

Inborn Errors of Metabolism And Genetic Syndromes Descriptions & Diagnosis



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INBORN ERRORS OF METABOLISM AND GENETIC SYNDROMES DISEASE DESCRIPTIONS AND DIAGNOSES

Below are descriptions and definitive diagnoses for selected inborn errors of metabolism and genetic syndromes I originally compiled in 2002. There are now over 500 described inborn errors of metabolism and countless other genetic syndromes making this list representative of only a fraction of all known genetic disorders. The goal of this manuscript is to include some of the more common problems you may encounter in your practice. The majority of this information was obtained from *The Metabolic and Molecular Bases of Inherited Disease*, 7th ed. New York:McGraw-Hill. Editors: Scriver CR, Beaudet AL, Sly WS, Valle D.

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Note: The information contained here is not meant to be comprehensive and definitive in all circumstances but merely to offer guidelines and assistance to physicians and health care providers in their evaluation of and approach to patients with possible genetic and metabolic disorders. Further assistance should be sought by contacting a qualified genetic metabolic specialist.

ACUTE INTERMITTENT PORPHYRIA

- Pathophysiology - Disorder in heme biosynthesis due to a deficiency in porphobilinogen deaminase
- Clinical Presentation - Approximately 90% of individuals who inherit this gene and disorder never develop clinical symptoms. For those who do become symptomatic, their disorder is latent before puberty and problems occur more often in females than males. Hormonal, drug, and nutritional factors likely aggravate the disease. Typical presentation includes abdominal pain, nausea and vomiting, ileus, hypertension and tachycardia, motor neuropathy, hyponatremia, and, often, dark or red urine.
- Definitive Laboratory Testing - Urine ALA and PBG; PBG deaminase activity in erythrocytes
- Inheritance - Autosomal dominant
- Prenatal Diagnosis - Available

ADRENOLEUKODYSTROPHY (ALD), X-LINKED

- Pathophysiology - Disorder in the metabolism of very long chain fatty acids (VLCFAs) due to a peroxisomal deficiency of a single enzyme, lignoceroyl CoA lyase.
- Clinical Presentation - There are several distinct phenotypes attributable to X-linked ALD. The childhood form is the most common and accounts for almost 50% of cases. Affected males typically present between 5-7 years of age with school difficulties after a period of normal development. Dementia develops and a progressive neurodegeneration follows that leads to a vegetative state. The neurological problems typically precede the onset of adrenal insufficiency. There are several other phenotypes including the progressive adolescent and adult cerebral forms, adrenomyeloneuropathy which causes progressive paraparesis and sphincter disturbance in affected males due to spinal cord involvement and biochemical manifestations in asymptomatic individuals. Ten percent of patients have adrenal insufficiency only.
- Definitive Laboratory Testing - Blood VLCFAs; skin fibroblast oxidation of VLCFAs DNA mutational analysis



Inheritance - X-linked recessive
Prenatal Diagnosis - Available

ANGELMAN SYNDROME

Pathophysiology - Disorder caused by a deletion of the maternal chromosome 15q11-q13 or the presence of two copies of the paternal chromosome 15 (uniparental disomy)

Clinical Presentation - Affected individuals typically have severe mental retardation, microcephaly, paroxysms of inappropriate laughter, absent speech, ataxia and jerky arm movements resembling a puppet gait, dysmorphic facies characterized by a large mandible and open-mouthed expression revealing the tongue and widely spaced teeth and seizures. Additional features include hypopigmentation and sleep difficulties typically between the ages of 2 to 6 years.

Definitive Laboratory Testing - Chromosome 15 analysis for detection of a deletion or presence of two chromosome 15 copies from the same parent

Inheritance - Typically sporadic

Prenatal Diagnosis - Available

ARGINASE DEFICIENCY

Pathophysiology - Disorder in waste ammonium nitrogen metabolism due to a deficiency in arginase, an enzyme of the urea cycle.

Clinical Presentation - This disorder typically presents with progressive spastic di- or quadriplegia and mental retardation. Symptomatic hyperammonemia (vomiting, lethargy, and other changes in mentation) occurs neither as severely or as commonly as in the other disorders of the urea cycle. Amino acid analysis notes an increase in glutamine and a marked increase in both blood and urine arginine. Orotic acid is present on organic acid analysis.

Definitive Laboratory Testing - Plasma and urine amino acids; urine organic acid; enzymatic assay in erythrocytes and/or liver; DNA linkage analysis.

Inheritance - Autosomal recessive

Prenatal Diagnosis - Available

ARGININOSUCCINIC ACID LYASE (ASAL) DEFICIENCY

Pathophysiology - Disorder in waste ammonium nitrogen metabolism due to a deficiency of argininosuccinic acid lyase, an enzyme in the urea cycle.

Clinical Presentation - The clinical manifestations may appear in the neonatal period or anytime thereafter with varying degrees of severity. Neonatal cases typically present with vomiting, increasing lethargy, hypothermia and hyperventilation sometime between 24 and 72 hours of life. If undiagnosed, the infant quickly progresses to coma and requires mechanical ventilation. Death will usually ensue if the child remains undiagnosed. Routine chemistries typically reveal only low serum urea nitrogen, sometimes as low as 1 mg/dl. Plasma ammonium is markedly elevated, often 10-30 times normal. The finding of



hyperammonemia will direct diagnostic efforts toward an inborn error of metabolism. An elevation of blood glutamine and citrulline and the presence of argininosuccinic acid in both blood and urine are found on amino acid analysis. Urine organic acids analysis will demonstrate the presence of orotic acid. In the late onset group, symptoms present from the first year of life to adulthood. In infants, symptoms may develop following a transition from either breast milk or a low-protein formula to cow's milk. In older children and adults episodes may be precipitated by the ingestion of high protein foods. Infections may also trigger episodes of decompensation. Such episodes are usually marked by vomiting, lethargy, other neurological signs such as irritability, agitation, ataxia and, at times, apnea and seizures, and the same biochemical abnormalities seen with neonatal onset cases. In addition, many individuals with this disorder develop hepatomegaly of unknown etiology and the characteristic hair finding trichorrhexis nodosa is seen in others.

- Definitive Laboratory Testing - Plasma and urine amino acids; urine organic acid analysis for orotic acid; enzymatic in skin fibroblasts and/or liver.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

ARGININOSUCCINIC ACID SYNTHETASE DEFICIENCY (CITRULLINEMIA)

- Pathophysiology - Disorder in waste ammonium nitrogen metabolism due to a deficiency of argininosuccinic acid synthetase, an enzyme in the urea cycle.
- Clinical Presentation - The clinical manifestations may appear in the neonatal period or anytime thereafter with varying degrees of severity. Neonatal cases typically present with vomiting, increasing lethargy, hypothermia and hyperventilation sometime between 24 and 72 hours of life. If undiagnosed, the infant quickly progresses to coma and requires mechanical ventilation. Death will usually ensue if the child remains undiagnosed. Routine chemistries typically reveal only low serum urea nitrogen, sometimes as low as 1 mg/dl. Plasma ammonium is markedly elevated, often 10-30 times normal. The finding of hyperammonemia will direct diagnostic efforts toward an inborn error of metabolism. An elevation of blood glutamine and a marked elevation in citrulline is found on amino acid analysis. Urine organic acids analysis will demonstrate the presence of orotic acid. In the late onset group, symptoms present from the first year of life to adulthood. In infants, symptoms may develop following a transition from either breast milk or a low-protein formula to cow's milk. In older children and adults episodes may be precipitated by the ingestion of high protein foods. Infections may also trigger episodes of decompensation. Such episodes are usually marked by vomiting, lethargy, other neurological signs such as irritability, agitation, ataxia and, at times, apnea and seizures, and the same biochemical abnormalities seen with neonatal onset cases.
- Definitive Laboratory Testing - Plasma and urine amino acids; urine organic acid analysis for orotic acid*; enzymatic activity in skin fibroblasts and/or liver; DNA linkage studies.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available



BECKER MUSCULAR DYSTROPHY

- Pathophysiology - Disorder caused by mutation in the dystrophin gene located on the X chromosome
- Clinical Presentation - Affected males typically present before 5 years of age with muscle weakness in comparison to the onset of symptoms by 1-2 years in patients with Duchenne muscular dystrophy. A combination of axial weakness, a tendency for toe walking and muscular hypertrophy is the typical presenting picture. Patients are usually ambulatory until after 16 years. The natural history of this disorder is not well defined but survival may be into the fourth decade or later. Patient CPK levels are markedly elevated (50-100 times normal) and EMG studies note a reduction in the duration and amplitude of action potentials and an enhanced frequency of polyphasic potentials.
- Definitive Laboratory Testing - Analysis of dystrophin in muscle biopsy tissue; dystrophin gene mutational analysis
 - Inheritance - X-linked
 - Prenatal Diagnosis - Available

BIOTINIDASE DEFICIENCY

- Pathophysiology - Disorder causing a functional deficiency of biotin due to failure to cleave biocytin into biotin and lysine by biotinidase. This results in deficient activity of multiple carboxylase enzymes including propionyl CoA carboxylase, 3-methylcrotonyl CoA carboxylase and pyruvate carboxylase.
- Clinical Presentation - Although clinical expression is highly variable, the most common features include seizures, hypotonia, ataxia, breathing problems, hearing loss, optic atrophy, developmental delay, skin rash, and alopecia. The age of onset of symptoms ranges from several weeks to several years of age with some known patients presenting as late as 10 years of age. Most, but not all, symptomatic children develop metabolic ketolactic acidosis and organic aciduria. Organic acid profiles often show 3-hydroxyisovalerate, lactate, 3-hydroxypropionate, 3-methylcrotonylglycine and methylcitrate.
- Definitive Laboratory Testing - Organic acids in some cases; biotinidase activity in serum
 - Inheritance - Autosomal recessive
 - Prenatal Diagnosis - Available
 - Note: The organic acid profiles in at least 20% of patients with enzymatically confirmed biotinidase def'y are normal.

CANAVAN DISEASE

- Pathophysiology - Disorder in metabolism of the brain chemical N-acetylaspartic acid due to a deficiency of aspartoacylase
- Clinical Presentation - Affected infants are typically normal at birth but develop poor head control, seizures and abnormal muscle tone between 2 to 4 months of life. Although usually hypotonic at presentation, the transition to spasticity may be rapid and hypertonia may be the initial finding. Increased deep tendon reflexes, skill regression and a progression to decerebrate or decorticate posturing follows.



Macrocephaly is almost always present by 6 months of age. Additional findings may include seizures, dysphagia, optic atrophy and nystagmus. Brain imaging studies typically demonstrate diffuse symmetrical abnormalities of white matter.

- Definitive Laboratory Testing - N-acetylaspartic acid in urine and plasma organic acids; aspartoacylase activity in skin fibroblasts; DNA mutational analysis in many cases
- Inheritance - Autosomal recessive, more common in Ashkenazi Jews
- Prenatal Diagnosis - Available

CARBAMYL PHOSPHATE SYNTHETASE (CPS) DEFICIENCY

- Pathophysiology - Disorder in waste ammonium nitrogen metabolism due to a deficiency of carbamyl phosphate synthetase, an enzyme in the urea cycle.
- Clinical Presentation - The clinical manifestations may appear in the neonatal period or anytime thereafter with varying degrees of severity. Neonatal cases typically present with vomiting, increasing lethargy, hypothermia and hyperventilation sometime between 24 and 72 hours of life. If undiagnosed, the infant quickly progresses to coma and requires mechanical ventilation. Death will usually ensue if the child remains undiagnosed. Routine chemistries typically reveal only low serum urea nitrogen, sometimes as low as 1 mg/dl. Plasma ammonium is markedly elevated, often 10-30 times normal. The finding of hyperammonemia will direct diagnostic efforts toward an inborn error of metabolism. An elevation of blood glutamine and an absence in citrulline is found on amino acid analysis. Orotic acid will be absent on organic acid analysis, distinguishing this disorder from ornithine transcarbamylase deficiency, another defect in the urea cycle. In the late onset group, symptoms present from the first year of life to adulthood. In infants, symptoms may develop following a transition from either breast milk or a low-protein formula to cow's milk. In older children and adults episodes may be precipitated by the ingestion of high protein foods. Infections may also trigger episodes of decompensation. Such episodes are usually marked by vomiting, lethargy, other neurological signs such as irritability, agitation, ataxia and, at times, apnea and seizures, and the same biochemical abnormalities seen with neonatal onset cases.
- Definitive Laboratory Testing - Plasma and urine amino acids; urine organic acid analysis for orotic acid; enzymatic activity in the liver; DNA linkage studies.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

CARBOHYDRATE DEFICIENT GLYCOPROTEIN (CDG) SYNDROME

- Pathophysiology - disorder caused by the hypoglycosylation of glycoproteins due to the deficiency of one of several enzymes including phosphomannomutase (CDG type Ia) and phosphomannose isomerase (CDG type Ib)
- Clinical Presentation - There are multiple forms of CDG (up to 19 forms as classified by Dr. Hudson Freeze in 2006 Nature Reviews article) typically present with neurological, liver, hematological and/or intestinal problems. Children and adults with CDG type Ia, the most well known, typically present with multisystem disease with



early severe neurologic dysfunction, including significant developmental delay and motor dysfunction that often results in patients being wheelchair bound. Type Ib usually present with protein-losing enteropathy and liver disease without neurological impairment. The other types have mainly neurological problems, hepatic problems and/or enteropathy. Some of the multisystem clinical findings include cardiomyopathy and pericardial effusions, inverted breast nipples, abnormal buttock fat pads, coagulation difficulties, renal cysts and the nephrotic syndrome, cerebellar hypoplasia, optic nerve atrophy, olivopontocerebellar atrophy, stroke-like episodes, nystagmus, esotropia, retinitis pigmentosa, failure to thrive and peripheral neuropathy.

- Definitive Laboratory Testing - Transferrin isoelectric focusing studies, enzyme assay in leukocytes and skin fibroblasts and mutation analysis in some cases
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available for some cases.

CARNITINE PALMITOYLTRANSFERASE I (CPT I) DEFICIENCY

- Pathophysiology - Deficiency of carnitine palmitoyltransferase I in the liver resulting in failure of acylcarnitine formation and limited entry of long chain substrates into the mitochondria for oxidative metabolism.
- Clinical Presentation - Most affected patients present between 8 to 18 months of age with hypoketotic hypoglycemia without dicarboxylic aciduria as noted on organic acid analysis in the setting of a viral illness associated with fasting. Coma, seizures and hepatomegaly are also commonly seen. Plasma carnitine levels are normal to elevated. Renal tubular acidosis was seen in one patient. Most patients develop recurrent episodes and often have neurological deficits resulting from the initial insult. Avoidance of fasting and dietary therapy can prevent episodic decompensation.
- Definitive Laboratory Testing - Urine organic acids; CPT I enzyme activity in skin fibroblasts, leukocytes and other tissues; gene sequencing.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

CARNITINE PALMITOYLTRANSFERASE II (CPT II) DEFICIENCY

- Pathophysiology - Deficiency of carnitine palmitoyltransferase II resulting in inability to convert long-chain acylcarnitines to their acyl-CoAs in the mitochondrial matrix for subsequent oxidation.
- Clinical Presentation - There are two distinct phenotypes including the more common "classical" muscular form which typically presents between 15 to 30 years of age with episodic myoglobinuria and muscle weakness prompted by prolonged exercise. Occasionally fasting, mild infection, emotional stress, or cold exposure triggers these episodes. Although it is an autosomal recessive disorder males are more frequently affected. Carnitine values are usually normal and CPK is normal between episodes. About 25% of patients develop renal failure as a result of the episodic myoglobinuria. The often-fatal infantile form of the disorder typically presents with coma, seizures, hypoketotic hypoglycemia without dicarboxylic aciduria (on organic acid profile),



hepatomegaly, cardiomegaly, cardiac arrhythmias, and low plasma and tissue carnitine values. Renal dysgenesis has been reported in three patients.

Definitive Laboratory Testing - Urine organic acid; CPT I enzyme activity in skin fibroblasts, leukocytes and other tissues; gene sequencing.

Inheritance - Autosomal recessive

Prenatal Diagnosis - Available

DUCHENNE MUSCULAR DYSTROPHY

Pathophysiology - Disorder caused by mutation in the dystrophin gene located on the X chromosome

Clinical Presentation - Affected males typically present at 1- 2 years of age with muscle weakness, often first notable when the child begins to walk. He is usually less agile than others and falls frequently. By 4 to 5 years of age, he will have trouble climbing stairs and arising from a sitting position. These children typically have a tendency to walk and balance on the ball of the foot. Muscular hypertrophy is noted on exam. By age 9 to 10 years they are usually nonambulatory. Many also develop school problems including hyperactivity and distractibility and 20% of patients have a significant developmental delay. The disease is progressive causing such difficulties as scoliosis and respiratory compromise and usually leads to death in early adulthood. Patient CPK levels are markedly elevated (50-100 times normal) and EMG studies note a reduction in the duration and amplitude of action potentials and an enhanced frequency of polyphasic potentials.

Definitive Laboratory Testing - Analysis of dystrophin in muscle biopsy tissue; dystrophin gene mutational analysis

Inheritance - X-linked

Prenatal Diagnosis - Available

FABRY DISEASE

Pathophysiology - Disorder in glycosphingolipid catabolism due to a deficiency of the lysosomal hydrolase alpha galactosidase A

Clinical Presentation - The clinical manifestations of Fabry disease result primarily from the deposition of globotriaosylceramide in the vascular endothelium. Symptoms for affected males typically begin during childhood or adolescence but have been known to develop during the second and third decade of life. Early manifestations include periodic crises of severe pain in the extremities, the appearance of vascular cutaneous lesions (angiokeratoma), hypohidrosis, and corneal and lenticular opacities. Over time, proteinuria, hyposthenuria, and lymphedema appear and, ultimately, severe renal impairment leads to hypertension and uremia. Death usually occurs from renal failure or from cardiac or cerebrovascular disease. Milder variants may have late-onset, mild disease manifestations primarily limited to the heart. Heterozygote females are typically asymptomatic but, on occasion, may be as severely impaired as an affected male. Enzyme replacement therapy has recently become available and may alter the natural history of this disorder for affected individuals.

Definitive Laboratory Testing - Alpha galactosidase A activity in plasma or leukocytes; DNA mutational



analysis
Inheritance - X-linked
Prenatal Diagnosis - Available

FRAGILE X SYNDROME

Pathophysiology - A disorder caused by a mutation in the FMR-1 gene located on the X chromosome

Clinical Presentation - The most common form of INHERITED mental retardation, affected males with Fragile X classically present with mental retardation, large and prominent ears, a long narrow face and macroorchidism. Other less common characteristics of the disorder include additional signs of mild connective tissue dysplasia such as hyperextensible fingers, flat feet and scoliosis, macrocephaly and behavioral difficulties such as hyperkinetic behavior, emotional instability, autism and autistic like features. However, significant phenotypic variation exists, making clinical ascertainment of many cases more difficult, particularly in affected females.

Definitive Laboratory Testing - DNA analysis for detection of CGG trinucleotide repeat expansion in the FMR-1 gene on the X chromosome

Inheritance - X-linked
Prenatal Diagnosis - Available

GALACTOSEMIA

Pathophysiology - Disorder in galactose metabolism due to a deficiency of galactose-1-phosphate uridylyltransferase (classical galactosemia), UDPGal epimerase or galactokinase

Clinical Presentation - Since the institution of newborn screening in the United States beginning in the 1960s many states have developed a test for the detection of classical galactosemia (galactose-1-phosphate uridylyltransferase deficiency) resulting in fewer children with this disorder presenting with clinical symptoms. These children are typically diagnosed within the first week of life by any number of screening tests that detect an elevation of blood galactose-1-phosphate. Undetected cases of classical galactosemia and UDPGal epimerase deficiency typically present within the first several weeks of life with vomiting, lethargy, liver dysfunction and cataracts. Sepsis can be seen in about 30% of untreated undetected cases. Those who survive their sepsis or continue to go undiagnosed will develop mental retardation and persistent cataracts and "hepatitis" features. Females, even if treated, develop ovarian failure. Patients with undiagnosed galactokinase deficiency typically present with cataracts and pseudotumor cerebri.

Definitive Laboratory Testing - Galactose-1-phosphate level, RBC galactose-1-phosphate uridylyltransferase activity (or enzymatic analysis of UDPGal epimerase or galactokinase); DNA mutational analysis

Inheritance - Autosomal recessive
Prenatal Diagnosis - Available



GAUCHER DISEASE

- Pathophysiology - Disorder in the lysosomal degradation of the glycolipid glucocerebroside to ceramide and glucose due to a deficiency of glucocerebrosidase
- Clinical Presentation - Three types of Gaucher disease has been delineated. Type I is by far the most common and is distinguished from the other types by it's lack of central nervous system dysfunction. The clinical symptoms in type I include hepatosplenomegaly, bone infarctions and fractures, and bleeding due to thrombocytopenia. Anemia is usually present but typically mild although it has been known to be severe with hemoglobin levels as low as 5 mg/dl. Although patients can present at any age and have been known to be diagnosed in the eighth and ninth decade of life the median age at onset is 33 years. Some rare complications associated with type I include pulmonary failure due to lung infiltration of Gaucher cells, diffuse brown or yellow-brown skin pigmentation and increased risk for lymphoproliferative diseases. Type II Gaucher disease typically presents in infancy with oculomotor abnormalities such as bilateral fixed strabismus or oculomotor apraxia. Hepatosplenomegaly are also found. As the disease progresses the children develop spasticity, skill regression, and seizures. Death typically occurs by age 2 years. Type III is an intermediate form with onset of massive hepatosplenomegaly around 1 year of life. Neurological findings develop in about one half of the children during their first decade of life and are usually disorders of eye movement.
- Definitive Laboratory Testing - Leukocyte glucocerebrosidase enzyme activity; DNA mutational analysis in some cases.
- Inheritance - Autosomal recessive, type I prevalent in Ashkenazi Jews, type III prevalent in Northern Swedes.
- Prenatal Diagnosis - Available

GLUTARIC ACIDEMIA TYPE I

- Pathophysiology - A disorder in the metabolism of the amino acids tryptophan and lysine due to a deficiency of glutaryl CoA dehydrogenase
- Clinical Presentation - This disorder often presents with macrocephaly at birth. Typically the disorder then progresses after a period of normal development with the sudden onset of hypotonia, loss of head control, seizures, opisthotonos, and dystonia, with slow and incomplete recovery. Neurologic manifestations may then progress slowly, punctuated by episodes of ketosis, vomiting, hepatomegaly and encephalopathy brought on by stressors such as illness. Other cases may remain static taking on the form of extrapyramidal cerebral palsy. In some patients motor delay, hypotonia, dystonia, and dyskinesia develop gradually during the first few years of life. Ketoacidosis, hypoglycemia, hyperammonemia and mild parenchymal liver disease may develop during acute episodes. Precipitating factors for a crisis include catabolic stressors such as infections, surgery, neonatal stress and excessive protein intake.
- Definitive Laboratory Testing - Urine organic acids*; skin fibroblast glutaryl CoA dehydrogenase assay.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available
- Notes - * There are several case reports in which urine organic acids were normal.



GLUTARIC ACIDEMIA TYPE II (MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY)

- Pathophysiology - Disorder caused by a deficiency of the electron-accepting proteins electron transfer flavoprotein (ETF) and ETF-ubiquinone oxidoreductase (ETF-QO)
- Clinical Presentation - Affected patients present with either neonatal-onset disease associated with congenital anomalies, neonatal disease without other anomalies and late-onset disease. The children with neonatal-onset disease with anomalies typically present with metabolic acidosis (partly due to elevated lactate), hypoglycemia, hyperammonemia, sweaty feet odor, hypotonia and hepatomegaly. They will often have dysmorphic facial features, genital anomalies, cystic kidneys and often die within the first week of life after lapsing into a coma. The others with neonatal-onset disease without anomalies typically have the same biochemical features and die within days of presentation. Late-onset glutaric aciduria type II is extremely variable and can present with episodic vomiting, acidosis, and hypoglycemia in infancy but has been reported to present in adulthood with similar biochemical findings as well as hepatomegaly and a proximal myopathy. Several other presentations have also been reported including progressive myopathy and a movement disorder. The development of stroke-like episodes has also been seen in some patients.
- Definitive Laboratory Testing - Urine organic acids and plasma and urine amino acid; skin fibroblast ETF/ETF-QO assays.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

GLYCOGEN STORAGE DISEASE (GSD)

- Pathophysiology - Group of disorders caused by deficient activity in one of many proteins involved in the synthesis or degradation of glycogen and its regulation
- Clinical Presentation - The various glycogen storage diseases typically affect liver and/or muscle, the two tissues with the most abundant glycogen stores, and present with symptoms accordingly. Those disorders affecting liver glucose homeostasis typically present with hepatomegaly and hypoglycemia. Those patients with disorders affecting muscle generally demonstrate muscle cramps, exercise intolerance, fatigue and progressive weakness. Following are several of the more common disorders:

GSD TYPE I (VON GIERKE DISEASE)-

Due to a deficiency in glucose 6-phosphatase activity in liver, kidney and intestinal mucosa, patients typically present between 3-4 months of age with hepatomegaly and/or hypoglycemic seizures. These children often also have doll-like faces with excess adipose tissue in their cheeks, protuberant abdomens, relatively thin extremities and short stature. Their kidneys are also enlarged. Biochemically they are found to have hypoglycemia, metabolic acidosis, elevated lactate, hyperuricemia, and hyperlipidemia. Liver transaminases are usually normal or only slightly elevated.

GSD TYPE II (POMPLE DISEASE) –

A deficiency of acid maltase results in two major presentations. The most



severe is the classic infantile-onset disease that results in cardiomyopathy, hypotonia and death by 1 year of age. The second presentation is a more slowly progressive muscular disorder essentially limited to skeletal muscle, with onset of symptoms between childhood and adult life. Enzyme replacement therapy is now available and may impact long term outcome for affected patients.

GSD TYPE V (MCARDLE DISEASE) –

Due to a deficiency of muscle phosphorylase, affected patients classically present in adulthood with exercise intolerance and muscle cramps. About one half of the patients develop rhabdomyolysis and myoglobinuria with burgundy colored urine following exercise. There are several reports of acute renal failure secondary to significant myoglobinuria, usually following intense exercise. Brief, intense episodes of exercise and sustained activity tend to promote episodes. Patients are found to have elevated CPK levels even at rest and during exercise blood ammonia and uric acid also increase.

- Definitive Laboratory Testing - Depending on the disorder enzyme assay in muscle, liver, leukocytes and erythrocytes, and cultured fibroblasts; some disorders with direct DNA mutational analysis.
- Inheritance - Most autosomal recessive
- Prenatal Diagnosis - Available in some cases

HEMOCHROMATOSIS

- Pathophysiology - Excessive absorption of iron due to a defect in the HLA-linked iron-loading gene located on chromosome 6
- Clinical Presentation - The development of clinical symptoms depends on the severity of the metabolic defect and on the presence of sufficient amounts of iron in the diet. The typical American diet often results in disease expression in affected males by the 5th decade. Because of menstruation and decreased iron intake, full disease expression occurs about 10 times less frequently in affected women. The liver, heart, pancreas, endocrine organs, skin and joints are primarily affected. The most common clinical problems that develop are cirrhosis, cardiomyopathy, diabetes mellitus, hypogonadism, skin pigmentation, and arthritis. Plasma iron, transferrin saturation, and plasma ferritin are all elevated.
- Definitive Laboratory Testing - DNA mutational analysis
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

HOMOCYSTINURIA

- Pathophysiology - Impaired metabolism of homocysteine secondary to either a deficiency of cystathionine B synthase (classical homocystinuria) or methylenetetrahydrofolate reductase, defects in B12 metabolism (cobalamin and transcobalamin II defects), or nutritional deficiencies of B12 and/or folic acid
- Clinical Presentation - Since the institution of newborn screening in the United States beginning in



the 1960s many states have developed a test for the detection of classical homocystinuria (cystathionine B synthase deficiency) resulting in fewer children with this disorder presenting with clinical symptoms. These children are diagnosed within the first week of life by any number of screening tests that detect an elevation of blood methionine. Subsequent amino acid analysis confirms an elevation of homocystine and methionine. However, undiagnosed cases typically go on to develop ectopia lentis, mental retardation, thromboembolic episodes and osteoporosis. The other enzymatic or nutritional disorders that can cause homocystinuria are not associated with elevated methionine and will not be detected by newborn screening. These disorders often present with a variety of symptoms including such difficulties as megaloblastic anemia (cobalamin defects) or mental retardation, microcephaly and seizures in methylenetetrahydrofolate reductase deficiency.

- Definitive Laboratory Testing - Plasma and urine amino acids including total homocysteine; B12 and folate levels; urine organic acids; measurement of cystathionine B synthase activity (in skin fibroblasts, liver or photohemagglutinin-stimulated lymphocytes), cobalamin pathways (skin fibroblasts); DNA sequencing in some cases
- Inheritance - Autosomal recessive for genetic causes
- Prenatal Diagnosis - Available

ISOVALERIC ACIDEMIA

- Pathophysiology - Disorder is the metabolism of the amino acid leucine due to a deficiency in isovaleryl CoA dehydrogenase.
- Clinical Presentation - There are two clinical phenotypes for this disorder. The severe, neonatal form typically presents during the first two weeks of life with poor feeding, vomiting, lethargy, hypothermia and often seizures. There is an associated "sweaty feet" odor, metabolic acidosis, ketonuria, lactic acidemia, hyperammonemia, transient bone marrow suppression and hypocalcemia. In the chronic intermittent form of this disorder patients typically develop an episode during the first year of life in association with an acute illness or increased protein ingestion. Clinical symptoms and findings include vomiting, lethargy that can progress to coma, acidosis with ketonuria, and the characteristic odor. Diarrhea, bone marrow suppression, alopecia, and hyperglycemia have also been reported. Patients who survive the acute presentation of the neonatal form usually follow a chronic intermittent course.
- Definitive Laboratory Testing - Urine organic acids; skin fibroblast isovaleryl CoA dehydrogenase assay.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

KRABBE DISEASE (GLOBOID-CELL LEUKODYSTROPHY)

- Pathophysiology - Disorder in the lysosomal degradation of galactocerebroside to ceramide and galactose due to a deficiency of galactocerebroside B-galactosidase
- Clinical Presentation - Although there are early and late onset forms of the disorder, patients classically presents between 3 to 6 months of life with nonspecific changes



such as irritability and hypersensitivity to various stimuli. Skill regression or delay may also be apparent at that time. Some children develop seizures and vomiting. This presentation is followed by rapid and severe regression with the development of marked hypertonicity and increased reflexes. In the final stages of the disorder the child is decerebrate, blind, and often deaf and is non-interactive. Cerebrospinal fluid protein is increased in the infantile and late infantile forms of the disorder. It may be normal in the other variants. Peripheral neuropathy is usually noted on EMG and nerve conduction studies and white matter disease is often seen on brain imaging.

- Definitive Laboratory Testing - Leukocyte and/or skin fibroblast assay of galactocerebroside B-galactosidase
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

MAPLE SYRUP URINE DISEASE

- Pathophysiology - A disorder in the metabolism of the amino acids valine, leucine, and isoleucine due to a deficiency in branched chain ketoacid dehydrogenase.
- Clinical Presentation - There are several clinical phenotypes for this disorder, seemingly dependent upon the severity of the molecular defect. The neonatal or classical phenotype, the most severe, is characterized by a marked metabolic ketoacidosis, lethargy and obtundation within the first few days of life. The intermediate form is often characterized by failure to thrive, neurological difficulties, and ketoacidosis. An intermittent form manifests as episodic ataxia and ketoacidosis, often associated with increased protein consumption or intercurrent illness. Finally, a "thiamin-responsive form" exists in which metabolic abnormalities are ameliorated with large doses of thiamin. An acute crisis in this disorder is associated with metabolic ketoacidosis, and, often, hypoglycemia and hyperammonemia. Symptoms during a metabolic crisis include anorexia, vomiting, lethargy, ataxia and seizures, sometimes progressing to coma. Precipitating factors for a crisis in the classical, intermediate and intermittent forms include catabolic stressors such as infections, surgery, neonatal stress and excessive protein intake.
- Definitive Laboratory Testing - Urine organic acids; plasma amino acids; skin fibroblast and/or lymphocyte assays of branched chain ketoacid dehydrogenase activity; blood DNA mutational analysis in some cases.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

MEDIUM CHAIN ACYL COA DEHYDROGENASE (MCAD) DEFICIENCY

- Pathophysiology - A disorder in the metabolism of fatty acids due to a deficiency of medium chain acyl CoA dehydrogenase.
- Clinical Presentation - One of the most common inborn errors of metabolism, MCAD deficiency typically presents between 7 months and 3 years of age with recurrent Reye-like episodes characterized by hypoketotic hypoglycemia and metabolic acidosis following a period of fasting. There may have been a prior viral infection associated with decreased oral intake. Along with the hypoglycemia and metabolic acidosis, blood ammonia levels, uric acid, and liver function



tests may be abnormally high. On presentation, the child is often comatose. However, between episodes affected individuals are asymptomatic. Unfortunately, this disorder has a relatively high incidence of sudden and unexpected death. Although unusual, both neonatal onset and life-long symptom free periods have been described.

- Definitive Laboratory Testing - Urine organic acids; blood acylcarnitines; skin fibroblast fatty acid oxidation assay; blood DNA mutational analysis for common mutation.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

MENKES (STEELY HAIR) DISEASE

- Pathophysiology - Disorder resulting from excessive accumulation of copper accompanied by deficient activity of copper enzymes.
- Clinical Presentation - Affected infants are often premature and develop neonatal hypothermia and hyperbilirubinemia. Many of these infants appear otherwise normal but others show dysmorphic faces (sagging jowls, pudgy cheeks, abnormal eyebrows) and the classic tangled, lusterless, broken hair (pili torti microscopically). Some infants may demonstrate a resolution of neonatal onset problems while for others the difficulties persist. However, by 3 months of age developmental delay, skill regression and seizures appear. Cerebral deterioration and vascular complications, in particular subdural hematomas, develop as the disease progresses with death typically occurring by 12 months of age. Other complications include diverticulae of the bladder or ureters and rib fractures. Skeletal x-rays typically show osteoporosis and widening of the flared metaphyses with spiky protrusions at the edges and wormian bones are usually seen in the skull.
- Definitive Laboratory Testing - Serum copper and ceruloplasmin; liver copper content; duodenal copper content; copper handling in skin fibroblasts; direct DNA mutational analysis
- Inheritance - X-linked recessive
- Prenatal Diagnosis - Available

METACHROMATIC LEUKODYSTROPHY (MLD)

- Pathophysiology - Disorder resulting from the accumulation of sulfatides in the white matter of the central nervous system and in the peripheral nerves due to a deficiency of the lysosomal enzyme arylsulfatase A.
- Clinical Presentation - MLD includes a number of variant forms, primarily distinguishable by age of onset. The most common forms are the late infantile, early and late juvenile, and adult types. The late infantile patients typically present between 15 months and 2 years of age with death occurring 1 to 7 years later. They usually present with developmental delay, ataxia, weakness, loss of speech (skill regression), optic atrophy and progressive spastic quadriplegia. Most cases of juvenile MLD present by 5 years of age with mental confusion and/or cognitive difficulties. This progresses to slurred speech, gait disturbances, increased tone and tremor and ultimately to spastic quadriparesis and often seizures. However, the early onset juvenile form often presents first with gait disturbances followed by the intellectual deterioration. The majority of



patients die during their teenage years.

Definitive Laboratory Testing - Urine sulfatides; assay of arylsulfatase A in skin fibroblasts and/or leukocytes; DNA mutational analysis

Inheritance - Autosomal recessive

Prenatal Diagnosis - Available

METHYLMALONIC ACIDEMIA

Pathophysiology - A disorder in the metabolism of the amino acids methionine, threonine, valine and isoleucine due to a deficiency of methylmalonyl CoA mutase or cobalamin (vitamin B12) defect.

Clinical Presentation - There are several clinical phenotypes for this disorder, seemingly dependent upon the severity of the molecular defect. The neonatal phenotype, the most severe, is characterized by a marked metabolic acidosis, lethargy and obtundation within the first few days of life. The infantile, late-onset phenotype is often characterized by failure to thrive, developmental delay, and/or neurological difficulties including seizures. These children may decompensate acutely during a stressor such as illness and present for the first time at several months or even years of age. An acute crisis in this disorder is associated with metabolic acidosis ketosis, often hypoglycemia, hyperammonemia, bone marrow suppression, and in some cases (those caused by a cobalamin defect) increased homocysteine levels. Hyperammonemia is probably related to a secondary inhibition of the urea cycle, the pathway that processes waste nitrogen. An elevated blood glycine (amino acid) is also observed at these times and is likely related to inhibition of the glycine cleavage enzyme. Symptoms during a metabolic crisis include anorexia, vomiting, lethargy, ataxia and seizures, sometimes progressing to coma. Precipitating factors for a crisis include catabolic stressors such as infections, surgery, neonatal stress and excessive protein intake.

Definitive Laboratory Testing - Urine organic acids; total homocysteine; skin fibroblast methylmalonyl CoA mutase activity and cobalamin synthesis pathways.

Inheritance - Autosomal recessive

Prenatal Diagnosis - Available

MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION DISORDERS (MELAS, MERRF, NARP)

Pathophysiology - Group of disorders affecting both nuclear and mitochondrial DNA genes and any number of the five complexes of the oxidative phosphorylation system that results in decreased ATP production.

Clinical Presentation - There is a vast array of clinical phenotypes for disorders affecting mitochondrial energy production. Affected individuals can present at any age, including the neonatal onset congenital lactic acidosis phenotype. In general, a patient can present with any combination of developmental delays, seizures, vision and hearing problems, autonomic nervous system dysfunction (breathing problems, temperature instability), liver and kidney disease, muscle weakness, failure to thrive, and endocrine disorders such as diabetes. However, certain mutations (for example, the mitochondrial DNA mutation causing MELAS) have a propensity to present with a specific array of



difficulties. Typically, symptoms of these disorders are aggravated by stressors such as illness or surgery. In general, these disorders are progressive and worsen over time.

- Definitive Laboratory Testing - Mitochondrial DNA testing; gene sequencing; oxidative phosphorylation enzymatic testing.
- Inheritance - Autosomal recessive, autosomal dominant, maternal, and X-linked.
- Prenatal Diagnosis - Not readily OR reliably available

MOLYBDENUM COFACTOR DEFICIENCY

- Pathophysiology - Deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase caused by a defect in one of the steps in the synthesis of the active molybdenum cofactor
- Clinical Presentation - Affected patients typically present with neonatal onset of seizures, microcephaly, and severe mental retardation. The onset of symptoms occurs usually after the 1st or 2nd week of life and includes refractory tonic-clonic seizures, axial hypotonia and peripheral hypertonicity. Lens dislocation occurs in patients who survive the neonatal period. Other findings include brain atrophy, dilated ventricles and hydrocephalus and enophthalmos and nystagmus. Routine chemistries typically note a decreased serum uric acid and blood amino acids often show low cystine values.
- Definitive Laboratory Testing - Urine S-sulfocystine
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

MUCOPOLYSACCHARIDOSES (MPS)

- Pathophysiology - A group of lysosomal storage diseases caused by a deficiency of enzymes catalyzing the stepwise degradation of glycosaminoglycans (mucopolysaccharides).
- Clinical Presentation - The 15 types and subtypes of MPS caused by the variable deficiency of one of ten different enzymes share many features in common including a chronic and progressive course, multisystem involvement, hepatosplenomegaly, dysostosis multiplex, and dysmorphic (coarsened) facies. Hearing, vision, cardiovascular function, and joint mobility may be affected. Severe mental retardation is seen in MPS I (Hurler syndrome), many cases of MPS II (Hunter syndrome) and all cases of MPS III (Sanfilippo syndrome). Normal intellect can be seen in the other types.

MPS I (HURLER SYNDROME) –

Patients with the severe form of this disorder typically appear normal at birth but may have umbilical or inguinal hernias. However, between 6-24 months of age affected individuals present with hepatosplenomegaly, skeletal deformities and joint stiffness, and coarsened facial features. Developmental delay is typically apparent by 1 year of age. Hearing loss, cataracts, recurrent upper respiratory tract and ear infections are also seen. Distinct radiographic changes are seen on skeletal survey (dysostosis multiplex) and include a large, thickened calvarium with premature suture closure. Death typically ensues by 10 years of age. Bone marrow transplant has been used with variable success.



Enzyme Replacement Therapy (ERT) is available but also has limited efficacy. MPS I and its variants are due to a deficiency of alpha-L-iduronidase.

MPS II (HUNTER SYNDROME) –

The only X-linked MPS, MPS II is caused by a deficiency of iduronate sulfatase, and can be either severe or mild. The severe form of MPS II is similar to MPS I, except for lack of corneal clouding and slower progression of multisystem problems. The mild form of the disease is associated with minimal to no central nervous system dysfunction, slow somatic course, and prolonged lifespan (5th to 6th decade with oldest survivor age 87). Bone marrow transplant has been used with variable success. Enzyme Replacement Therapy (ERT) is available but also has limited efficacy.

- Definitive Laboratory Testing - Urine glycosaminoglycans (mucopolysaccharides); skin fibroblast, leukocytes or serum enzymatic assays
- Inheritance - Autosomal recessive, except for MPS II, Hunter syndrome, which is X-linked
- Prenatal Diagnosis - Available

MYOTONIC DYSTROPHY

- Pathophysiology - Disorder caused by a mutation in the myotonin kinase gene on chromosome 19
- Clinical Presentation - Affected individuals frequently exhibit progressive weakness, myotonia, cataracts, cardiac arrhythmias, cardiomyopathy and insulin resistance. Infants may have severe disease manifestations characterized by congenital onset of feeding difficulties, failure to thrive, weakness, hypotonia and mental retardation. However, there is significant phenotypic heterogeneity in this disorder making diagnosis in some families very difficult.
- Definitive Laboratory Testing - DNA analysis for the detection of CTG trinucleotide repeat expansion in the myotonin kinase gene on chromosome 19
- Inheritance - Autosomal dominant
- Prenatal Diagnosis - Available

NEONATAL ADRENOLEUKODYSTROPHY (NALD)

- Pathophysiology - Disorder caused by the defective synthesis of peroxisomes, resulting in a deficiency of multiple enzymes involved in 1) the oxidation of very long chain fatty acids, polyunsaturated fatty acids, dicarboxylic fatty acids, prostaglandins, and the side chain of cholesterol; 2) the biosynthesis of plasmalogens and bile acids; and 3) hydrogen peroxide metabolism.
- Clinical Presentation - The clinical course of NALD varies from onset of symptoms shortly after birth with death during infancy to relatively stable patients with significant retardation in their teens. Typical symptoms include severe hypotonia and weakness, development delay, seizures, deafness, cataracts and glaucoma and blindness, and, often, dysmorphic features including high forehead, large fontanelle and wide sutures, and flattened nasal bridge. The dysmorphic features often resemble those seen in Down syndrome. Overall, they present with a less severe phenotype than Zellweger syndrome and live longer with most dying during the first several years of life. In contrast, most patients with



Zellweger syndrome die in infancy. NALD patients often demonstrate more significant leukodystrophy because they live longer. Most demonstrate impaired cortisol response to ACTH but rarely do they develop overt adrenal insufficiency.

Definitive Laboratory Testing - Plasma or serum very long chain fatty acids, pipercolic acid (in children over 1 month), phytanic acid (in children older than 10 months), red blood cell plasmalogens (in children under 5 months); skin fibroblast peroxisomal enzyme activity.

Inheritance - Autosomal recessive

Prenatal Diagnosis - Available

NIEMANN-PICK DISEASE (NPD) TYPES A AND B

Pathophysiology - Lysosomal storage disorders due to a deficiency of acid sphingomyelinase

Clinical Presentation - NPD type A typically presents with hepatosplenomegaly and a protuberant abdomen between 4-6 months of age. Hypotonia and weakness and associated feeding difficulties may also be seen. By 6 months of age developmental delay is apparent and skill regression ensues. Other difficulties include recurrent bronchitis and pneumonia and the skin may develop a brownish-yellow hue. Eye examination will reveal cherry-red spots between 1-2 years of age in 50% of patients. Neurological deterioration continues with spasticity and rigidity developing and death by 2-3 years. NPD type B is more variable in presentation and often presents with asymptomatic hepatosplenomegaly during infancy or childhood. Pulmonary involvement is more prominent in NPD type B and most patients have evidence of mild pulmonary involvement at the time of diagnosis with the development of significant pulmonary compromise by 15-20 years of age. Neurologically, these patients are usually intact with a normal intellect and only 10% demonstrating the cherry red spots seen in NPD type A. Death usually occurs for patients with NPD type B during childhood or adulthood.

Definitive Laboratory Testing - Bone marrow biopsy with presence of characteristic NPD foam cells; enzyme assay in leukocytes, lymphoblasts, skin fibroblasts; DNA mutational analysis in some cases

Inheritance - Autosomal recessive, higher incidence in Ashkenazic Jews

Prenatal Diagnosis - Available

NIEMANN-PICK DISEASE (NPD) TYPE C

Pathophysiology - Disorder caused by error in cellular trafficking of exogenous cholesterol that is associated with the lysosomal accumulation of cholesterol

Clinical Presentation - The clinical presentation on NPC is heterogeneous and patients are known to develop symptoms from infancy through adulthood. Classic NPC presents with transient neonatal jaundice followed by an asymptomatic period. Patients then develop variable hepatosplenomegaly, vertical supranuclear ophthalmoplegia, progressive ataxia, dystonia and dementia (neurodegeneration) with death usually occurring during the teenage years. Other presentations include fatal neonatal liver disease. The later onset forms typically present with progressive neurological deterioration.



- Definitive Laboratory Testing - Demonstration of both impaired cholesterol esterification and intralysosomal accumulation of unesterified cholesterol, as demonstrated by intense perinuclear fluorescence in filipin-stained fibroblasts.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available in some cases

NONKETOTIC HYPERGLYCINEMIA (NKH)

- Pathophysiology - Disorder in glycine degradation due to a defect in the glycine cleavage system
- Clinical Presentation - There are two presentations, the more common neonatal and late-onset forms of the disease. In the neonatal presentation, patients develop rapidly progressive neurological difficulties including seizures, hypotonia, apnea, lethargy and coma. Most patients die within several weeks. Survivors have severe developmental delays. Late-onset patients are normal in the neonatal period but thereafter develop variable neurological problems.
- Definitive Laboratory Testing - Absolute CSF glycine value on CSF amino acid analysis and plasma to CSF glycine ratio; enzymatic analysis of glycine cleavage system in liver and lymphoblasts; mutational analysis in some cases
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available but some false negative CVS results reported

ORNITHINE TRANSCARBAMYLASE DEFICIENCY (OTC)

- Pathophysiology - Disorder in waste ammonium nitrogen metabolism due to a deficiency of ornithine transcarbamylase, an enzyme in the urea cycle.
- Clinical Presentation - The clinical manifestations may appear in the neonatal period or anytime thereafter with varying degrees of severity. Because OTC deficiency is X-linked, the neonatal onset cases are almost always confined to males and typically present with vomiting, increasing lethargy, hypothermia and hyperventilation sometime between 24 and 72 hours of life. If undiagnosed, the infant quickly progresses to coma and requires mechanical ventilation. Death will usually ensue if the child remains undiagnosed. Routine chemistries typically reveal only low serum urea nitrogen, sometimes as low as 1 mg/dl. Plasma ammonium is markedly elevated, often 10-30 times normal. The finding of an elevated ammonium will direct diagnostic efforts toward an inborn error of metabolism and blood amino acids typically show an elevation of glutamine and absence of citrulline while urine organic acids will show orotic acid. In the late onset group, symptoms present from the first year of life to adulthood. In infants, symptoms may develop following a transition from either breast milk or a low-protein formula to cow's milk. In older children and adults episodes may be precipitated by the ingestion of high protein foods. Infections as well as the use of oral steroids may also trigger episodes of decompensation. Such episodes are usually marked by vomiting, lethargy, other neurological signs such as irritability, agitation, ataxia and, at times, apnea and seizures, and the same biochemical abnormalities seen with neonatal onset cases.
- Definitive Laboratory Testing - Plasma and urine amino acids; urine organic acid analysis for orotic acid; DNA testing in some cases; liver tissue OTC enzyme activity



Inheritance - X-linked
Prenatal Diagnosis - Available

PHENYLKETONURIA (PKU)

- Pathophysiology - Disorder in the metabolism of the amino acid phenylalanine to tyrosine due to a deficiency of phenylalanine hydroxylase
- Clinical Presentation - Since the institution of mandatory newborn screening for PKU in the United States beginning in the 1960s few children with this disorder present with clinical symptoms. Most children are diagnosed within the first week of life by any number of screening tests that detect an elevation of blood phenylalanine. Subsequent amino acid analysis confirms an elevation of phenylalanine and a decrease in tyrosine. DHPR and Urine pterin studies are normal ruling out a rare cofactor defect. Depending on the phenylalanine level, an affected individual will generally fall into one of three categories: classical PKU; atypical PKU or mild hyperphenylalaninemia. There are also rare transient forms of the disorder. Although long-term outcome is typically excellent, lifelong compliance with treatment is essential for this prognosis. New treatment using the phenylalanine hydroxylase cofactor, sapropterin dihydrochloride, has resulted in increased protein tolerance for some patients with PKU. The rare, undetected case of PKU is likely to present with severe mental retardation, microcephaly, lighter pigmentation than family members, unusual body and urine odor and, in some cases rash and eczema.
- Definitive Laboratory Testing - Blood amino acids; DHPR and urine pterin studies; DNA gene analysis
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

PRADER-WILLI SYNDROME

- Pathophysiology - Disorder caused by a deletion of the paternal chromosome 15q11-q13 or the presence of two copies of the maternal chromosome 15 (uniparental disomy)
- Clinical Presentation - Affected individuals typically present with profound hypotonia at birth and secondary marked feeding difficulties and failure to thrive that often result in supplemental nasogastric or gastric tube feeds. Despite these early feeding and growth issues, there is an onset of obesity between 6 months and 6 years of age. Although delayed motor development with walking after about 2 years of age is also related to the significant early-onset hypotonia, long-term development varies from mild (63%) to severe (6%) mental retardation. Additional features include dysmorphic facies characterized by high forehead, small almond-shaped eyes, triangular-shaped mouth, fair hair and blue eyes, small hands and feet noticeable first in mid-childhood, growth difficulties beginning in adolescence, diabetes, seizures and obstructive apnea.
- Definitive Laboratory Testing - Chromosome 15 analysis for detection of a deletion or presence of two chromosome 15 copies from the same parent*
- Inheritance - Typically sporadic
- Prenatal Diagnosis - Available



PROPIONIC ACIDEMIA

- Pathophysiology - A disorder in the metabolism of the amino acids methionine, threonine, valine, and isoleucine due to a deficiency of propionyl CoA carboxylase.
- Clinical Presentation - There are several clinical phenotypes for this disorder, seemingly dependent upon the severity of the molecular defect. The neonatal phenotype, the most severe, is characterized by a marked metabolic acidosis, lethargy and obtundation within the first few days of life. The infantile, late-onset phenotype is often characterized by failure to thrive, developmental delay, and/or neurological difficulties including seizures. These children may decompensate acutely during a stressor such as illness and present for the first time at several months or even years of age. An acute crisis in this disorder is associated with metabolic acidosis, ketosis, often hypoglycemia, hyperammonemia and bone marrow suppression. Hyperammonemia is probably related to a secondary inhibition of the urea cycle, the pathway that processes waste nitrogen. An elevated blood glycine (amino acid) is also observed at these times and is likely related to inhibition of the glycine cleavage enzyme. Symptoms during a metabolic crisis include anorexia, vomiting, lethargy, ataxia and seizures, sometimes progressing to coma. Precipitating factors for a crisis include catabolic stressors such as infections, surgery, neonatal stress and excessive protein intake.
- Definitive Laboratory Testing - Urine organic acids; skin fibroblast propionyl CoA carboxylase activity
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

REFSUM DISEASE

- Pathophysiology - Disorder in the degradation of phytanic acid caused by a deficiency of the peroxisomal enzyme phytanoyl CoA hydroxylase
- Clinical Presentation - Affected individuals typically demonstrate normal growth and development during infancy with the onset of symptoms occurring from early childhood through the 5th decade. However, most patients develop problems before age 20. The earliest symptom is almost always night blindness (due to retinitis pigmentosa) with other presenting problems including extremity weakness (due to peripheral polyneuropathy) and unsteady gait. Other clinical features of the disorder include high cerebrospinal fluid protein, nerve deafness, and ichthyosislike skin changes. The disease course is progressive deterioration often interrupted by periods of remission. Exacerbations can occur with stressors including illness, surgery and pregnancy. The clinical course has been reported to be altered by therapy.
- Definitive Laboratory Testing - Serum or plasma phytanic acid; skin fibroblast assay of phytanic acid oxidation
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

SHORT CHAIN ACYL COA DEHYDROGENASE (SCAD) DEFICIENCY

- Pathophysiology - Disorder in fatty acid oxidation due to a deficiency of short chain acyl CoA



- dehydrogenase.
- Clinical Presentation - Clinical onset and presenting symptoms are variable. Muscle weakness, lethargy, failure to thrive, developmental delay, ketosis, and acidosis are variable features. Of note, many patients picked up on expanded newborn screening remain clinically stable over a number of years indicating that the clinical significance of this disorder remains unknown. Organic acid profiles can be normal but can show the presence of the short chain organic acids ethylmalonic acid, methylsuccinic acid and butyrylglycine.
- Definitive Laboratory Testing - Urine organic acids; skin fibroblast or muscle SCAD activity; DNA testing in few cases
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Not readily available

SHORT CHAIN 3-HYDROXYACYL COA DEHYDROGENASE (SCHAD) DEFICIENCY

- Pathophysiology - Disorder in fatty acid oxidation due to a deficiency of short chain 3-hydroxy acyl CoA dehydrogenase.
- Clinical Presentation - Limited information available. Known cases present in adolescence with cardiomyopathy, muscle weakness, lethargy and vomiting. Patients have myoglobinuria, elevated CPK values, hypoglycemia, ketosis, and elevated AST/ALT. Urine organic acids can demonstrate dicarboxylic aciduria but can be normal.
- Definitive Laboratory Testing - Enzymatic assay of SCHAD in muscle tissue.
- Inheritance - Likely autosomal recessive
- Prenatal Diagnosis - Availability unknown

SPINAL MUSCULAR ATROPHY (SMA)

- Pathophysiology - Disorder characterized by anterior horn cell degeneration due to a mutation in the survival motor neuron gene on chromosome 5
- Clinical Presentation - Degeneration of anterior horn cells results in the development of symmetrical muscle weakness and muscle wasting in affected individuals. There are three forms of SMA described as follows:
- TYPE I (WERDNIG-HOFFMAN DISEASE)**
- the most severe form of the disorder with onset of symptoms by 6 months and death by 2 years of age. The children are typically described as alert and bright-eyed.
- TYPE II (INTERMEDIATE FORM)**
- intermediate in severity between types I and III with onset of symptoms between 6-18 months and death after 2 years.
- TYPE III (WOHLFART-KUGELBERG-WELANDER DISEASE)**
- mildest form of the disorder and presents between 18 months and 17 years of age. Survival into adulthood is typical.
- Definitive Laboratory Testing - DNA mutational analysis of the survival motor neuron gene on chromosome 5



Inheritance - Autosomal recessive
Prenatal Diagnosis - Available

SULFITE OXIDASE DEFICIENCY

- Pathophysiology - Disorder in the degradation of sulfur amino acids due to a deficiency of the terminal pathway enzyme sulfite oxidase
- Clinical Presentation - Although few cases of isolated sulfite oxidase deficiency have been reported, the clinical presentation appears to be almost indistinguishable from that of molybdenum cofactor deficiency. There is typically a neonatal onset of seizures, microcephaly, and severe mental retardation. The onset of symptoms occurs usually after the 1st or 2nd week of life and includes refractory tonic-clonic seizures, axial hypotonia and peripheral hypertonicity. Lens dislocation occurs in patients who survive the neonatal period. Other findings include brain atrophy, dilated ventricles and hydrocephalus and enophthalmos and nystagmus. Unlike molybdenum cofactor deficiency, uric acid is normal. However, blood amino acids also often show low cystine values.
- Definitive Laboratory Testing - Urine S-sulfocystine
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

TYROSINEMIA TYPE I (HEPATORENAL TYROSINEMIA)

- Pathophysiology - Disorder in tyrosine metabolism secondary to a deficiency of fumarylacetoacetate hydrolase (FAH).
- Clinical Presentation - Although clinically heterogeneous, most patients present with either the acute or chronic form of the disorder. The acute form typically presents in the first few months of life with severe liver and kidney disease. Failure to thrive, vomiting, jaundice, hypoglycemia, ascites and bleeding abnormalities are often presenting symptoms. Many children develop sepsis and vitamin D resistant rickets, the later due to impaired renal tubular function. The chronic form of the disorder usually presents somewhere between 1 year of life and early childhood and is characterized by hepatomegaly, bruising and failure to thrive due to the associated renal tubular dysfunction. Both forms can be complicated by neurological crises resembling acute intermittent porphyria. Unless treated, ultimately by a liver transplantation, death ensues usually from liver failure or hepatocellular carcinoma. Blood amino acid profiles in these patients typically demonstrated elevated tyrosine and methionine values. Alpha-fetoprotein values are usually markedly elevated. Although several cases have been reported with normal values, urine organic acids demonstrate the presence of the pathognomonic succinylacetone.
- Definitive Laboratory Testing - Blood amino acids; urine amino acids; urine organic acids for succinylacetone; FAH assay in leukocytes, erythrocytes and skin fibroblasts; DNA mutational analysis in some cases.
- Inheritance - Autosomal recessive with high incidence in French-Canadian and Norwegian populations.



Prenatal Diagnosis - Available

TYROSINEMIA TYPE II (OCULOCUTANEOUS TYROSINEMIA)

- Pathophysiology - Disorder in tyrosine metabolism due to a deficiency in the enzyme tyrosine aminotransferase (TAT)
- Clinical Presentation - Although there is marked variability in age of symptom onset ranging from birth to the fourth decade of life, most affected individuals present in the first year of life with corneal lesions and secondary lacrimation, photophobia, redness and pain. Skin disease usually presents after 1 year of age and includes painful, nonpruritic hyperkeratotic plaques on the soles and palms. About half of the patients have mental retardation. Blood amino acid profiles note elevated tyrosine and usually normal phenylalanine. Renal and liver function tests are normal. Urine organic acids show 4-hydroxyphenyllactate, 4-hydroxyphenylpyruvate, and 4-hydroxyphenylacetic acid.
- Definitive Laboratory Testing - Plasma and urine amino acids; urine organic acids; TAT enzyme assay in liver (not usually indicated)
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Availability unknown

TYROSINEMIA TYPE III (4-HYDROXYPHENYLPYRUVATE DIOXYGENASE DEF'Y)

- Pathophysiology - Disorder in tyrosine metabolism due to a deficiency of liver 4-hydroxyphenylpyruvate dioxygenase.
- Clinical Presentation - Only a few patients have been documented to have this disorder. Episodes of ataxia have been reported in one patient and severe epilepsy and cerebral atrophy seen in another. Blood amino acids note elevated tyrosine and urine organic acids show 4-hydroxyphenyllactate, 4-hydroxyphenylpyruvate, and 4-hydroxyphenylacetic acid.
- Definitive Laboratory Testing - Plasma and urine amino acids; urine organic acids; enzyme activity in liver tissue.
- Inheritance - Likely autosomal recessive
- Prenatal Diagnosis - Availability unknown

WILSON DISEASE

- Pathophysiology - Disorder due to a defect in the Wilson protein gene on chromosome 13 resulting in an interruption of the transport of copper into the secretory pathway interfering with holoceruloplasmin synthesis and biliary copper excretion.
- Clinical Presentation - Most patients present with either liver disease or neurological symptoms sometime in mid to late childhood but as late as 60 years of age. Females are more likely to present with liver disease whereas males often first develop neurological problems. Liver involvement can include jaundice and vomiting but can present with asymptomatic hepatomegaly. Neurological changes include dysarthria, loss of coordination of voluntary movements, onset of involuntary movements and posture and tone abnormalities. Other problems



include acute hemolytic crisis, joint symptoms, cardiomyopathy, renal stone and renal tubular acidosis and pancreatic disease. Copper deposition in the cornea produces the characteristic yellow-brown Kayser-Fleischer rings. Untreated, this disorder will be progressive.

- Definitive Laboratory Testing - Serum copper and ceruloplasmin levels; urine copper (24 hour collection); copper content in liver biopsy; ceruloplasmin copper isotope incorporation study; direct DNA analysis in some patients
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

ZELLWEGER SYNDROME

- Pathophysiology - Disorder caused by the defective synthesis of peroxisomes, resulting in a deficiency of multiple enzymes involved in 1) the oxidation of very long chain fatty acids, polyunsaturated fatty acids, dicarboxylic fatty acids, prostaglandins, and the side chain of cholesterol; 2) the biosynthesis of plasmalogens and bile acids; and 3) hydrogen peroxide metabolism.
- Clinical Presentation - Zellweger syndrome is the most severe of the disorders of peroxisomal biogenesis with findings apparent at birth and death within the first year of life. Typical symptoms include severe hypotonia and weakness, severe retardation, seizures, deafness, cataracts and glaucoma as well as blindness, and characteristic dysmorphic features including high forehead, large fontanelle and wide sutures, flattened nasal bridge, epicanthal folds and micrognathia. The dysmorphic features often resemble those seen in Down syndrome. Other features include hepatomegaly, renal cysts and impaired adrenocortical function. Brain imaging notes neuronal migrational abnormalities as well as white matter disease.
- Definitive Laboratory Testing - Plasma or serum very long chain fatty acids, pipecolic acid (in children over 1 month), phytanic acid (in children older than 10 months), red blood cell plasmalogens (in children under 5 months); skin fibroblast peroxisomal enzyme activity.
- Inheritance - Autosomal recessive
- Prenatal Diagnosis - Available

The information contained here is not meant to be comprehensive and definitive in all circumstances but merely to offer guidelines and assistance to physicians and health care providers in their evaluation of and approach to patients with possible genetic and metabolic disorders. Further assistance should be sought by contacting a qualified genetic metabolic specialist.

The majority of this information was obtained from The Metabolic and Molecular Bases of Inherited Disease. 7th ed. New York:McGraw-Hill. Editors: Scriver CR, Beaudet AL, Sly WS, Valley D.