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The Organic Acidemias: An Overview

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Summary

Disease characteristics. The term "organic acidemia" or "organic aciduria" (OA) applies to a group of disorders characterized by the excretion of non-amino organic acids in urine. Most organic acidemias result from dysfunction of a specific step in amino acid catabolism, usually the result of deficient enzyme activity. The majority of the classic organic acid disorders are caused by abnormal amino acid catabolism of branched-chain amino acids or lysine. They include maple syrup urine disease (MSUD), propionic acidemia, methylmalonic acidemia (MMA), methylmalonic aciduria and homocystinuria, isovaleric acidemia, biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency, ketothiolase deficiency, and glutaricacidemia type I (GA I). A neonate affected with an OA is usually well at birth and for the first few days of life. The usual clinical presentation is that of toxic encephalopathy and includes vomiting, poor feeding, neurologic symptoms such as seizures and abnormal tone, and lethargy progressing to coma. Outcome is enhanced by diagnosis in the first ten days of life. In the older child or adolescent, variant forms of the OAs can present as loss of intellectual function, ataxia or other focal neurologic signs, Reye syndrome, recurrent keto-acidosis, or psychiatric symptoms. A variety of MRI abnormalities have been described in the OAs, including distinctive basal ganglia lesions in GA I, white matter changes in MSUD, and abnormalities of the globus pallidus in methylmalonic acidemia.

Diagnosis/testing. Clinical laboratory findings that should suggest an organic acidemia include acidosis, ketosis, hyperammonemia, abnormal liver function tests, hypoglycemia, and neutropenia. Propionic acidemia may present with isolated hyperammonemia early in its course. First-line diagnosis in the organic acidemias is urine organic acid analysis using gas chromatography with mass spectrometry (GC/MS), utilizing a capillary column. The organic acids found in the urine provide a high degree of suspicion for the specific pathway involved. The urinary organic acid profile is nearly always abnormal in the face of acute illness with decompensation; however, in some disorders the diagnostic analytes may be present only in small or barely detectable amounts when the affected individual is not acutely ill. Depending on the specific disorder, plasma amino acid analysis can also be helpful. Plasma amino acid analysis requires a quantitative method such as column chromatography, high-performance liquid chromatography (HPLC), or GC/MS. Once the detection of specific analytes narrows the diagnostic possibilities, the activity of the deficient enzyme is measured in lymphocytes or cultured fibroblasts as a confirmatory test. Molecular genetic testing is clinically available for detection of MSUD, proprionic acidemia, MMA, biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, isovaleric acidemia, and GA I.

Management. The aim of therapy in the organic acidemias is to restore biochemical and physiologic homeostasis. Neonates demand emergency diagnosis and treatment depending on

the specific biochemical lesion, the position of the metabolic block, and the effects of the toxic compounds. Treatment strategies include: 1) dietary restriction of the precursor amino acids; and 2) use of adjunctive compounds to a) dispose of toxic metabolites or b) increase activity of deficient enzymes. Adjunctive compounds to dispose of toxic metabolites include thiamine to treat thiamine-responsive MSUD and hydroxocobalamin and intermittent administration of non-absorbed antibiotics to reduce the production of propionate by gut bacteria in disorders of propionate metabolism. Frequent monitoring of growth, development, and biochemical parameters is essential. Decompensation caused by catabolic stress, such as vomiting, diarrhea, febrile illness, and decreased oral intake requires prompt and aggressive intervention; treatment strategies aim to eliminate toxic amino acid precursors by restriction of their intake and the use of adjunctive measures such as hemodialysis. During acute decompensation, critical care support is often required, acidosis may need to be corrected, and careful and frequent biochemical monitoring is crucial. Liver transplantation has been successful in a small number of affected individuals. Post partum monitoring of women with isovaleric acidemia, MSUD, propionic acidemia, methylmalonic acidemia, and mitochondrial β-ketothiolase deficiency is important as this is a time of particular metabolic stress.

Genetic counseling. The organic acidemias considered in this overview are inherited in an autosomal recessive manner. The parents are obligate heterozygotes and, therefore, carry a single copy of a disease-causing mutation. Heterozygotes are asymptomatic. At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. An unaffected sib of an affected individual has a 2/3 chance of being heterozygous. Three approaches to prenatal diagnosis are possible, depending on the disorder. These include measurement of analytes in amniotic fluid, measurement of enzyme activity in cells obtained by chorionic villus sampling or in cultured amniocytes, and molecular genetic testing of cells obtained by CVS or amniocentesis to identify the relevant mutations. Carrier testing using molecular genetic techniques is available for at-risk family members on a clinical basis once the mutations have been identified in the proband, with the exception of biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency.

Definition

The term "organic acidemia" or "organic aciduria" (OA) applies to a diverse group of disorders characterized by the excretion of non-amino organic acids in urine. The organic acidemias share many clinical similarities.

Most organic acidemias result from dysfunction of a specific step in amino acid catabolism, and are usually the result of deficient enzyme activity at that step. The pathophysiology results from accumulation of precursors and deficiency of products of the affected pathway. The accumulated precursors are themselves toxic or are metabolized to produce toxic compounds. The pathophysiology of these disorders is the result of toxicity of small molecules to brain, liver, kidney, pancreas, retina, and other organs. Some of these molecules, such as the glutaric acid metabolites, are thought to be excitotoxic to neurons and may affect N-methyl-D-asparate (NMDA) receptors [Hoffman & Zschocke 1999]. Evidence suggests that methylmalonic acid is excitotoxic to neurons. In maple syrup urine disease (MSUD), leucine is believed to be toxic to neurons, but in some cases high concentrations of leucine have not been associated with brain damage [Riviello et al 1991, Nyhan et al 1998, Kolker et al 2000, Wajner et al 2000]. In addition, because catabolism of amino acids provides energy for other cellular processes, energy deficiency during metabolic crisis may contribute to the clinical syndrome. As coenzyme A derivatives form a complex with carnitine, deficiency of carnitine may develop and contribute to disordered homeostasis.

Clinical Manifestations

Presentation. A neonate affected with an organic acidemia (OA) is usually well at birth and for the first few days of life. The usual clinical presentation is that of toxic encephalopathy and includes vomiting, poor feeding, neurologic symptoms such as seizures and abnormal tone, and lethargy progressing to coma. This non-distinct clinical picture may initially be attributed to sepsis, poor breast-feeding, or neonatal asphyxia. While a family history of neonatal death should prompt consideration of an organic acidemia, a negative family history does not exclude the possibility. Outcome is enhanced by diagnosis in the first ten days of life [Clarke 1996, Acosta & Ryan 1997, Baric et al 1998, Saudubray & Charpentier 2001].

Several rare OAs present with neurologic signs without concomitant biochemical findings such as hyperammonemia and acidosis; however, these disorders have a distinctive pattern of organic acids. They include 4-hydroxybutyric aciduria, D-2-hydroxyglutaric aciduria, 3-methylglutaconic aciduria caused by 3-methylglutaconic acid dehydratase deficiency, and malonic aciduria. Methylmalonic aciduria, cblC variant, may present with developmental delay, minor dysmorphology, and hypotonia without acidosis. Late-onset 3-methylcrotonyl carboxylase deficiency may present as developmental delay without Reye-like syndrome, in contrast to the early-onset form.

In the older child or adolescent, variant forms of the OAs can present as loss of intellectual function, ataxia or other focal neurologic signs, Reye syndrome, recurrent keto-acidosis, or psychiatric symptoms. A variety of MRI abnormalities have been described in the OAs, including distinctive basal ganglia lesions in glutaricacidemia type I (GA I), white matter changes in maple syrup urine disease (MSUD), and abnormalities of the globus pallidus in methylmalonic acidemia. Macrocephaly is common in GA I.

Clinical course. Even with appropriate management, individuals with organic acidemias have a greater risk of infection and a higher incidence of pancreatitis, which can be fatal. Methylmalonic acidemia is associated with an increased frequency of renal failure and the cblC variant of methylmalonic acidemia is associated with pigmentary retinopathy [Kaplan et al 1991, Peinemann & Danner 1994, Leonard 1995, Al-Bassam et al 1998, Al Essa et al 1998, Nicolaides et al 1998].

Establishing the Diagnosis

Clinical laboratory findings that should suggest an organic acidemia (Table 1):

Acidosis. Serum bicarbonate lower than:

- 22 mmol/L in individuals younger than one month of age
- 17 mmol/L in neonates

Note: In most organic acidemias, the acidosis is severe, with an anion gap higher than 20. Early in the course, however, the acidosis may be less severe and the anion gap smaller.

Ketosis

- A positive (not trace) urine dipstick for ketones or Acetest tablet (Ames), which detects acetoacetic acid and acetone

OR

- A urine organic acid profile containing excess β-hydroxybutyrate and acetoacetic acid as defined by the norms of the laboratory performing the test

Note: Because they do not normally produce much acetoacetate, ketosis detected in neonates by dipstick or Acetest tablet is unusual and should therefore prompt serious consideration of an organic acidemia.

Hyperammonemia. Plasma ammonium concentration exceeding the reference range for the laboratory performing the test and the age of the affected individual, usually greater than:

- 150 µg/dL in neonates
- 70 µg/dL in infants to one month of age
- 35-50 µg/dL in older children and adults

Abnormal liver function tests

- **Hypoglycemia.** Serum glucose lower than:
  - 40 mg/dL in term and preterm infants
  - 60 mg/dL in children
  - 76 mg/dL over age 16 years
- **Neutropenia.** Absolute neutrophil count (ANC) less than 1500/mm^3. Total white cell counts vary with age and local laboratory reference ranges may need to be taken into account.

  Note: Reference ranges listed are taken from Robertson & Shilkofski (2005). However, the clinician should note the reference ranges in the laboratory used for testing, as reference ranges and units may vary among laboratories.

Table 1. Clinical Findings in Organic Acidemias Caused by Abnormal Amino Acid Catabolism

Disorder	Distinctive Features		
	Ketosis	Acidosis	Other
Maple syrup urine disease (MSUD)	X		Maple syrup odor
Propionic acidemia [1]	X	X	Neutropenia
Methylmalonic acidemia (MMA)	X	X	Neutropenia
Methylmalonic aciduria and homocystinuria, cblC type	Rare	Rare	Vomiting, poor feeding, neurologic symptoms
Isovaleric acidemia		X	Sweaty feet odor
Biotin-unresponsive 3-methylcrotonyl -CoA carboxylase deficiency		X	Hypoglycemia
3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency			Reye syndrome, hypoglycemia
Ketothiolase deficiency (mitochondrial acetoacetyl-CoA thiolase deficiency)	X	X	Hypoglycemia
Glutaricacidemia type I (GA I)			Basal ganglia injury with movement disorder

Note: In MSUD and isovaleric acidemia, distinctive smells in urine, sweat, and even the affected individual's room suggest the diagnosis.

1. Propionic acidemia may present with isolated hyperammonemia early in its course.

Newborn screening tests. The increasing performance of expanded newborn screening using tandem mass spectrometry to diagnose organic acidemias may result in earlier diagnosis of more affected individuals. It is important to remember that these tests are screening tests, and the diagnosis must be confirmed using an independent gas chromatography with mass spectrometry (GC/MS) analysis of urinary organic acids as well as other appropriate tests when available [Goodman & Markey 1981, Chalmers & Lawson 1982, Blau et al 1996, Seashore 1998].

Gas chromatography/mass spectrometry (GC/MS). First-line diagnosis in the organic acidemias is urine organic acid analysis by GC/MS, utilizing a capillary column. Organic acids can be measured in any physiologic fluid. However, it is most effective to use urine to identify the organic acids that signal these disorders, as semi-quantitative methods may not identify the important compounds in plasma. The organic acids found in the urine provide a high degree of suspicion for the specific pathway involved (Table 1).

In special circumstances, quantitative methods using such techniques as stable isotope dilution may allow quantitation of specific organic acids, such as methylmalonic acid. When in excess, some of the coenzyme A derivatives of the organic acids that accumulate are conjugated with carnitine or glycine; thus, assessment of the plasma acylcarnitine profile and quantitation of urinary acylglycines is helpful in establishing a specific diagnosis.

The urinary organic acid profile is nearly always abnormal in the face of acute illness with decompensation. However, in some disorders the diagnostic analytes may be present only in small or barely detectable amounts when the affected individual is not acutely ill. Thus, it is critical to obtain a urine sample during the acute phase of the illness, even if the sample needs to be frozen and saved until the testing can be performed.

Many laboratories have difficulty performing and/or interpreting urine organic acid analysis by GC/MS; it is important that the biochemical genetic testing be performed in an experienced laboratory and interpreted by an individual trained in biochemical genetics.

Differential Diagnosis

The organic acidemias are important in the differential diagnosis of metabolic and neurologic derangement in the neonate and of new-onset neurologic signs in the older child.

Organic aciduria. Several disorders, not classified as primary disorders of organic acid metabolism, have a characteristic urinary organic acid profile that suggests the appropriate diagnosis.

- Mevalonic aciduria, a disorder of cholesterol biosynthesis, shows mevalonic acid in the urine.
- Glutaricacidemia type II (GA II, EMA-adipic aciduria), a disorder of fatty acid oxidation, has multiple organic acids in abnormal concentration in urine. These organic acids include ethylmalonic acid, glutaric acid, dicarboxylic acids, and glycine conjugates of medium chain dicarboxylic acids.
- The fatty acylCoA-glycine conjugates that signal incomplete fatty acid oxidation may be identified during GC/MS analysis of urine and serve as signals to the diagnosis of MCAD deficiency and other disorders of fatty acid oxidation and transport.
- Biotinidase deficiency, a disorder of biotin recycling, results in the urinary excretion of several unusual organic acids, including 3-hydroxy-isovaleric, 3-methylcrotonic, 3-hydroxypropionic, methylcitric, 3-hydroxybutyric acids, and acetoacetate. Propionyl glycine and tiglylglycine may also be seen.
- Mitochondrial diseases (see Mitochondrial Disorders Overview) with disordered oxidative phosphorylation often demonstrate the presence of abnormal organic acids in the urine, including lactate and 3-methylglutaconic, 2-hydroxybutyric, 3-hydroxybutyric, 2-methyl-3-hydroxybutyric, and ethylmalonic acids.

Acidosis. The differential diagnosis includes all causes of acidosis including renal tubular acidosis and inherited metabolic disorders of lactate and pyruvate metabolism and oxidative phosphorylation. Disorders of the Krebs cycle can also cause neurologic symptoms, usually

accompanied by metabolic acidosis with elevations of specific organic acids in urine. Fumarase deficiency (fumarate) and 2-ketoglutarate dehydrogenase deficiency (2-ketoglutarate) are two examples. Non-genetic conditions, such as shock and sepsis, also cause acidosis [Rustin et al 1997].

Hyperammonemia. Disorders of the urea cycle (see Urea Cycle Disorders Overview) and the hyperammonemia-hypoglycemia syndrome (see Familial Hyperinsulinism) caused by mutations in the gene encoding glutamate dehydrogenase need to be considered, although the urinary organic acid profile is likely to be diagnostic in the organic acid disorders. In the urea cycle disorder OTC deficiency, and others later in the cycle, orotic acid may be identified in the urine organic acid profile.

Developmental delay. The differential diagnosis of developmental delay with other neurologic findings unaccompanied by acidosis or hyperammonemia is extremely long. A high index of suspicion is required to keep an organic acidemia in mind when these symptoms prevail.

Prevalence

While each individual disorder comprising the organic acidurias is rare, disorders of organic acid metabolism in the aggregate are not. More than 100 inborn errors of metabolism, many of which are organic acidemias, present in the neonatal period, with an approximate incidence of 1/1000 neonates [Saudubray & Charpentier 2001].

Causes

Heritable Causes

The majority of the classic organic acid disorders result from abnormal amino acid catabolism of branched-chain amino acids or lysine. Characteristics of the disorders are summarized in Table 1 (Clinical Findings), Table 2 (Metabolic Findings), and Table 3 (Molecular Genetics).

Table 2. Metabolic Findings in Organic Acidemias Caused by Abnormal Amino Acid Catabolism

Disorder	Amino Acid Pathway(s) Affected	Enzyme	Diagnostic Analytes by GC/MS [1] and Quantitative Amino Acid Analysis
Maple syrup urine disease (MSUD)	Leucine, isoleucine, valine	Branched-chain ketoacid dehydrogenase	Branched-chain ketoacids and hydroxyacids in urine Alloisoleucine in plasma
Propionic acidemia	Isoleucine, valine, methionine, threonine	Propionyl CoA carboxylase	Propionic acid, 3-OH propionic acid, methyl citric acid, propionyl glycine in urine Propionyl carnitine, increased glycine in blood
Methylmalonic acidemia (MMA)	Isoleucine, valine, methionine, threonine	Methylmalonyl CoA mutase	Methylmalonic acid in blood and urine Propionic acid, 3-OH propionic acid, methyl citrate in urine Acyl carnitines, increased glycine in blood
Methylmalonic aciduria and homocystinuria, cblC type	Isoleucine, valine, methionine, threonine	MMACHC protein	Methylmalonic acid in blood and urine Total homocysteine in plasma
Isovaleric acidemia	Leucine	Isovaleryl CoA dehydrogenase	3-OH isovaleric acid, isovaleryl glycine in urine
Biotin-unresponsive 3-methylcrotonyl- CoA carboxylase deficiency	Leucine	3-methylcrotonyl- CoA carboxylase	3-hydroxy-isovaleric acid, 3-methylcrotonyl glycine in urine
3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency	Leucine	HMG-CoA lyase	3-OH-3-methyl glutaric acid, 3-methylglutaconate, 3-OH-isovalerate, 3-methylglutarate in urine
Ketothiolase deficiency	Isoleucine	Mitochondrial acetoacetyl-CoA thiolase	2-methyl-3-hydroxybutyric acid, 2-methylacetoacetic acid, tiglylglycine in urine
Glutaricacidemia type I (GA I)	Lysine, hydroxylysine, tryptophan	Glutaryl CoA dehydrogenase	Glutaric acid, 3-OH-glutaric acid in urine Glutarylcarnitine in blood

1. Gas chromatography/mass spectrometry

Table 3. Molecular Genetics of the Organic Acidemias and Availability of Molecular Genetic Testing

Disorder	Gene Symbol	Chromosomal Locus	Protein Name	OMIM #	Molecular Genetic Test Availability
Maple syrup urine disease (MSUD)	*BCKDHA*	19q13.1-q13.2	2-oxoisovalerate dehydrogenase alpha subunit	248600, 608348 (Type IA)	Clinical Testing
	BCKDHB	6p22-p21	2-oxoisovalerate dehydrogenase beta subunit	248611 (Type IB)	
	DBT	1p31	Lipoamide acyltransferase component of branched-chain alpha-keto acid dehydrogenase complex	248610 (Type II)	
Propionic acidemia	*PCCA*	13q32	Propionyl-CoA carboxylase alpha chain	606054, 232000 (Type I)	Clinical Testing
	PCCB	3q21-q22	Propionyl-CoA carboxylase beta chain	232050, 606054 (Type II)	Clinical Testing
Methylmalonic acidemia (MMA)	*MUT*	6p21	Methylmalonyl-CoA mutase	251000, 609058	Clinical Testing
	MMAA	4q31.1-q31.2	Methylmalonic aciduria type A protein	607481, 251100	
	MMAB	12q24	Cob(I)yrinic acid a,c-diamide adenosyltransferase	607568, 251110	
Methylmalonic aciduria and homocystinuria, cblC type	*MMACHC*	1p34.1	Methylmalonic aciduria and homocystinuria type C protein	609831, 277400	Clinical Testing
Isovaleric acidemia	*IVD*	15q14-q15	Isovaleryl CoA dehydrogenase	243500, 607036	Clinical Testing
Biotin-unresponsive 3-methylcrotonyl- CoA carboxylase deficiency	*MCCC1* or *MCCA*	3q25-q27	Methylcrotonyl-CoA carboxylase alpha chain	210200, 609010	Clinical Testing
	MCCC2 or *MCCB*	5q12-q13	Methylcrotonyl-CoA carboxylase beta chain	210210	
3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency	*HMGCL*	1p33-pter	Hydroxymethyl-glutaryl-CoA lyase	246450	Research only
Mitochondrial acetoacetyl-CoA thiolase deficiency (β-ketothiolase deficiency)	*ACAT1*	11q22.3-q23.1	Acetyl-CoA acetyltransferase	203750, 607809	Clinical Testing
Glutaricacidemia type I (GA I)	*GCDH*	19p13.2	Glutaryl-CoA dehydrogenase	231670	Clinical Testing

Evaluation Strategy

Determining the specific cause of organic acidemia is important for establishing prognosis, appropriate treatment strategy, and genetic counseling.

Plasma amino acid analysis. Depending on the specific disorder, plasma amino acid analysis can be helpful because specific abnormalities in plasma amino acid concentrations provide an important clue to identifying the disordered pathway. Plasma amino acid analysis requires a

quantitative method such as column chromatography, high-performance liquid chromatography (HPLC), or GC/MS.

Enzyme analysis. Once the detection of specific analytes narrows the diagnostic possibilities, the activity of the deficient enzyme is measured in lymphocytes or cultured fibroblasts as a confirmatory test.

Molecular genetic testing. Molecular genetic testing can be used to confirm the diagnosis in some affected individuals. The genes causing the organic acid disorders and the availability of molecular genetic testing are listed in Table 3.

Compound heterozygosity for two different mutations is common in these autosomal recessive disorders. Carrier detection using molecular methods can be difficult if only one mutation in a proband can be identified.

As with many other genetic conditions, particular sets of mutations are prevalent within specific ethnic groups. Examples include MSUD in the Old Order Amish and specific mutations in many organic acidurias among Arab populations in Saudi Arabia.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

The organic acidemias considered in this overview are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and, therefore, carry a single copy of a disease-causing mutation.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. All offspring of affected individuals are obligate carriers.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

With the exception of biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, carrier testing using molecular genetic techniques is available for at-risk family members on a clinical basis once the organic acidemia-causing mutations have been identified in the proband.

Methods other than molecular genetic testing are for the most part not reliable for carrier testing because the ranges of enzyme activity in carriers and non-carriers can overlap. This has been well shown for propionic acidemia and appears to be true for methylmalonic acidemia.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

Diagnosis of newborn at-risk sibs. If prenatal diagnosis has not been performed in an at-risk pregnancy, immediate diagnostic testing of the newborn must be performed. Expectant treatment, including elimination of fasting stress until the presence of the disorder is confirmed or excluded, is prudent.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only or when the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Three approaches to prenatal diagnosis are possible, depending on the disorder. These include measurement of analytes in amniotic fluid, measurement of enzyme activity in cells obtained by chorionic villus sampling or in cultured amniocytes, and molecular genetic testing of DNA extracted from fetal cells obtained by CVS or amniocentesis to identify the relevant mutations if the two disease-causing mutations in the previously affected child (or carrier parents) are known.

Biochemical genetic testing. Prenatal diagnosis for pregnancies at increased risk for propionic acidemia, methylmalonic acidemia, biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, glutaricacidemia type 1, ketothiolase deficiency, methylmalonic aciduria and homocystinuria, cblC type, and isovaleric acidemia is possible by analysis of amniotic fluid if highly accurate quantitative methods are used to measure the appropriate analytes. Amniocentesis is usually performed at about 15-18 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Prenatal diagnosis for pregnancies at increased risk for MSUD is possible by measurement of enzyme activity in fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation. (If cells from CVS are used, extreme care must be taken to assure that they are fetal, not maternal.)

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for glutaricacidemia type 1, methylmalonic acidemia, biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, maple syrup urine disease (MSUD), isovaleric academia,

methylmalonic aciduria and homocystinuria, cblC type, and propionic acidemia is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

No laboratories offering molecular genetic testing for prenatal diagnosis of 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Management

Treatment of Manifestations

Many of the organic acidemias respond to treatment, and in the neonate especially, they demand emergency diagnosis and management. The aim of therapy is to restore biochemical and physiologic homeostasis [Clarke 1996, Acosta & Ryan 1997, Baric et al 1998, Saudubray & Charpentier 2001]. The treatments, while similar in principle, depend on the specific biochemical lesion and are based on the position of the metabolic block and the effects of the toxic compounds. Treatment strategies include: (1) dietary restriction of the precursor amino acids; (2) use of adjunctive compounds to dispose of toxic metabolites; and (3) use of adjunctive compounds to increase activity of deficient enzymes.

Dietary. Table 2 indicates the amino acids involved in the classic disorders. The use of specific metabolic foods (formulas) deficient in the particular precursor amino acids for each disorder is a critical part of management as it provides the essential amino acids in an otherwise protein-deficient diet. Adequate calories to inhibit catabolism are supplied as carbohydrate and fat and appropriate protein must be supplied to support anabolism. Total parenteral nutrition has been used during gastrointestinal illness or surgery but must be monitored with careful attention to biochemical parameters.

Adjunctive compounds to dispose of toxic metabolites. Examples include use of thiamine to treat thiamine-responsive MSUD and hydroxocobalamin, but usually not cyanocobalamin to treat methylmalonic acidemia. For the disorders of propionate metabolism, intermittent administration of non-absorbed antibiotics can reduce the production of propionate by gut bacteria.

Long-term care. Ongoing care requires the support of knowledgeable nutritionists and physicians. Frequent monitoring of growth, development, and biochemical parameters is essential. Long-term outcome can be excellent in the organic acidemias. However, appropriate management does not guarantee a good outcome, as individuals affected with an OA are medically fragile [de Baulny et al 2005].

Frequent episodes of decompensation can be devastating to the central nervous system. Any source of catabolic stress, such as vomiting, diarrhea, febrile illness, and decreased oral intake can lead to decompensation, which requires prompt and aggressive intervention. During acute decompensation, treatment strategies are directed toward elimination of the toxic amino acid precursors by restriction of their intake and the use of adjunctive measures such as hemodialysis. During acute decompensation, critical care support is often required, acidosis may need to be corrected, and careful and frequent biochemical monitoring is crucial.

The first episode of decompensation in glutaricacidemia type I (GA I) usually results in severe damage to the basal ganglia with resultant movement disorder. Early diagnosis with aggressive prevention of decompensation can prevent this damage. The pathophysiology may involve acute striatal necrosis; management of acute illness based on a model of stroke-like damage and brain energy deficiency has been advocated [Strauss & Morton 2003]. Early diagnosis of MSUD has a major effect on outcome. The cblC form of methylmalonic acidemia does not appear to respond well to therapy, even when undertaken early [Rosenblatt et al 1997]. A late-onset form of cblC may respond better to treatment with hydroxocobalamin than the early-onset form [Bodamer et al 2001].

Liver transplantation. While liver transplantation has been performed on small numbers of affected individuals and thus cannot be considered a first-line treatment, the outcome has been successful in many cases. In the case of mutase-deficient methylmalonic acidemia, combined liver-kidney transplantation has corrected the renal disease that many such individuals suffer and resulted in near-normal metabolic status. In propionic acidemia, liver transplantation alone ameliorates the disease, but does not completely eliminate the disorder because the kidney also makes propionic acid. The usual complications of liver transplantation, including cyclosporin toxicity and rejection, have been reported [Schlenzig et al 1995, Burdelski & Ullrich 1999, Saudubray et al 1999]. Survival rates have been reported to be comparable to those in children undergoing transplant for non-metabolic diagnoses and quality of life is good [Leonard et al 2001, Kayler et al 2002].

Pregnancy. With careful metabolic management, successful pregnancy has been achieved by women with isovaleric acidemia, MSUD, propionic acidemia, methylmalonic acidemia, and mitochondrial ß-ketothiolase deficiency, without apparent adverse outcome to mother or fetus [Walter 2000]. Careful monitoring post partum, a period of particular metabolic stress for the mother, is crucial.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
3-hydroxy-3-methylglutaryl-CoA lyase deficiency
3-methylcrotonyl-CoA carboxylase deficiency
Beta-ketothiaolase deficiency
Glutaric acidemia type 1
Isovaleric acidemia
Maple syrup urine disease
Propionic acidemia

Organic Acidemia Association
13210 35th Avenue North
Plymouth MN 55441
Phone: 763-559-1797
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Email: oaanews@aol.com
www.oaanews.org

Children Living with Inherited Metabolic Diseases (CLIMB)
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Chapter Notes

Revision History

- 26 June 2007 (cd) Revision: genetic testing (sequence analysis) for isovaleric academia available clinically and for prenatal diagnosis. Molecular genetic and biochemical testing clinically available for methylmalonic academia and homocystinuria, cb1C type and prenatal diagnosis.
- 27 December 2006 (ms) Revision: biochemical prenatal diagnosis for ketothiolase deficiency available
- 27 October 2006 (ms) Revision: targeted mutation analysis for p.A282V mutation clinically available
- 2 May 2006 (ms) Revision: addition of methylmalonic aciduria and homocystinuria, cblC type
- 24 March 2006 (me) Comprehensive update posted to live Web site
- 28 June 2004 (cd) Revision: change in test availability
- 9 December 2003 (me) Comprehensive update posted to live Web site

- 27 June 2001 (ms) Overview posted to live Web site
- 13 January 2001 (ms) Original submission