Inborn Errors of Metabolism in Infancy and Early Childhood: An Update

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Recent innovations in medical technology have changed newborn screening programs in the United States. The widespread use of tandem mass spectrometry is helping to identify more inborn errors of metabolism. Primary care physicians often are the first to be contacted by state and reference laboratories when neonatal screening detects the possibility of an inborn error of metabolism. Physicians must take immediate steps to evaluate the infant and should be able to access a regional metabolic disorder subspecialty center. Detailed knowledge of biochemical pathways is not necessary to treat patients during the initial evaluation. Nonspecific metabolic abnormalities (e.g., hypoglycemia, metabolic acidosis, hyperammonemia) must be treated urgently even if the specific underlying metabolic disorder is not yet known. Similarly, physicians still must recognize inborn errors of metabolism that are not detected reliably by tandem mass spectrometry and know when to pursue additional diagnostic testing. The early and specific diagnosis of inborn errors of metabolism and prompt initiation of appropriate therapy are still the best determinants of outcome for these patients. (Am Fam Physician 2006;73:1981-90. Copyright © 2006 American Academy of Family Physicians.)

ACF This article exemplifies the AAFP 2006 Annual Clinical Focus on caring for children and adolescents.

The topic of inborn errors of metabolism is challenging for most physicians. The number of known metabolic disorders is probably as large as the number of presenting symptoms that may indicate metabolic disturbances *(Table 1*[1-3]*)*. Furthermore, physicians know they may not encounter certain rare inborn errors of metabolism during a lifetime of practice. Nonetheless, with a collective incidence of one in 1,500 persons, at least one of these disorders will be encountered by almost all practicing physicians.[1-3]

Improvements in medical technology and greater knowledge of the human genome are resulting in significant changes in the diagnosis, classification, and treatment of inherited metabolic disorders. Many known inborn errors of metabolism will be recognized earlier or treated differently because of these changes. It is important for primary care physicians to recognize the clinical signs of inborn errors of metabolism and to know when to pursue advanced laboratory testing or referral to a children's subspecialty center.

Early Diagnosis and Screening in Asymptomatic Infants

The principles of population screening to identify persons with biologic markers of disease and to apply interventions to prevent disease progression are well established. Screening tests must be timely and effective with a high predictive value. Current approaches to detecting inborn errors of metabolism revolve around laboratory screening for certain disorders in asymptomatic newborns, follow-up and verification of abnormal laboratory results, prompt physician recognition of unscreened disorders in symptomatic persons, and rapid implementation of appropriate therapies.

The increasing application of new technologies such as electrospray ionization–tandem mass spectrometry to newborn screening[4] in asymptomatic persons allows earlier identification of clearly defined inborn errors of metabolism. It also detects some conditions of uncertain clinical significance.[5] The inborn errors of metabolism detected by tandem mass spectrometry generally include aminoacidemias, urea cycle disorders, organic acidurias, and fatty acid oxidation disorders. Earlier recognition of these inborn errors of metabolism has the potential to reduce morbidity and mortality rates in these infants.[6]

Tandem mass spectrometry has been introduced or mandated in many states, with some states testing for up to seven conditions and others screening for up to 40 conditions. Therefore, physicians must

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Tandem mass spectrometry in newborn screening allows earlier identification of inborn errors of metabolism in asymptomatic persons.	A	4
Earlier recognition of inborn errors of metabolism has the potential to reduce morbidity and mortality rates in affected infants.	A	6
Special consideration for pregnant women with phenylketonuria includes constant monitoring of phenylalanine concentrations to prevent intrauterine fetal malformation.	A	12

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1874 or http://www.aafp.org/afpsort.xml.

TABLE 1
Inborn Errors of Metabolism and Associated Symptoms*

Diarrhea
Lactase deficiency (common)
Mitochondrial disorders (1:30,000; e.g., Pearson's syndrome [rare])
Abetalipoproteinemia (rare)
Enteropeptidase deficiency (rare)
Lysinuric protein intolerance (rare)
Sucrase-isomaltase deficiency (rare)

Exercise intolerance
Fatty acid oxidation disorders (1:10,000)
Glycogenolysis disorders (1:20,000)
Mitochondrial disorders (1:30,000; e.g., lipoamide dehydrogenase deficiency [rare])
Myoadenylate deaminase deficiency (1:100,000)

Familial myocardial infarct/stroke
5,10-methylenetetrahydrofolate reductase deficiency (common)
Familial hypercholesterolemia (1:500)
Fabry's disease (1:80,000 to 1:117,000)
Homocystinuria (1:200,000)

Muscle cramps/spasticity
Multiple carboxylase deficiency (e.g., holocarboxylase synthetase [rare]) and biotinidase deficiencies (1:60,000)
Metachromatic leukodystrophy (1:100,000)
HHH syndrome (rare)

Peripheral neuropathy
Mitochondrial disorders (1:30,000)
Peroxisomal disorders (1:50,000; e.g., Zellweger syndrome, neonatal adrenoleukodystrophy, Refsum's disease)
Metachromatic leukodystrophy (1:100,000)
Congenital disorders of glycosylation (rare)

Recurrent emesis
Galactosemia (1:40,000)
3-oxothiolase deficiency (1:100,000)
D-2-hydroxyglutaricaciduria (rare)

Symptoms of pancreatitis
Mitochondrial disorders (1:30,000; e.g., cytochrome-c oxidase deficiency; MELAS syndrome; Pearson's syndrome [all rare])
Glycogenosis, type I (1:70,000)
Hyperlipoproteinemia, types I and IV (rare)
Lipoprotein lipase deficiency (rare)
Lysinuric protein intolerance (rare)

Upward gaze paralysis
Mitochondrial disorders (1:30,000; e.g., Leigh disease, Kearns-Sayre syndrome [rare])
Niemann-Pick disease, type C (rare)

NOTE: *Disorders are listed as possible diagnostic considerations in order of descending incidence. Incidence in the general U.S. population is comparable to international estimates; however, disorders may occur more often in select ethnic populations. Rare is defined as an estimated incidence of fewer than 1:250,000 persons.*

HHH = hyperornithinemia-hyperammonemia-homocitrullinuria; MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.

**—Inborn errors of metabolism can induce disease manifestations in any organ at various stages of life, from newborn to adulthood. Whereas advanced newborn screening programs using tandem mass spectrometry will detect some inherited metabolic disorders before clinical signs appear, most of these disorders will be detected by the primary care physician before the diagnosis is made. Reliable determination of certain metabolic disorders varies between laboratories. Changes in screening reflect a growing field.*

Information from references 1 through 3.

be aware of variability in newborn screening among individual hospitals and states. Current state-by-state information on newborn screening programs can be obtained through the Internet resource GeNeS-R-US (Genetic and Newborn Screening Resource Center of the United States; http://genes-r-us.uthscsa.edu/).[7] Primary care physicians are most likely to be the first to inform parents of an abnormal result from a newborn screening program. In many instances, primary care physicians may need to clarify preliminary laboratory results or explain the possibility of a false-positive result.[6]

Early Diagnosis in Symptomatic Infants

Within a few days or weeks after birth, a previously healthy neonate may begin to show signs of an underlying metabolic disorder. Although the clinical picture may vary, infants with metabolic disorders typically present with lethargy, decreased feeding, vomiting, tachypnea (from acidosis), decreased perfusion, and seizures. As the metabolic illness progresses, there may be increasing stupor or coma associated with progressive abnormalities of tone (hypotonia, hypertonia), posture (fisting, opisthotonos), and movements (tongue-thrusting, lip-smacking, myoclonic jerks), and with sleep apnea.[8] Metabolic screening tests should be initiated. Elevated plasma ammonia levels, hypoglycemia, and metabolic acidosis, if present, are suggestive of inborn errors of metabolism *(Table 2*[1-3]*).* In addition, the parent or physician may notice an unusual odor in an infant with certain inborn errors of metabolism (e.g., maple syrup urine disease, phenylketonuria [PKU], hepatorenal tyrosinemia type 1, isovaleric acidemia). A disorder similar to Reye's syndrome (i.e., nonspecific hepatic encephalopathy, possibly with hypoglycemia) may be present secondary to abnormalities of gluconeogenesis, fatty acid oxidation, the electron transport chain, or organic acids.

Table 3[1-3] shows a partial list of metabolic disorders associated with organ system manifestations. Most of these disorders are not detected by tandem mass spectrometry screening. These highly diverse presentations of inborn errors of metabolism may be associated with dysfunction of the central nervous system (CNS), liver, kidney, eye, bone, blood, muscle, gastrointestinal tract, and integument. Infants with symptoms of acute or chronic encephalopathy usually require a focused but systematic evaluation by a children's neurologist and appropriate testing (e.g., magnetic resonance imaging, additional genetic or metabolic analysis). Subspecialty referral is likewise necessary for infants or children presenting with hepatic, renal, or cardiac syndromes; dysmorphic syndromes; ocular findings; or significant orthopedic abnormalities.

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A "pattern recognition" approach helps guide the physician toward a differential diagnosis and targeted biochemical and molecular testing.[9] However, this approach is not to be confused with the identification of congenital malformations, particularly those related to chromosomal disorders. Patients generally have a normal appearance in the early stages of most inborn metabolic disorders. Because most inborn errors of metabolism are single-gene disorders, chromosomal testing usually is not indicated.

Considerations in Older Infants and Children

Older infants with inborn errors of metabolism may demonstrate paroxysmal stupor, lethargy, emesis, failure to thrive, or organomegaly. Neurologic findings of neurometabolic disorders are acquired macrocephaly or microcephaly (CNS storage, dysmyelination, atrophy), hypotonia, hypertonia/spasticity, seizures, or other movement disorders. General nonneurologic manifestations of neurometabolic disorders include skeletal abnormalities and coarse facial features (e.g., with mucopolysaccharidoses), macular or retinal changes (e.g., with leukodystrophies, poliodystrophies, mitochondrial disorders), corneal clouding (e.g., with Hurler's syndrome, galactosemia), skin changes (e.g., angiokeratomas in Fabry's disease), or hepatosplenomegaly (with various storage diseases; *Table 2*[1-3]).

Consistent features of metabolic disorders in toddlers and preschool-age children

include stagnation or loss of cognitive milestones; loss of expressive language skills; progressive deficits in attention, focus, and concentration; and other behavioral changes. The physician should attempt to make fundamental distinctions between primary-genetic and secondary-acquired causes of conditions that present as developmental delay or failure to thrive. Clues can be extracted through careful family, social, environmental, and nutritional history-taking. Syndromes with metabolic disturbances may lead to the identification of clinically recognizable genetic disorders. Referral to a geneticist often is indicated to further evaluate physical findings of primary genetic determinants.

Initial laboratory investigations for older children are the same as for infants. Infants and children presenting with acute metabolic decompensation precipitated by periods of prolonged fasting should be evaluated further for those organic acid, fatty acid oxidation, or peroxisomal disorders that are not detected

TABLE 2
Inborn Errors of Metabolism and Associated Laboratory Findings*

Abnormal liver function tests (e.g., elevated transaminase or hyperbilirubinemia levels)
Hemochromatosis (1:300)
α_1-antitrypsin deficiency (1:8,000)
Hereditary fructose intolerance (1:20,000 to 1:50,000)
Mitochondrial disorders (1:30,000; e.g., mitochondrial DNA depletion syndromes)
Galactosemia (1:40,000)
Wilson's disease (1:50,000)
Gaucher's disease (1:60,000; type 1–1:900 in Ashkenazi Jews)
Hypermethioninemia (1:160,000)
Cholesteryl ester storage disease (rare)
Glycogen storage disease, type IV (rare)
Niemann-Pick disease, types A and B (both rare)
Type 1 tyrosinemia (rare)
Wolman's disease (rare)

Hypoglycemia
Carbohydrate metabolism disorders (> 1:10,000)
Fatty acid oxidation disorders (1:10,000)
Hereditary fructose intolerance (1:20,000 to 1:50,000)
Glycogen storage diseases (1:25,000)
Galactosemia (1:40,000)
Organic acidemias (1:50,000)
Phospho*enol*pyruvate carboxykinase deficiency (rare)
Primary lactic acidosis (rare)

Hypophosphatemia
Fanconi syndrome (1:7,000; e.g., cystinosis)
X-linked hypophosphatemic rickets (1:20,000)

Hypouricemia
Fanconi syndrome (1:7,000; e.g., cystinosis)
Xanthine oxidase deficiency (1:45,000)
Molybdenum cofactor deficiency (rare)
Purine-nucleoside phosphorylase deficiency (rare)

Increased CSF protein
Mitochondrial disorders (1:30,000; e.g., MELAS syndrome [rare], MERRF syndrome, Kearns-Sayre syndrome [rare])
Peroxisomal disorders (1:50,000; e.g., Zellweger syndrome, neonatal adrenoleukodystrophy, Refsum's disease)
Leukodystrophies (e.g., Krabbe's disease; metachromatic leukodystrophy [1:100,000]; multiple sulfatase deficiency [rare])
L-2-hydroxyglutaricaciduria (rare)
Congenital disorders of glycosylation (rare)

Ketosis
Aminoacidopathies (1:40,000)
Organic acidurias (1:50,000)

Metabolic acidosis
Aminoacidopathies (1:40,000)
Organic acidurias (1:50,000)
Primary lactic acidosis (rare)
Renal tubular acidosis (rare)

NOTE: *Disorders are listed as possible diagnostic considerations in order of decreasing incidence. Incidence in the general U.S. population is comparable to international estimates; however, disorders may occur more often in select ethnic populations. Rare is defined as an estimated incidence of fewer than 1:250,000 persons.*

CSF = cerebrospinal fluid; MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERRF = myoclonus with epilepsy and with ragged red fibers.

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Information from references 1 through 3.

by tandem mass spectrometry or certain regional neonatal screening programs.

Cerebrospinal fluid (CSF) may be helpful in the evaluation of certain metabolic disorders after neuroimaging studies and basic blood and urine analyses have been completed. Common CSF studies include cells (to rule out inflammatory disorders), glucose (plus plasma glucose to evaluate for blood-brain barrier or glucose transporter disorders), lactate (as a marker of energy metabolism or mitochondrial disorders), total protein, and quantitative amino acids. Nuclear magnetic resonance spectroscopy can provide a noninvasive, in vivo evaluation of proton-containing metabolites and can lead to the diagnosis of certain rare, but potentially treatable, neurometabolic disorders.[10] Electron microscopic evaluation of a skin biopsy is a highly sensitive screening tool that provides valuable clues to stored membrane material or ultrastructural organelle changes.[11]

Table 4 lists some of the more common inborn errors of metabolism, classified by type of metabolic disorder. Such prototypical inborn errors of metabolism include PKU, ornithine transcarbamylase deficiency, methylmalonicaciduria, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, galactosemia, and Gaucher's disease.

PKU

PKU is an autosomal-recessive disorder most commonly caused by a mutation in the gene coding for phenylalanine hydroxylase, an enzyme responsible for the conversion of phenylalanine to tyrosine. Sustained phenylalanine concentrations higher than 20 mg per dL (1,211 μmol per L) usually correlate with classic symptoms of PKU, such as impaired head circumference growth, poor cognitive function, irritability, and lighter skin pigmentation. Infants diagnosed with PKU are treated with a special low-phenylalanine formula. Tyrosine is given at approximately 25 mg per kg of weight per day; amino acids are given at about 3 g per kg per day in infancy and 2 g per kg per day in childhood. Infants and children must be monitored regularly during the developmental period, and it is recommended that strict dietary therapy be continued for life. Special considerations for pregnant women with PKU include constant monitoring of phenylalanine concentrations to prevent intrauterine fetal malformation.[12]

ORNITHINE TRANSCARBAMYLASE DEFICIENCY

Ornithine transcarbamylase deficiency is the most common urea cycle disorder. Signs of ornithine transcarbamylase deficiency in infant boys include severe emesis, hyperammonemia, and progressive encephalopathy. Heterozygous girls, who demonstrate partial expression of the X-linked ornithine transcarbamylase deficiency disorder, may present with symptoms such as mild hyperammonemia and notable avoidance of dietary protein. Acute treatment options include sodium benzoate, sodium phenylacetate, and arginine. Certain persons may benefit from liver transplantation.

METHYLMALONICACIDURIA DISORDERS

The most common genetic causes of methylmalonicaciduria are deficiencies in methylmalonyl-CoA mutase activity and in enzymatic synthesis of cobalamin. Pernicious anemia and dietary cobalamin deficiency also can result in abnormal methylmalonicacid metabolism. Metabolic ketoacidosis is the clinical hallmark of methylmalonicaciduria in infants. Therapy consists of protein restriction, restriction of methylmalonate precursors, and pharmacologic doses of vitamin B_{12}.

MCAD DEFICIENCY

The most common fatty acid oxidation disorder is MCAD deficiency. The majority of infants diagnosed with MCAD deficiency are homozygous for the A985G missense mutation and have northwestern European ancestry. Infants with MCAD deficiency appear to develop normally but present with rapidly progressive hypoglycemia, lethargy, and seizures, typically secondary to acute vomiting or fasting. Treatment of MCAD deficiency includes frequent cornstarch feeds and avoidance of fasting. Parents must have a basic understanding of the metabolic deficit in their child and should carry a letter from their treating physicians to alert emergency

caregivers about the need for urgent attention in a crisis situation.

GALACTOSEMIA

There are three known enzymatic errors in galactose metabolism. The most common defect is confirmed by measuring decreased activity of erythrocyte galactose 1-phosphate uridyltransferase (GALT). Clinical manifestations of galactosemia include lethargy, hypotonia, jaundice, hypoglycemia, elevated liver enzymes, and coagulopathy. It is important to distinguish the galactosemia disease genotype (G/G) from asymptomatic variant genotypes (e.g., G/D, G/N, D/D), which can be picked up as "positive" in newborn screening.

TABLE 3
Inborn Errors of Metabolism and Associated Organ System Manifestations*

Central nervous system
- Acute encephalopathy
  - Mitochondrial disorders (1:30,000)
  - CPS deficiency (1:70,000 to 1:100,000)
- Acute stroke
  - 5,10-methylene tetrahydrofolate reductase deficiency (common)
  - Fabry's disease (1:80,000 to 1:117,000)
  - Ethylmalonic-adipicaciduria (rare)
- Agenesis of the corpus callosum
  - Mitochondrial disorders (1:30,000; e.g., PDH deficiency [1:200,000])
  - Peroxisomal disorders (1:50,000; e.g., Zellweger syndrome, neonatal adrenoleukodystrophy, Refsum's disease)
  - Maternal PKU (1:35,000 pregnancies)
  - Nonketotic hyperglycinemia (1:250,000 in United States)
  - Pyruvate carboxylase deficiency (rare)
- Cerebral calcifications
  - Adrenoleukodystrophy (1:15,000)
  - Mitochondrial disorders (1:30,000)
  - GM_2 gangliosidosis (rare)
- Encephalopathy (rapidly progressive)
  - Adenylosuccinate lyase deficiency (rare)
  - Atypical PKU (e.g., biopterin defects [rare])
  - Molybdenum cofactor deficiency or sulfite oxidase deficiency (both rare)
- Macrocephaly
  - Hurler's syndrome (MPS I; 1:100,000)
  - Neonatal adrenoleukodystrophy (1:100,000)
  - Tay-Sachs disease (1:222,000)
  - 4-hydroxybutyricaciduria (rare)
  - Glutaricaciduria, type II (rare)

Central nervous system (continued)
- Macrocephaly (continued)
  - L-2-hydroxyglutaricaciduria (rare)
  - 3-hydroxy-3-methylglutaricaciduriayl (rare)
  - Canavan disease (rare)
  - Krabbe's disease (rare)
  - Mannosidosis (rare)
  - Multiple sulfatase deficiency (rare)
- Stroke-like episodes
  - Ornithine transcarbamylase deficiency (1:70,000)
  - Chédiak-Higashi syndrome (rare)
  - MELAS syndrome (rare)
- Subacute necrotizing encephalomyelopathy (Leigh disease)
  - ETC disorders (e.g., complex I deficiency)
  - Multiple carboxylase deficiency (e.g., holocarboxylase synthetase [rare]) and biotinidase deficiencies (1:60,000)
  - PDH deficiency (1:200,000)
  - 3-methylglutaconicaciduria (rare)
  - Fumarase deficiency (rare)
  - Pyruvate carboxylase deficiency (rare)

Skin/eye
- Angiokeratomas
  - Fabry's disease (1:117,000)
  - Fucosidosis (rare)
  - GM_1 gangliosidosis (rare)
  - Sialidosis (rare)
- Cataracts—lenticular
  - Mitochondrial disorders (1:30,000)
  - Galactosemia (1:40,000)
  - Fabry's disease (1:80,000 to 1:117,000)

Skin/eye (continued)
- Cataracts—lenticular (continued)
  - Cerebrotendinous xanthomatosis (rare)
  - Galactokinase deficiency (rare)
  - Hyperornithinemia (ornithine aminotransferase deficiency; rare)
  - Lowe syndrome (rare)
  - Lysinuric protein intolerance (rare)
  - Mannosidosis (rare)
  - Mevalonicaciduria (rare)
- Cherry red macula
  - Tay-Sachs disease (1:222,000)
  - Galactosialidosis (rare)
  - GM_1 gangliosidosis (rare)
  - Mucolipidosis I (rare)
  - Multiple sulfatase deficiency (rare)
  - Niemann-Pick disease, types A and B (rare)
  - Sandhoff's disease (rare)
  - Sialidosis (rare)
- Corneal opacity
  - Fabry's disease (1:80,000 to 1:117,000)
  - Hurler's syndrome (MPS I; 1:100,000)
  - Cystinosis (1:100,000 to 1:200,000)
  - I-cell disease (mucolipidosis II or mucolipidosis III [rare])
  - Galactosialidosis (rare)
  - GM_1 gangliosidosis (rare)
  - Mannosidosis (rare)
  - Multiple sulfatase deficiency (rare)

NOTE: *Disorders are listed as possible diagnostic considerations in order of decreasing incidence. Incidence in the general U.S. population is comparable to international estimates; however, disorders may occur more often in select ethnic populations. Rare is defined as an estimated incidence of fewer than 1:250,000 persons.*

CPS = carbamoyl phosphate synthetase; ETC = electron transport chain; HPRT = hypoxanthine phosphoribosyltransferase; MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MPS = mucopolysaccharidosis; PDH = pyruvate dehydrogenase; PKU = phenylketonuria.

The main treatment for infants with the G/G mutation or very low GALT activity is lactose-free formula followed by dietary restriction of all lactose-containing foods later in life. Untreated infants who survive the neonatal period may have severe growth failure, mental retardation, cataracts, ovarian failure, and liver cirrhosis. Despite early and adequate intervention, some children still may develop milder signs of these clinical manifestations.

GAUCHER'S DISEASE

Type 1 Gaucher's disease, the most common lysosomal storage disorder, typically presents with hepatosplenomegaly, pancytopenia, and

Skin/eye (continued)

- Dermatosis
  - Acrodermatitis enteropathica (rare)
  - Multiple carboxylase deficiency (e.g., holocarboxylase synthetase [rare]) and biotinidase deficiencies (1:60,000)
- Hair abnormalities
  - Menkes syndrome (rare; e.g., pili torti, trichorrhexis nodosa, monilethrix)
- Ichthyosis
  - Sjögren-Larsson syndrome (fatty aldehyde dehydrogenase deficiency, <1:100,000)
  - X-linked ichthyosis (1:6,000 boys and men; e.g., steryl-sulfatase deficiency)
- Inverted nipples
  - Congenital disorders of glycosylation (rare)
  - Tetrahydrobiopterin synthesis disorders (rare)
- Lens dislocation (ectopia lentis)
  - Marfan syndrome (1:10,000)
  - Homocystinuria (1:200,000)
  - Molybdenum cofactor deficiency or sulfite oxidase deficiency (both rare)
- Optic atrophy
  - Peroxisomal disorders (1:50,000; Zellweger syndrome, neonatal adrenoleukodystrophy, Refsum's disease)
- Xanthomas
  - Familial hypercholesterolemia (1:500)
  - Lipoprotein lipase deficiency (rare)
  - Niemann-Pick disease, types A and B (both rare)
  - Cerebrotendinous xanthomatosis (rare)

Muscle/bone/kidney

- Arthrosis
  - Farber's disease (acid ceramidase deficiency; < 1:40,000)
  - Gaucher's disease (1:60,000; type 1–1:900 in Ashkenazi Jews)
  - HPRT deficiency (Lesch-Nyhan syndrome; 1:100,000)
  - Homocystinuria (1:200,000)
  - Alkaptonuria (rare)
- Cardiomyopathy
  - Hemochromatosis (1:300)
  - Fatty acid oxidation disorders (1:10,000)
  - Mitochondrial disorders (1:30,000)
  - Pompe's disease (1:40,000)
  - MPS (1:50,000)
  - Glycogenosis, type III (1:125,000)
  - D-2-hydroxyglutaricaciduria (rare)
  - 3-methylglutaconicaciduria (Barth syndrome; rare)
- Dysostosis multiplex
  - MPS (e.g., Hurler's syndrome [MPS I; 1:100,000], Hunter's syndrome [MPS II; 1:70,000], Sanfilippo's syndrome [MPS III; 1:24,000 in Netherlands, 1:66,000 in United States]; Maroteaux-Lamy syndrome [MPS VI; rare]; Sly's syndrome [MPS VII; rare])
  - I-cell disease (mucolipidosis II or mucolipidosis III [rare])
  - Multiple sulfatase deficiency (rare)
  - Galactosialidosis (rare)
  - GM_1 gangliosidosis (rare)

Muscle/bone/kidney (continued)

- Osteoporosis
  - Xanthine oxidase deficiency (1:45,000)
  - Gaucher's disease, (1:60,000; type 1–1:900 in Ashkenazi Jews)
  - Glycogenosis (1:70,000)
  - Adenosine deaminase deficiency (1:100,000)
  - I-cell disease (mucolipidosis II or mucolipidosis III [rare])
  - Refsum's disease
  - Lysinuric protein intolerance (rare)
  - Menkes syndrome (rare)
- Renal calculi
  - Cystinuria (1:7,000)
  - HPRT deficiency (Lesch-Nyhan syndrome; 1:100,000)
  - Adenine phosphoribosyltransferase deficiency (rare)
  - Oxaluria (rare)
  - Phosphoribosylpyrophosphate synthetase deficiency (rare)
- Renal Fanconi syndrome
  - Hereditary fructose intolerance (1:20,000 to 1:50,000)
  - Mitochondrial disorders (1:30,000; e.g., ETC disorders)
  - Galactosemia (1:40,000)
  - Wilson's disease (1:50,000)
  - Cystinosis (1:100,000 to 1:200,000)
  - Type 1 tyrosinemia (rare)
  - Lowe syndrome (rare)

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Information from references 1 through 3.

TABLE 4
Examples of Inborn Errors of Metabolism by Disorder

Disorder	*~Incidence*	*Inheritance*	*Metabolic error*
Amino acid metabolism			
Phenylketonuria	1:15,000	Autosomal recessive	Phenylalanine hydroxylase (>98 percent) Biopterin metabolic defects (<2 percent)
Maple syrup urine disease	1:150,000 (1:1,000 in Mennonites)	Autosomal recessive	Branched-chain α-keto acid dehydrogenase
Carbohydrate metabolism			
Galactosemia	1:40,000	Autosomal recessive	Galactose 1-phosphate uridyltransferase (most common); galactokinase; epimerase
Glycogen storage disease, type Ia (von Gierke's disease)	1:100,000	Autosomal recessive	Glucose-6-phosphatase
Fatty acid oxidation			
Medium-chain acyl-CoA dehydrogenase deficiency	1:15,000	Autosomal recessive	Medium-chain acyl-CoA dehydrogenase
Lactic acidemia			
Pyruvate dehydrogenase deficiency	1:200,000	X-linked	E_1 subunit defect most common
Lysosomal storage			
Gaucher's disease	1:60,000; type 1–1:900 in Ashkenazi Jews	Autosomal recessive	β-glucocerebrosidase
Fabry's disease	1:80,000 to 1:117,000	X-linked	α-galactosidase A
Hurler's syndrome	1:100,000	Autosomal recessive	α-L-iduronidase
Organic aciduria			
Methylmalonicaciduria	1:20,000	Autosomal recessive	Methylmalonyl-CoA mutase, cobalamin metabolism
Propionic aciduria	1:50,000	Autosomal recessive	Propionyl-CoA carboxylase
Peroxisomes			
Zellweger syndrome	1:50,000	Autosomal recessive	Peroxisome membrane protein
Urea cycle			
Ornithine transcarbamylase deficiency	1:70,000	X-linked	Ornithine transcarbamylase

destructive bone disease. Types 2 and 3 Gaucher's disease present with strabismus, bulbar signs, progressive cognitive deterioration, and myoclonic seizures. Treatment options for type 1 Gaucher's disease include regular infusions with recombinant human acid β-glucosidase.

Importance of Early Treatment

Often, empiric therapeutic measures are needed before a definitive diagnosis is available. In a critically ill infant, aggressive treatment before the definitive confirmation of diagnosis is lifesaving and may reduce neurologic sequelae.

Key manifestation	*Key laboratory test*	*Therapy approach*
Mental retardation, acquired microcephaly	Plasma phenylalanine concentration	Diet low in phenylalanine hydroxylase
Acute encephalopathy, metabolic acidosis, mental retardation	Plasma amino acids and urine organic acids Dinitrophenylhydrazine for ketones	Restriction of dietary branched-chain amino acids
Hepatocellular dysfunction, cataracts	Enzyme assays, galactose and galactose 1-phosphate assay, molecular assay	Lactose-free diet
Hypoglycemia, lactic acidosis, ketosis	Liver biopsy enzyme assay	Corn starch and continuous overnight feeds
Nonketotic hypoglycemia, acute encephalopathy, coma, sudden infant death	Urine organic acids, acylcarnitines, gene test	Avoid hypoglycemia, avoid fasting
Hypotonia, psychomotor retardation, failure to thrive, seizures, lactic acidosis	Plasma lactate Skin fibroblast culture for enzyme assay	Correct acidosis; high-fat, low-carbohydrate diet
Coarse facial features, hepatosplenomegaly	Leukocyte β-glucocere-brosidase assay	Enzyme therapy, bone marrow transplant
Acroparesthesias, angiokeratomas hypohidrosis, corneal opacities, renal insufficiency	Leukocyte α-galactosidase A assay	Enzyme replacement therapy
Coarse facial features, hepatosplenomegaly	Urine mucopolysaccharides Leukocyte α-L-iduronidase assay	Bone marrow transplant
Acute encephalopathy, metabolic acidosis, hyperammonemia	Urine organic acids Skin fibroblasts for enzyme assay	Sodium bicarbonate, carnitine, vitamin B_{12}, low-protein diet, liver transplant
Metabolic acidosis, hyperammonemia	Urine organic acids	Dialysis, bicarbonate, sodium benzoate, carnitine, low-protein diet, liver transplant
Hypotonia, seizures, liver dysfunction	Plasma very-long-chain fatty acids	No specific treatment available
Acute encephalopathy	Plasma ammonia, plasma amino acids Urine orotic acid Liver (biopsy) enzyme concentration	Sodium benzoate, arginine, low-protein diet, essential amino acids; dialysis in acute stage

Infants with a treatable organic acidemia (e.g., methylmalonicacidemia) may respond to 1 mg of intramuscular vitamin B_{12}. Metabolic acidosis should be treated aggressively with sodium bicarbonate. Seizures in infancy should be treated initially with traditional antiepileptic drugs, but patients with rare inborn errors of metabolism may respond to other treatments (e.g., oral pyridoxine in a dosage of 5 mg per kg per day) if rare disorders such as pyridoxine-dependent epilepsy are clinically suspected by the consulting neurologist.

Long-term Treatment

Traditional therapies for metabolic diseases include dietary therapy such as protein restriction, avoidance of fasting, or cofactor supplements *(Table 4)*. Evolving therapies include organ transplantation and enzyme replacement. Efforts to provide treatment through somatic gene therapy are in early stages, but there is hope that this approach will provide additional therapeutic possibilities. Even when no effective therapy exists or when an infant dies from a metabolic disorder, the family still needs an accurate diagnosis for clarification, reassurance, genetic counseling, and potential prenatal screening. Additional resources, including information about regional biochemical genetic consultation services, are available online.[13-15]

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The authors thank Amy E. Wolf for her assistance in manuscript preparation.

Author disclosure: Nothing to disclose.

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