFA (C22:0, C24:0). Two phenotypes have been described. The first is a childhood cerebral form that has an onset in the first decade after birth (mean age of 7 years) and has subtle initial manifestations of school behavioral problems (hyperactivity), emotional lability, and school failure. These initial features are followed by adrenal insufficiency and rapid progression of neurologic abnormalities believed to be due to an inflammatory reaction, with demyelination and gliosis of the parietal-occipital areas.

Adrenomyeloneuropathy (AMN) is a milder form of disease that presents with a later-onset, slowly progressive paraparesis (20s and 30s) that often is associated with adrenal insufficiency. AMN generally does not initially involve the brain, as does the childhood cerebral form of ALD, but 20% of affected patients eventually have brain abnormalities similar to those of childhood cerebral X-linked ALD. This group is referred to as AMN-cerebral.

Testing for elevation of VLCFA identifies patients who have defects of peroxisomal B-oxidation. Test results for other peroxisomal functions are normal. An enzyme assay on fibroblasts and DNA mutation analysis helps to separate the single-enzyme defects.

Plasmalogen Synthesis

Two enzyme defects of plasmalogen synthesis have been identified and present with a clinical picture similar to that of RCDP. In fact, the two defects are referred to as RCDP types 2 and 3. As with RCDP type 1, plasmalogen values are low, and this compound can be measured in red blood cells. Studies on skin fibroblasts often are necessary to distinguish the type of RCDP.

Peroxisomal Alpha-oxidation of Fatty Acids

Phytanic acid, a branched-chain fatty acid, whose only source is from dietary intake, undergoes alpha-oxidation in peroxisomes. Loss of this pathway results in accumulation of phytanic acid, which is the cause of Refsum disease (not infantile Refsum disease, which is a peroxisomal biogenesis disorder in the Zellweger spectrum). Clinically, Refsum disease is characterized by a tetrad of retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and increased cerebrospinal fluid (CSF) protein without increased cells. Symptoms usually are apparent before 20 years of age, with night blindness often being the first clinical symptom. Loss of the sense of smell and hearing loss also are common.

For patients who have Refsum disease, only phytanic acid concentrations are elevated. Although patients who have the Zellweger spectrum of disorders have elevated phytanic acid concentrations, VLCFA values also are abnormal.

Mitochondrial Fatty Acid Oxidation Defects and Carnitine Transport Defects

Mitochondrial Fatty Acid Oxidation Defects

Four enzymatic reactions are involved in the removal of 2-carbon fragments as acetyl-CoA from saturated fatty acids, which then are used for energy production. These steps are repeated in a spiral of B-oxidation that continues until only one 2-carbon fragment is left. Each of the four steps involved in B-oxidation of fatty acids has two or more enzymes that show specificity for different length fatty acids. The first step (acyl-CoA dehydrogenase) has four different enzymes, each with its own specificity. Short-chain acyl-CoA dehydrogenase (SCAD) shows specificity for fatty acids that are 4 to 6 carbons in length, medium-chain acyl-CoA dehydrogenase (MCAD) for those of 4 to 12 carbons, long-chain acyl-CoA dehydrogenase (LCAD) for those of 12 to 18 carbons, and very long-chain acyl-CoA dehydrogenase (VLCAD) for fatty acids 14 to 20 carbons in length. Disorders involving deficiencies of SCAD, MCAD, and VLCAD have been described, but patients who have deficiencies of LCAD have yet to be identified.

The third step has two known disorders and involves one of two 3-hydroxyacyl-CoA dehydrogenases. The first, short-chain 3-hydroxyacyl-CoA dehydrogenase, despite its name, acts on fatty acids of 4 to 16 carbons in length. The second, long-chain 3-hydroxyacyl-CoA dehydrogenase, favors the longer-chain fatty acids.

The unifying feature for disorders of mitochondrial fatty acid oxidation is the presence of hypoketotic hypoglycemia. SCAD, which catalyzes the last step and has C4 (butyl-CoA) as a substrate, may be the exception and rarely presents with hypoglycemia. Some of the enzyme deficiencies have a variant form, which produces myoglobinuria and muscle weakness. In general, if a fatty acid oxidation disorder is being considered, glucose concentration (both in the laboratory and by finger stick) should be measured, as well as concentrations of electrolytes, ammonia, liver transaminases, CPK, lactic acid, and uric acid. A complete blood count also should be obtained. Urine should be assessed for organic acids, and a routine urinalysis should be performed to help determine if there is myoglobinuria (positive blood on urinalysis but no red blood cells on microanalysis). An acylcarnitine profile can be helpful, as can assessment of urine for organic acids. A skin biopsy may be needed for enzyme analysis on fibroblasts to narrow down the actual enzymatic defect.

Carnitine Transport Defects

Carnitine helps to transport the longer-chain fatty acids (14 to 20 carbons in length) into mitochondria because unlike the medium-chain and short-chain fatty acids, they cannot pass through the mitochondrial membrane without assistance. Carnitine palmitoyltransferase I (CPT I) attaches carnitine to the fatty acid molecule, carnitine acylcarnitine translocase (CACT) transports the resulting molecule across the mitochondrial membrane, and finally, CPT II removes the carnitine and releases the fatty acid for B-oxidation.

Defects in the carnitine transport enzymes share some of the features of fatty acid oxidation defects, such as manifesting with hypoglycemia associated with hypoketosis, lethargy, and sometimes a Reye-like syndrome (hepatomegaly, elevated transaminases and ammonia). Seizures are not uncommon because of the hypoglycemia. The most common presentation of CPT II is an adult onset that involves muscle weakness, elevated CPK, and myoglobinuria after prolonged exertion.

If a carnitine transport defect is suspected, an acylcarnitine profile is a helpful initial test. CPT II and CACT have similar abnormalities that distinguish them from CPT I. In addition, CPT I may have normal-to-elevated carnitine concentrations. A skin biopsy with fibroblast studies may be necessary to distinguish between these disorders.

Mitochondrial Disease

Mitochondrial Disease Due to Mitochondrial DNA Alterations

As noted previously, mitochondria are involved in fatty acid oxidation (including carnitine transport). Mitochondria also have a role in the urea cycle, citric acid cycle, and most importantly, the energy production pathway of oxidative phosphorylation (OXPHOS). It is for defects in the energy-producing pathway, OXPHOS, that the term mitochondrial disease is reserved.

Mitochondria have their own DNA (mtDNA). The circular molecule encodes 37 proteins, including a translational system (2 ribosomal RNAs and 22 tRNAs) that differs from the cellular protein synthesis components and 13 OXPHOS proteins. The remaining (more than 70) OXPHOS proteins as well as nearly 900 proteins involved in other mitochondrial pathways are encoded by the nuclear DNA (nDNA). All mitochondria are derived from the ovum, so mtDNA disorders are maternally inherited. Mitochondrial disease due to nDNA mutations have been reported to have autosomal recessive, autosomal dominant, and X-linked inheritance patterns.

Mitochondria have multiple copies (3 to 10) of the mtDNA. Not all of the hundreds of mitochondria in the ovum are incorporated into the developing embryo. If incorporated into the embryo, the abnormal mitochondria may not be distributed equally to all tissues. The presence of different mtDNA molecules within a cell or individual is referred to as heteroplasmy. Energy production is affected by the presence of heteroplasmy within a mitochondrion. The mitochondria harboring mtDNA mutations generally are less able to produce energy. Clinical symptoms become apparent when the energy production is below the energy requirements of a particular tissue. Tissues that have high energy requirements, such as brain, liver, and kidney, are more susceptible to mitochondrial disease.

A number of mtDNA disorders have been described. Kearns-Sayre syndrome, Pearson syndrome, and chronic progressive external ophthalmoplegia (CPEO) have deletions or duplications of the mtDNA. MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke), MERRF (myoclonic epilepsy with ragged red fibers), NARP (neurogenic weakness, ataxia, and retinitis pigmentosa), MILS (maternally inherited Leigh syndrome), hypertrophic cardiomyopathy, mitochondrial myopathy, LHON (Leber hereditary optic neuropathy), and SNHL (nonsyndromic aminoglycoside-induced sensory neural hearing loss) have point mutations of the mtDNA.

Mitochondrial Disease (OXPHOS) Due to Nuclear DNA Mutations

Because most of the mitochondrial genes are coded by nDNA, it is not surprising that now more than 30 known OXPHOS disorders are due to nDNA mutations. Some of these disorders involve OXPHOS genes directly, some involve the importation of mitochondrial enzymes synthesized in the cytosol, and others affect mtDNA synthesis or importation of nucleotides or nucleotide synthesis.

Diagnostic Testing

Mitochondrial disease can affect many types of tissues. Brain, heart, liver, kidney, and pancreas involvement, as well as hearing loss and endocrine dysfunction have been reported. Often, muscle weakness, stroke, cardiomyopathy, hearing loss, or endocrine dysfunction suggests a mitochondrial disorder. In fact, the somewhat unrelated involvement of multiple tissues often adds mitochondrial disease to the differential diagnosis.

Screening with lactic acid cannot identify all patients who have mitochondrial disease because this is an inconsistent finding with the disorders. A markedly elevated lactate concentration, however, should raise concern about a mitochondrial disorder. Elevation of lactate often occurs after use of a tourniquet, but the elevation also can be caused by dehydration, seizure activity, or improper specimen handing.

Determination of a lactate-to-pyruvate ratio may be helpful; a ratio greater than 30 is indicative of an OXPHOS defect. CSF lactate and pyruvate values also are helpful for some patients.

A biopsy, generally of muscle, is the most definitive method for diagnosis. The specimen should be examined for ragged red fibers as well as accumulation of mitochondria in the subsarcolemma layer of the muscle. Staining for succinate dehydrogenase and cytochrome C oxidase should be performed. Electron microscopy may show abnormal mitochondria or crystalline inclusions. A muscle specimen should be sent to a specialized laboratory for enzyme analysis of the OXPHOS pathway.

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