

# Inborn Errors of Metabolism (Metabolic Disorders)

Gregory M. Rice, MD,\* Robert D. Steiner, MD\*†

\*Department of Pediatrics and the Waisman Center, University of Wisconsin School of Medicine and Public Health, Madison, WI.

†Marshfield Clinic Research Foundation, Marshfield, WI.

## Educational Gaps

1. Clinicians should be able to recognize the proper metabolic laboratory testing to evaluate for a suspected inborn error of metabolism.
2. Clinicians should recognize the common presentations and treatments of inborn errors of metabolism.

## OBJECTIVES After completing this article, readers should be able to:

1. Use basic and specific laboratory tests to aid in the diagnosis of metabolic disease.
2. Understand the capabilities and limitations of modern newborn screening approaches.
3. Recognize that urea cycle disorders can result in hyperammonemia, which is a medical emergency that requires prompt diagnosis and treatment.
4. Develop a basic framework for understanding inborn errors of metabolism to aid in recognition and diagnosis of these conditions.
5. Appreciate that although most classic metabolic disorders present in infancy, most conditions can also present with milder variants later in life.

## INTRODUCTION

Metabolic disorders can appear to be a frustratingly complex group of disorders to master. Many individual disorders have clinical presentations that initially seem very similar to one another. In addition, classification systems can be difficult to apply because of the multitude and variety of metabolic pathways involved. This review serves as an update of previously published information (1)(2)(3) and attempts to impose a basic classification framework and diagnostic approach that can be applied by the general pediatrician or primary pediatric clinician in the initial triage and identification of metabolic diseases.

**AUTHOR DISCLOSURE** Dr Rice has disclosed that he is a site principal investigator for BioMarin Pharmaceutical and that he is a collaborator on and receives support from FDA grant R01 FD003711-01A1. Dr Steiner has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

The classification groups disorders into those caused by defects in the metabolism of energy sources (lipids, proteins, or carbohydrate) and those caused by dysfunction in pathways within cellular organelles (mitochondria, peroxisome, lysosome). Metabolic disorders caused by defects in protein metabolism include the amino acidopathies, organic acidemias, and urea cycle disorders. Disorders of lipid metabolism encompass defects in fatty acid  $\beta$ -oxidation and the carnitine shuttle. Carbohydrate disorders include galactosemia and glycogen storage disorders (GSDs) among others.

Lysosomal storage disorders are due to an inability to digest or recycle large complex macromolecules and may present with variable features, depending on the enzymatic block, that may include “coarse” facial features, hepatosplenomegaly, and developmental regression.

Energy source problems include defects in protein, lipid, and carbohydrate metabolism (Table). Many of these disorders can be detected in modern newborn screening (NBS) programs. In fact, with the addition of tandem mass spectrometry (which includes acylcarnitine profile and amino acid

TABLE. Summary of Clinical Features and Treatment of Disorders of Energy Sources

	<b>FATTY ACID OXIDATION DISORDERS</b>	<b>ORGANIC ACIDEMIAS</b>	<b>AMINOACIDOPATHIES</b>	<b>UREA CYCLE DISORDERS</b>
Metabolism	<b>Fat</b> Defect in $\beta$ -oxidation of fatty acids.	<b>Protein</b> Defect in amino acid breakdown leads to accumulation of organic acid byproducts	<b>Protein</b> Defect in amino acid breakdown leads to accumulation of certain intact amino acids	<b>Protein</b> Defect in making urea (blood urea nitrogen) from ammonia that results from amino acid breakdown
Disorders	Medium-chain acyl CoA dehydrogenase Long-chain 3-hydroxy acyl CoA dehydrogenase Very long-chain acyl CoA dehydrogenase	Propionic  Methylmalonic  Isovaleric	Maple syrup urine  Phenylketonuria  Homocystinuria tyrosinemia	Ornithine transcarbamylase (X-linked) Citrullinemia  Arginosuccinic aciduria
Presentation	<b>Hypoketotic Hypoglycemia</b>  Lethargy, vomiting Sudden infant death syndrome, Reye syndrome Long-chain disorders have cardiomyopathy and rhabdomyolysis	<b>Metabolic Acidosis With Anion Gap</b>  Neonatal lethargy, vomiting, coma, strokes, death	<b>No Acidosis or Hyperammonemia</b>  Elevations in specific amino acids See text for clinical features	<b>Hyperammonemia Without Acidosis</b>  Neonatal lethargy, vomiting, coma, death
Laboratory Tests	Newborn Screen  <b>Plasma acylcarnitines</b> Hypoglycemia No or inappropriately low ketones	Newborn Screen  <b>Urine organic acids</b> Plasma acylcarnitines	Newborn Screen  <b>Plasma amino acids</b>	Newborn Screen (not for ornithine transcarbamylase) <b>Hyperammonemia</b> <b>Plasma amino acids</b> <b>Urine orotic acid</b>
Acute Treatment	Dextrose (10% with salt) Early use of fluids to prevent hypoglycemia	Dextrose (10% with salt) Early use of fluids No protein Intravenous lipid emulsion Dialysis may be needed in sick neonate	For maple syrup urine disease, similar to organic acidemias Avoid hyponatremia	Dextrose (10% with salt) Early use of fluids Sodium benzoate/phenylacetate Arginine Dialysis
Chronic Management	Low-fat diet Avoid prolonged fasts Nighttime feedings when sick Carnitine Echocardiography for long-chain fatty acid oxidation disorders	Low-protein diet Supplemental medical food Carnitine Liver transplantation	Restrict offending amino acid Supplemental food Monitor plasma amino acids	Low-protein diet Supplemental food Phenylbutyrate Arginine/citrulline Liver transplantation

analysis), more than 40 disorders of intermediate metabolism can now be detected. Because many of these conditions are treatable, their early detection and diagnosis can be lifesaving. Of note, no test has perfect sensitivity, and although NBS has excellent detection rates for many conditions, individuals can be missed. Further, milder presentations of classically severe metabolic disorders can present later in life. Therefore, the clinician must continue to include these disorders in the differential diagnosis of a sick child, despite advances in NBS. Many of the conditions related to defects in energy sources can be detected by several simple laboratory tests.

## BASIC LABORATORY EVALUATIONS

1. Electrolyte panel, including bicarbonate. This simple test, which is available in all hospitals and many outpatient settings, allows for the evaluation of acid-base status to determine the anion gap. Metabolic acidosis with an elevated anion gap is seen in the organic acidemias such as propionic acidemia.
2. Blood glucose. All children with changes in mental status and acute illness should have blood glucose measured. Hypoketotic hypoglycemia (HKHG) is the primary metabolic derangement in disorders of fatty acid oxidation.
3. Ammonia. Elevated ammonia concentrations can cause acute encephalopathy. In some cases, elevated plasma ammonia may be the only clue to the presence of a metabolic disorder. Hyperammonemia requires emergent intervention because a lack of treatment can result in permanent brain injury and death. Metabolically, hyperammonemia is seen primarily with urea cycle disorders and organic acidemias. In the absence of suspicion that prompts testing, hyperammonemia can be easy to miss because ammonia testing is not part of routine chemistry panels, often there is no acidosis, and there may be no clues other than clinical status (eg, lethargy, obtundation, and coma). Ammonia values may be spuriously elevated due to venous compression from tourniquet use or improper specimen handling. It is important to obtain a free-flowing sample when possible. Also, the specimen should be placed on ice at the bedside and immediately transported to the laboratory. Elevated values should be rapidly confirmed by a repeat specimen. Hyperammonemia is a medical emergency that requires the laboratory to test the sample immediately upon receipt. Whenever a result is not available within 1 hour, the accuracy of the result should be questioned because

this could indicate that the sample sat before analysis, which could lead to spuriously elevated values.

4. Urine ketones. Ketosis/ketonuria is a prominent feature of some metabolic disorders, such as organic acidemias. Fatty acid oxidation disorders (FAOD) and hyperinsulinism cause hypoketotic hypoglycemia.
5. Lactate. Elevated lactate is most commonly a marker of hypoxia and poor tissue perfusion. However, mitochondrial disorders are often associated with elevated blood or cerebrospinal fluid lactate in an elevated ratio to pyruvate ( $>20$ ).

## SPECIFIC BIOCHEMICAL LABORATORY EVALUATIONS

1. Plasma amino acids (PAA). Specific elevations or characteristic patterns in amino acids are seen in amino acidopathies such as phenylketonuria (PKU), tyrosinemia, maple syrup urine disease (MSUD), and several of the urea cycle disorders (eg, citrullinemia, argininosuccinic aciduria). Also, some organic acidemias are characterized by elevations in the amino acid glycine.
2. Urine organic acids (UOA): Organic acidemias can be diagnosed by characteristic patterns of elevated organic acid metabolites in the urine, but this test can also be used to support the diagnosis of other types of disorders, such as FAOD and amino acidopathies. The UOA test is most sensitive when performed while the patient is in a catabolic state, such as fasting or illness.
3. Plasma acylcarnitine (PAC) profile: This profile can be helpful in the diagnosis of FAOD, and characteristic patterns are seen for most organic acidemias. The PAC profiles carbon chains linked (esterified) to carnitine. C<sub>2</sub>-C<sub>18</sub> (chains with 2-18 carbon backbones) acylcarnitines are quantified in this assay and can indicate specific conditions. For example, elevations in medium-chain acylcarnitines (C<sub>6</sub>-C<sub>10</sub>) are indicative of medium-chain acyl CoA dehydrogenase (MCAD) deficiency, whereas elevations in the 3- or 5-carbon acylcarnitines (C<sub>3</sub> or C<sub>5</sub> acylcarnitines) are seen in some organic acidemias. The PAC profile has allowed for detection of most FAOD and organic acidemias on a single plasma sample or blood spot, which has revolutionized metabolic disease diagnosis and newborn screening.
4. Carnitine analysis: This test evaluates the concentrations of free and total carnitine and carnitine esters (unfractionated acylcarnitines) in the plasma or urine. Markedly low plasma free carnitine values can be seen in primary carnitine deficiency, a treatable disorder of carnitine uptake. Elevated carnitine esters (acylcarnitines) can

occur in any metabolic disorder that results in accumulation of acylcarnitines (organic acidemias, FOADs, and ketosis). Plasma carnitine values are usually more helpful than urine values.

5. Newborn screening: Many disorders of intermediate metabolism are detected by tandem mass spectrometry (acylcarnitine profile and amino acid analysis) on newborn dried blood spots, including most FAOD, some urea cycle disorders (citrullinemia and argininosuccinic aciduria), and the amino acidopathies. In addition, enzymology or specific analyte analysis (eg, galactose 1-phosphate) allows for detection of galactosemia and biotinidase deficiencies. As with any screening test, false-negative results can occur, and some disorders, such as ornithine transcarbamylase (OTC) deficiency, are not currently part of the screen. Therefore, clinicians should still consider the possibility of metabolic disorders, even in the context of a negative NBS result.

Some states have begun screening for lysosomal disorders, including Pompe disease, and there is ongoing discussion about adding other lysosomal conditions in the future. The National Newborn Screening & Global Resource Center website (<http://genes-r-us.uthscsa.edu>) provides a complete list of conditions screened in each state, and the Screening, Technology and Research in Genetics (STAR-G) Project (<http://www.newbornscreening.info>) offers detailed clinician and parental handouts on each condition.

## PROTEIN METABOLISM DISORDERS

These disorders include amino acidopathies, organic acidemias, and urea cycle disorders. When most amino acids are metabolized, the initial step is deamination, which removes the amine group and leaves ammonia and an organic acid. If an enzymatic block occurs in this initial step, that particular amino acid accumulates in the blood and urine. PKU is one example of such a block in which phenylalanine accumulates. If the block is in metabolism of the residual organic acid, the offending organic acid accumulates and an organic acidemia ensues. Finally, if the block is in the urea cycle, ammonia cannot be metabolized to urea and excreted, resulting in hyperammonemia. Laboratory diagnosis of these conditions relies primarily on three tests: plasma ammonia (NH<sub>4</sub>), PAA, analysis, and UOA analysis. Urine amino acids (UAA) analysis is sometimes useful as an ancillary test.

### Amino Acidopathies

Amino acidopathies are autosomal recessive genetic conditions resulting from an enzymatic block that prevents metabolism of specific amino acids (Figure), which leads

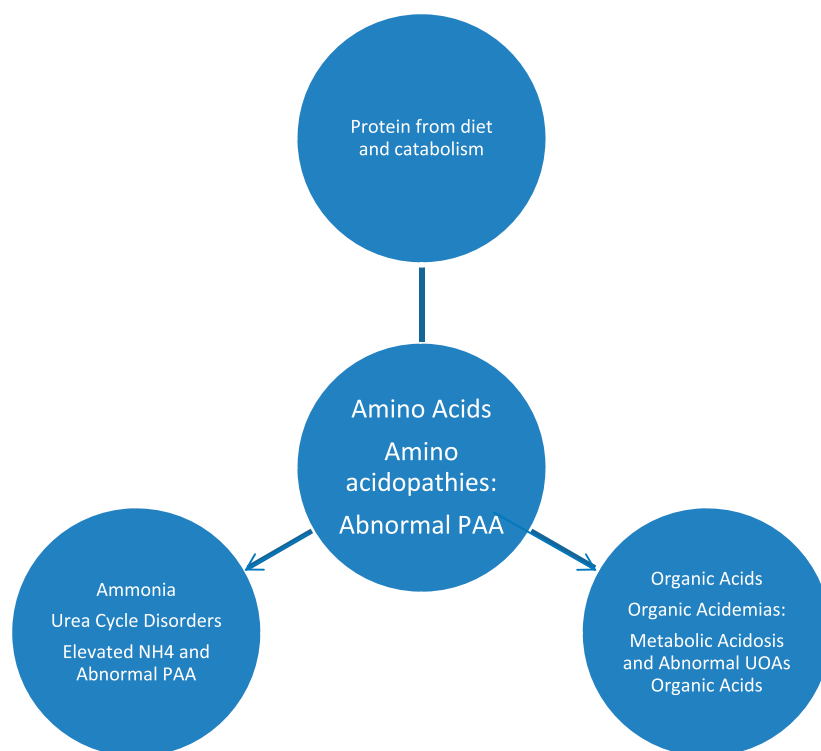
to their accumulation in the blood and urine. This is a heterogeneous group of disorders because the various amino acids have very different toxic and pathogenic effects on varying tissues. All can be diagnosed with the combination of PAA and UOA analysis.

**Phenylketonuria.** PKU is due to a deficiency in phenylalanine hydroxylase (PAH), the enzyme responsible for hydroxylation of phenylalanine (phe) to tyrosine. Tetrahydrobiopterin (BH<sub>4</sub>) is a required cofactor in this reaction. Population-based NBS for PKU is performed in all states in the United States via tandem mass spectrometry, which shows elevated concentrations of phe and low tyrosine. Subsequent diagnostic testing reveals elevated phe on PAA analysis and elevated phenylketones on UOA. When PKU is untreated, phe and phenylketones silently accumulate, causing permanent brain injury. Untreated infants develop microcephaly, global developmental delay, and eczematous rash. Early detection and treatment are very effective in preventing intellectual disability, but adults who stop the diet are still at risk for mood and cognitive disorders, including diminished executive function. (4) Therefore, lifelong treatment is advocated. Phe is a powerful teratogen; fetal exposure to increased concentrations in utero may result in “maternal PKU syndrome,” which consists of dysmorphic facial characteristics, microcephaly, intrauterine growth restriction, and congenital heart disease. Exposed children may have intellectual disability or learning disabilities. Therefore, women who have PKU should attempt to have their phe concentrations well-controlled before pregnancy and must maintain strict control of such concentrations throughout the duration of pregnancy. This can be difficult to achieve if the pregnancy is unexpected or the prospective mother has been off the PKU diet. Accordingly, preconception counseling is imperative.

Treatment of PKU requires strict lifelong restriction of phe via dietary protein restriction and supplementation with phe-free protein-containing medical foods/beverages to prevent protein deficiency. Blood phe concentrations must be monitored regularly and dietary protein intake adjusted accordingly. BH<sub>4</sub> supplementation is a relatively new therapy that has variable efficacy; it helps to lower plasma phe concentrations in some patients but usually does not replace the low-phe diet.

A small number of patients who have abnormal NBS results indicating elevated phe have a more severe disorder that is due to a defect in BH<sub>4</sub> metabolism rather than PAH deficiency. Phe is only mildly elevated in these patients, but they develop dystonia due to central dopamine deficiency. Treatment consists of dopamine and biopterin supplementation as well as more complex therapeutic strategies.

**Figure.** Simplified metabolism of protein to ammonia and organic acids. PAA=plasma amino acids, NH<sub>4</sub>=ammonia, UOA=urine organic acids



**Maple Syrup Urine Disease.** MSUD is due to a deficiency in the enzyme branched-chain  $\alpha$ -ketoacid dehydrogenase, which catalyzes the second step in metabolism of the branched-chain amino acids (BCAAs) isoleucine, valine, and leucine. The condition affects all ethnic groups but is most common among the Old Order Mennonites. In the United States, all states screen for MSUD by tandem mass spectrometry. Diagnostic testing shows elevated valine, isoleucine, leucine, and allo-isoleucine on PAA analysis and characteristic organic acids on UOA analysis. The severe form of MSUD often presents within the first postnatal week. The neonate frequently has diminished arousal and feeds poorly; if treatment is not initiated quickly, hypertonicity, coma, and death occur within hours. High leucine concentrations cause these effects.

Patients with MSUD may have little evidence of metabolic acidosis or ketosis during an acute episode. Cerumen and urine may smell like maple syrup, but only when leucine is markedly elevated. Therefore, this finding should not be relied on for screening. Affected patients develop acute episodes of metabolic decompensation associated with high leucine intake or catabolic stressors (febrile illness, prolonged fasting) throughout life. Affected patients are well between episodes, but when leucine concentrations rise, they develop headache, confusion, hallucinations, lethargy, and vomiting, which progress to coma and death

without treatment. Acute metabolic decompensation is related to the neurotoxic and osmotic effects of hyperleucinemia; interestingly, valine and isoleucine are not neurotoxic.

Management during an episode of decompensation includes: stopping all leucine intake, administering high-dextrose content isotonic intravenous fluids and intravenous lipid emulsion, and providing leucine-free nasogastric/gastrostomy feedings. (5) BCAA-free parenteral nutrition can be ordered from specialty pharmacies and allows for the delivery of protein without leucine. Patients with MSUD should never receive hypotonic fluids because cerebral edema in these patients can be fatal. Rapid reductions in serum osmolality must be strictly avoided, and serum sodium concentrations should be maintained in the high-normal range. In some cases, hypertonic saline and mannitol are indicated to prevent hyponatremia and resultant cerebral edema. Dialysis has been employed as an emergency rescue therapy, but proper and aggressive metabolic therapy can obviate the need for dialysis.

Management of hyperleucinemia is complex and requires admission to the pediatric intensive care unit and the involvement of a metabolic expert familiar with the acute management of MSUD. Chronic management involves strict dietary restriction of leucine. Early identification via NBS before the initial episode and tight lifelong metabolic control result in good outcomes, although unexpected late and devastating

attacks may occur throughout life. Liver transplantation has been an effective option for some patients and can help to prevent recurrent metabolic decompensations. (6)

A milder, intermittent form of MSUD exists in which patients have recurrent episodes of altered mental status due to hyperleucinemia associated with illness or excessive protein intake. Between episodes they are well and may have normal PAA analysis results.

**Homocystinuria.** Classic homocystinuria is caused by a deficiency in cystathionine  $\beta$ -synthetase. Laboratory testing shows marked elevations of homocystine in the blood and urine and methionine elevations on NBS and PAA. The condition is not associated with acute metabolic decompensation but may result in intellectual disability, tall stature, osteoporosis, recurrent thrombosis, and ectopia lentis (lens dislocation). Homocystinuria may be considered in the differential diagnosis of Marfan syndrome. A minority of patients responds to pyridoxine (vitamin B6), and a trial of high-dose vitamin B6 should be given if this is a possibility. Management includes betaine, which helps to decrease plasma homocystine concentrations, and aspirin to prevent stroke. Dietary methionine restriction and B vitamin supplements are also used.

**Tyrosinemia.** Hepatorenal tyrosinemia (also known as tyrosinemia type 1) is due to a defect in the enzyme fumarylacetoacetase (FAH). This deficiency results in accumulation of blood tyrosine and urine succinylacetone, elevation of which is pathognomonic for the condition. NBS involves the detection of succinylacetone by tandem mass spectrometry. Blood tyrosine may also be elevated on NBS dried blood spots, but this test lacks sensitivity and specificity for the condition because infants may have elevated tyrosine concentrations related to hepatic immaturity or other milder forms of tyrosinemia. In addition, normal tyrosine values can be seen in infants who have hepatorenal tyrosinemia in the newborn period. Plasma methionine is often more dramatically elevated than tyrosine, and elevations in both are likely due to secondary liver disease rather than the specific enzyme deficiency. Confirmation of the condition relies on UOA with a specific request for succinylacetone and PAA for elevated tyrosine and methionine. DNA testing of the FAH gene can be helpful in confirmation.

When untreated, hepatorenal tyrosinemia typically results in liver failure during infancy or early childhood. Renal tubular acidosis and recurrent episodes of neuropathic pain can also occur. Nitrofurantoin, along with dietary tyrosine restriction, is an effective treatment and may obviate the need for liver transplantation.

**Hyperglycinemia.** Another amino acidopathy is nonketotic hyperglycinemia, a typically lethal deficiency in glycine

cleavage that results in elevated cerebrospinal fluid glycine leading to neonatal seizures, hiccups, and apnea.

### Organic Acidemias

Organic acids are the deaminated remains of amino acids. Defects in their degradation result in their massive accumulation in the blood and urine, leading to metabolic acidosis. Affected infants develop poor feeding, tachypnea, vomiting, and lethargy in the first few days after birth. NBS is helpful in identifying some neonates before the initial episode, but others may present in crisis before NBS results become available. NBS identifies elevated odd-chain acylcarnitine (C<sub>3</sub> or C<sub>5</sub> acylcarnitines) species by tandem mass spectrometry. An organic acidemia is clinically suggested by metabolic acidosis with an elevated anion gap. Confirmation of disease is based on UOA analysis, which reveals a characteristic pattern of abnormal organic acids, and acylcarnitine profile and carnitine analysis are helpful. All of the common organic acidemias are inherited in an autosomal recessive pattern.

Treatment during an episode includes stopping all protein intake, administering high-dose carnitine supplements, and promoting an anabolic state with dextrose-containing fluids (10% dextrose in normal saline), intravenous lipid emulsions, and in some cases, insulin. Intravenous bicarbonate to correct the acidosis is often necessary. Some defects are partially or completely amenable to cofactor therapy with vitamins (eg, biotin for biotinidase deficiency and vitamin B<sub>12</sub> for some forms of methylmalonic acidemia). The profoundly ill child with an organic acidemia may require hemodialysis, which can be lifesaving, particularly to correct profound metabolic acidosis or hyperammonemia. Long-term treatment requires restriction of the offending amino acids via protein restriction and supplementation with metabolic formulas. Carnitine and cofactor supplementation are also given. Some minor illness can be managed at home with use of a sick day protocol, which often includes monitoring of urine ketones, decreased dietary protein intake, increased dietary calorie intake, and a local emergency department triage plan.

**Propionic Acidemia.** Propionic acidemia is caused by a defect in the enzyme propionyl CoA carboxylase, which leads to abnormal metabolism of isoleucine, valine, methionine, and threonine. UOA analysis shows elevated 3-OH propionic acid and methylcitrate, plasma acylcarnitines and NBS show an elevated C<sub>3</sub> acylcarnitine, and PAA analysis may show elevated glycine. Classically, patients present in the newborn period with overwhelming metabolic acidosis with a high anion gap. The newborn may have prominent ketosis, which is an otherwise rare feature in the first

postnatal weeks. Ammonia concentrations may be markedly elevated, but the presence of profound metabolic acidosis makes this condition easy to distinguish from urea cycle disorders. Low blood pH can lead to multiorgan dysfunction, including cardiac and respiratory failure. Pancytopenia and pancreatitis can occur during an episode. Brain injury, including stroke, often accompanies severe metabolic decompensations, which can lead to permanent intellectual disability or movement disorders. Recurrent episodes of metabolic acidosis and decompensation can occur with illness, fasting, or excessive protein intake. Elevated urine ketones are an early sign of metabolic crisis. Liver transplantation may decrease the frequency of recurrent metabolic crisis. Late-onset cardiomyopathy and cardiac dysrhythmia are being increasingly recognized. (7)

**Methylmalonic Acidemia.** Classically, methylmalonic acidemia is due to a deficiency in the enzyme methylmalonyl CoA mutase, which is the step immediately following propionyl CoA carboxylase in the metabolism of isoleucine, valine, methionine, and threonine. Methylmalonic acidemias can also be due to several defects in cobalamin (vitamin B<sub>12</sub>) metabolism, some of which also cause elevations in homocysteine. In the classic form, this condition presents in the newborn period similarly to propionic acidemia, with acidosis, ketosis, and hyperammonemia. UOA analysis shows elevated methylmalonic acid (MMA) and methylcitrate; plasma acylcarnitines and NBS show elevated C<sub>3</sub> acylcarnitine. Plasma alanine and glycine values are often elevated on PAA testing, and a specific, widely available test is plasma MMA, which shows marked elevations.

Metabolic crisis can cause stroke, resultant intellectual disability, and movement disorder. Many patients have recurrent episodes of metabolic acidosis due to illness, catabolic stress, or excessive protein intake throughout life. Late-onset complications include renal disease, which often necessitates transplantation in adolescence or adulthood. Milder variants of methylmalonic acidemia also exist, some of which may present in adulthood. Specifics of management depend on the enzyme defect. They generally include dietary restriction of the offending amino acids; administration of vitamin B<sub>12</sub> with specific form, dosing, and route of administration; and administration of carnitine. Organ transplantation can be very effective, as in many other inborn errors of metabolism. In this case, liver or combined liver and kidney transplantation is undertaken.

**Glutaric Acidemia.** Glutaric acidemia type I (GA<sub>I</sub>) is due to a defect in enzyme glutaryl CoA dehydrogenase, which is involved in the metabolism of the amino acids tryptophan and lysine. The condition is more common in Amish individuals but can occur in any ethnic group. GA<sub>I</sub> is a

severe “cerebral” organic acidemia, and in contrast to other organic acidemias, metabolic acidosis, ketosis, and hyperammonemia may not be present during an acute episode. Unfortunately, there is no easily obtainable marker of metabolic decompensation in this condition; initiation of metabolic care is based on results of the child’s physical examination and history. Patients have been known to develop permanent basal ganglia injury and resulting movement disorder following a fever associated with a mild illness. Therefore, the aggressive use of dextrose-containing fluids is indicated for any febrile illness.

GA<sub>I</sub> is a target of NBS, which shows elevated plasma C<sub>5</sub> dicarboxylic (C<sub>5</sub>DC) acylcarnitine in most affected individuals. Diagnostic testing may show elevated urine glutaric and 3-OH glutaric acid on UOA analysis, and C<sub>5</sub>DC acylcarnitine may be elevated on plasma or urine acylcarnitine analysis. Some affected patients, known as “low excretors,” have normal blood and urine metabolite testing results, which can make diagnosis challenging. DNA testing of the *GCDH* gene can be helpful in establishing a diagnosis in these patients.

Clinically, affected children often exhibit macrocephaly but are well until a catabolic crisis occurs. A febrile illness can be neurologically devastating, resulting in dystonia and movement disorders. Neuroimaging may reveal basal ganglia injury in the survivors of a crisis. Subdural hematomas can occur and have been mistaken for child abuse.

Chronic management consists of carnitine supplementation and dietary lysine and tryptophan restriction, but perhaps most important is avoidance of catabolism during routine illnesses by administration of glucose-containing fluids. Aggressive sick day management with dextrose-containing fluids can prevent the neurologic sequelae. The prognosis is excellent for children who avoid brain injury until age 6 years because GA<sub>I</sub> is unlikely to result in permanent brain injury after this age. (8)(9)

**Other Organic Acidemias.** Other organic acidemias screened for on NBS and diagnosable on UOA analysis include isovaleric acidemia and biotinidase deficiency.

## Urea Cycle Disorders

**Hyperammonemia.** The urea cycle disposes of toxic ammonia from the deamination of amino acids by converting it to nontoxic urea for renal excretion. If the urea cycle is dysfunctional, ammonia accumulates in the blood, leading to altered mental status, lethargy, vomiting, cerebral edema, and ultimately coma and death. Hyperammonemic encephalopathy can be rapidly fatal and is a medical emergency. Unlike the organic acidemias, severe metabolic acidosis is not a prominent finding; some ill patients have mild

acidosis related to dehydration and shock. Prolonged fasting and moderate illness with poor oral intake or fever can provoke a hyperammonemic crisis due to catabolism and increased proteolysis. Similarly, excessive protein intake results in increased production of ammonia and resultant encephalopathy. Severe forms may present in the first hours after birth. Recurrent unrecognized episodes can lead to global developmental delay, spasticity, and intellectual disability. Milder forms may present later in life with failure to thrive, developmental delay, and recurrent vomiting or protein aversion. Any child with unexplained acute encephalopathy, recurrent episodes of lethargy and vomiting, or failure to thrive with protein aversion should have ammonia measured. This might be the only marker of the disease. Evaluation for hyperammonemia includes liver function tests, electrolytes, UOA analysis (for orotic acid), and PAA analysis. Hyperammonemia can also result from valproic acid administration or liver dysfunction, so patients should be evaluated for these conditions as well.

Treatment of hyperammonemic encephalopathy must be implemented immediately and includes cessation of protein intake and reduction of catabolic stress. Intravenous 10% dextrose in normal saline and an intravenous lipid emulsion infusion should be started to provide protein-free energy. Central venous access should be established for the delivery of arginine hydrochloride with sodium phenylacetate and sodium benzoate once hyperammonemia is confirmed. This treatment should always be supervised by a metabolic disease specialist. Care should be taken to avoid hyponatremia, which can increase the risk of developing cerebral edema. Infants whose initial presentation is severe hyperammonemia may require hemodialysis, and the time spent in coma correlates with outcome, so preparation for dialysis should begin immediately upon diagnosis in infants. Long-term treatment includes dietary protein restriction, arginine or citrulline supplementation (depending on the deficiency), sodium or glycerol phenylbutyrate, and sick day management with an emergency department protocol. Liver transplantation reduces episodes of recurrent hyperammonemia. (10)

**Ornithine Transcarbamylase Deficiency.** OTC deficiency results in recurrent episodes of hyperammonemia associated with catabolic stress (illness, fasting, labor and delivery) or excessive protein intake. This condition is not universally screened for in newborns; a negative NBS result in most states does not rule out this condition. Testing during a catabolic episode reveals elevated plasma ammonia, and PAA analysis often shows elevated glutamine (a storage form of ammonia) with decreased citrulline and arginine. UOA analysis in affected males documents elevated orotic

acid, although this test result may be negative in well-compensated males and many female heterozygotes. When ordering UOA for patients in whom OTC deficiency is suspected, clinicians should specify that orotic acid identification is desired. DNA testing of the OTC gene confirms the diagnosis. Even though this is an X-linked condition, females can be affected, with a range from severe disease to asymptomatic. Some female heterozygotes and mildly affected males choose to avoid high-protein foods, likely due to the accumulation of toxic ammonia, which may result in failure to thrive during childhood. Female heterozygotes may also present with hyperammonemia during the immediate postpartum period when the protein turnover from involution of the uterus and the catabolic stress of delivery is high.

Long-term treatment typically includes citrulline supplementation, dietary protein restriction, and oral sodium or glycerol phenylbutyrate. Liver transplant is effective in preventing recurrent episodes of hyperammonemia. (8)

**Other Urea Cycle Disorders.** Other urea cycle disorders include citrullinemia, argininosuccinic aciduria, and carbamyl phosphate synthetase 1 (CPS 1) deficiencies, all of which are autosomal recessive and present with recurrent episodes of hyperammonemia. CPS 1 is not associated with elevated urine orotic acid. All United States states perform NBS for citrullinemia and argininosuccinic aciduria.

## LIPID METABOLISM DISORDERS

### Fatty Acid Oxidation Disorders

FAOD are caused by defects in the  $\beta$ -oxidation of fatty acids or derangement of carnitine metabolism. The key clinical feature of these disorders is a propensity to HKHG with prolonged fasting. During fasting, blood glucose from a recent meal is used, followed by breakdown of hepatic glycogen stores to maintain normal blood glucose concentrations. As glycogen becomes depleted, gluconeogenesis (GNG) is initiated to maintain normal blood glucose concentrations. GNG receives the energy for glucose biosynthesis from oxidation of fatty acids. Patients with FAOD cannot fully metabolize fatty acids and, therefore, cannot release their stored energy. Further, production of free acetyl CoA required for manufacture of ketone bodies is diminished, which leads to HKHG.

If FAOD are undiagnosed, the first hypoglycemic episode may occur in infancy or early childhood when the child has a prolonged fast in the context of an intercurrent illness. The presenting sign may be sudden death or severe HKHG, resulting in brain injury and seizure. The brain is particularly sensitive to HKHG because it relies on ketone body



utilization for energy during times of hypoglycemia. NBS has allowed for diagnosis before the initial episode in most cases, thereby prompting treatment and parental education, with the goal of preventing brain injury and disability.

The treatment of FAOD includes parental education to avoid prolonged fasting, particularly during an illness, and the use of intravenous dextrose-containing fluids to prevent hypoglycemia if the child cannot feed well due to illness or injury. An emergency department protocol outlining the condition and treatment should be given to all families of affected children. Supplemental carnitine may be prescribed. Long-chain FAOD (LCFAOD) are also associated with cardiomyopathy and recurrent rhabdomyolysis. All forms of FAOD have an autosomal recessive inheritance.

**Medium-chain Acyl CoA Dehydrogenase (MCAD) Deficiency.** The MCAD enzyme breaks down medium-chain fatty acids to short-chain fatty acids and acetyl CoA, which can be used to provide energy for GNG and ketone body formation. Prolonged fasting during an intercurrent illness triggers hypoglycemic episodes. During an illness with poor oral intake, a child's liver glycogen is depleted. When a prolonged fast is superimposed on this state, GNG cannot maintain adequate blood glucose concentrations due to defective  $\beta$ -oxidation of fatty acids. Children develop normally, but an unprevented initial episode of HKHG may result in sudden death or permanent brain injury. The clinical presentation of MCAD deficiency is related to the effects of HKHG and includes altered mental status, lethargy, and ultimately seizure and death.

MCAD deficiency is the most common of the FAOD and is typically found on NBS by blood spot acylcarnitine analysis, a diagnosis that occurs before the onset of the first episode. However, some infants present on the second or third postnatal day, which is too early for NBS to be helpful. NBS and confirmatory diagnostic PAC profile shows elevated C6, C8, and C10 acylcarnitines. UOA testing may show elevated hexanoylglycine and suberylglycine.

Parental education about avoiding fasting during intercurrent illness is the most important intervention. Many children receive carnitine supplementation. Patients are given emergency department protocols that explain the condition and treatment. If children avoid HKHG episodes during the first several years after birth, normal development is expected and the prognosis is excellent.

**Long-chain Fatty Acid Oxidation Disorders.** LCFAOD include very-long-chain acyl CoA dehydrogenase (VLCAD) and long-chain 3-hydroxy acyl CoA dehydrogenase (LCHAD) deficiencies. LCFAOD are severe conditions that may result in rhabdomyolysis, cardiomyopathy, liver dysfunction, and recurrent HKHG, even with appropriate treatment. LCHAD

may also result in retinopathy and peripheral neuropathy. Both conditions are screened for in NBS, but the sensitivity of this screening test is not 100%. Therefore, clinicians should remain vigilant for these disorders in children who have suggestive clinical histories, even if NBS results are normal. Diagnosis is by PAC profile, which shows elevated unsaturated long-chain acylcarnitines (C14:1) in VLCAD deficiency and 3-hydroxy-acylcarnitines (C16-OH) in LCHAD deficiency. Because biochemical abnormalities in these disorders (particularly VLCAD) can be minimal or nonexistent when a child is well, DNA testing or enzymology is often required to confirm the diagnosis.

Treatment involves dietary fat restriction and supplementation with medium-chain triglyceride oil to provide the muscle with a usable source of energy from fat. To prevent HKHG, patients must avoid fasting during intercurrent illnesses, similar to MCAD deficiency. Thus, parental education is vital. If a patient is unable to take sufficient energy by mouth, intravenous administration of dextrose-containing fluids should be initiated. Carnitine supplementation is controversial. Regular cardiac evaluations are indicated and creatine kinase (CK) should be followed during illness. Competitive and isometric sports must be restricted for many patients due to recurrent exercise-induced rhabdomyolysis.

**Primary Carnitine Deficiency.** Primary carnitine deficiency is a rare autosomal disorder caused by a defect in the OCTN2 carnitine transporter, which leads to systemic depletion of carnitine due to both diminished intestinal absorption and renal reabsorption. The condition is screened for on NBS, and the diagnosis is based on the finding of markedly low blood free carnitine concentrations with elevated urine carnitine excretion. DNA testing can be used to confirm the diagnosis. Untreated patients develop cardiomyopathy and recurrent episodes of HKHG. Reye-like encephalopathy can occur. Treatment with high-dose oral carnitine supplementation appears to prevent cardiomyopathy.

**Other Fatty Acid Oxidation Disorders.** Other FAOD that are screened for by NBS and can be diagnosed on PAC analysis include carnitine palmitoyltransferase 2 and multiple acyl-CoA dehydrogenase (also known as glutaric acidemia type 2) deficiencies.

## CARBOHYDRATE DISORDERS

Classic galactosemia is due to a deficiency in the enzyme galactose-1-phosphate uridylyltransferase (GALT), which leads to accumulation of galactose and galactose-1-phosphate. The initiation of lactose (glucose and galactose)-based

feedings in the newborn who has galactosemia leads rapidly to metabolic decompensation, with liver dysfunction, jaundice, and coagulopathy. *Escherichia coli* sepsis and cataracts can occur. Because initial symptoms may begin in the first few postnatal days, treatment must begin without delay. Late-diagnosed infants who survive the initial episode of metabolic decomposition often develop intellectual disability. Due to NBS, the natural course of classic galactosemia is rarely observed today, but even with early detection, appropriate treatment, and excellent control, many still develop tremor, specific learning disabilities, and speech/language deficits. Even with early and optimal treatment, most affected females develop ovarian failure, often requiring estrogen replacement in adolescence.

All states currently screen for galactosemia on NBS. Confirmation is via GALT enzyme activity and blood galactose-1-phosphate values. DNA testing can be helpful to look for milder mutations, which are associated with an excellent prognosis, such as the Duarte variant.

Chronic management is based on lifelong dietary restriction of galactose. Such restriction should be initiated immediately upon receipt of abnormal NBS results because treatment delays result in clinical morbidity. Affected school-age children should be screened for speech and learning disabilities.

## GLYCOGEN STORAGE DISORDERS

Glycogen storage disorders (GSDs) result from the inability to degrade stored glycogen in the liver and muscle. Hepatic (GSD I) forms primarily cause fasting hypoglycemia, whereas muscular (GSD V) forms result in recurrent rhabdomyolysis.

GSD type Ia (also known as von Gierke disease) is due to deficiency in the enzyme glucose-6-phosphatase, which results in massive hepatomegaly, growth failure, and recurrent episodes of ketotic hypoglycemia, often presenting in infancy. Patients have elevated lactic and uric acids and triglycerides. Frequent doses of cornstarch or continuous gastrostomy feedings are required to prevent recurrent hypoglycemia. Late complications include malignant transformation of hepatic adenomas, hypertension, and renal insufficiency. GSD type Ib is additionally associated with neutropenia, frequent infections, and inflammatory bowel disease. Treatment can be very successful but requires careful follow-up.

GSD type V (also known as McArdle disease) results from a defect in the enzyme myophosphorylase. Onset is usually in adolescence and is characterized by exercise-induced muscle pain, fatigue, and rhabdomyolysis. Myoglobinuria and resultant renal injury can occur. Muscle pain

and fatigue develop within a few minutes of starting to exercise, followed by a “second wind” phenomenon in which the patient briefly feels better. Patients have markedly elevated CK concentrations following exercise. Diagnosis is often by muscle biopsy, which demonstrates deficient myophosphorylase activity on enzymatic analysis and glycogen accumulation within the myocytes. DNA analysis of the *PYGM* gene may be the best method for diagnosis and obviates the need for biopsy. Avoidance of strenuous aerobic and isometric exercise is recommended. However, the patient should also avoid deconditioning by participating in light aerobic activity as tolerated.

Among the several other important carbohydrate disorders are other GSDs; hereditary fructose intolerance, a condition that results in vomiting and liver dysfunction following ingestion of sucrose or fructose (children often avoid sweets and classically have an absence of dental caries); and glycogen synthase deficiency (GSD 0), a condition that results from the inability to form hepatic glycogen and leads to recurrent ketotic hypoglycemia without hepatomegaly.

## LYSOSOMAL STORAGE DISORDERS

The lysosome is a cellular organelle that digests large complex macromolecules for recycling or degradation. Lysosomal storage disorders are progressive conditions related to the accumulation of these large macromolecules (mucopolysaccharides, sphingolipids, oligosaccharides) within vulnerable tissues. The lysosome can be thought of as a bag of individual enzymes, each dedicated to degradation of a particular macromolecule. When a lysosomal enzyme is deficient, the macromolecule that it normally digests accumulates within the cell, leading to space occupation and cellular dysfunction. Many of these disorders are characterized by progressive involvement of the liver, spleen, brain, or bones related to accumulation of the undigested materials in these tissues. Clinical features are specific to the particular disorder but may include hepatosplenomegaly, bony deformity, developmental regression, sensory loss (hearing and vision), and coarse facial characteristics. Most of these conditions have an autosomal recessive inheritance, except Fabry disease and mucopolysaccharidosis type II (Hunter disease), which are X-linked. Because the conditions can have significant phenotypic overlap, urine metabolite screening tests can be helpful in the initial evaluation. Specifically, urine glycosaminoglycan (GAG) analysis for mucopolysaccharidoses and urine oligosaccharides are useful screening tests for lysosomal disorders. Ultimately, the laboratory diagnosis involves demonstration of enzymatic

deficiency in lymphocytes or fibroblasts and, more recently, DNA testing.

Mucopolysaccharidoses (MPSs) result from the accumulation of polysaccharide-based macromolecules (GAGs) in tissues. Classically, children appear normal at birth and develop progressive symptomatology over subsequent years. Coarsened facial features, bony deformity, developmental regression, and visceromegaly are typical. Diagnosis is initially by urinary GAG analysis and confirmed by enzyme analysis or DNA. Skeletal radiographs may show the characteristic dysostosis multiplex appearance. Several of the disorders now have treatments available, including enzyme replacement therapy (ERT) (MPS I, II, IV, VI), and hematopoietic stem cell transplantation may be therapeutic for some of the disorders that have central nervous system involvement and are not currently amenable to treatment with ERT.

MPS I (Hurler syndrome) involves progressive coarsening of facial features, hepatosplenomegaly, corneal clouding, bony deformity, and developmental regression. Without treatment, the condition is fatal. Due to the efficacy of ERT and hematopoietic stem cell transplantation (HSCT), some have argued for inclusion of this condition on the expanded NBS. MPS II (Hunter syndrome) is similar to MPS I but without corneal clouding. MPS I and II both have milder forms without developmental regression that are amenable to ERT, which does not cross the blood-brain barrier. However, ERT is sometimes used in the severe forms with brain involvement to temporize progression and potentially improve the quality of life. MPS III (Sanfilippo syndrome) is primarily a neurodegenerative condition that results in slow developmental regression, with death often in the second decade of life. The visceral and bony manifestations are less prominent than in other MPS disorders. Children often present with behavioral and attention issues before the onset of motor and cognitive regression. MPS IV differs from the other conditions, with characteristic and often severe bony involvement and short stature. Finally, MPS VI is very similar to MPS I but never has developmental regression.

Tay-Sachs disease is caused by a deficiency in the enzyme  $\beta$ -hexosaminidase A. The enzymatic block results in accumulation of the sphingolipid GM<sub>2</sub> ganglioside in vulnerable tissues. Diagnosis is by DNA analysis of the *HEXA* gene or enzyme assay of  $\beta$ -hexosaminidase A in leukocytes. Tay-Sachs disease is more common in people of Ashkenazi Jewish descent, but it can be seen in any ethnic group. Symptoms usually begin in early infancy with weakness and an exaggerated startle reflex. Myoclonic jerks and developmental regression also occur early in the course of disease. A

funduscopic examination reveals cherry red spots on the maculae of most infants. The disorder progresses quickly, with vision loss, progressive macrocephaly, seizures, spasticity, and unresponsiveness to the environment. Visceromegaly does not occur. There is no effective treatment and Tay-Sachs disease is usually fatal by age 4 years. Carrier screening programs have reduced the incidence among Ashkenazi Jews.

Fabry disease is due to  $\alpha$ -galactosidase deficiency. In males, the condition presents in late childhood or early adolescence with episodes of acroparesthesias (painful hands and feet) or recurrent abdominal pain. Female heterozygotes may also present with abdominal pain in adolescence or early adulthood. Untreated patients develop proteinuria and resultant renal insufficiency, often requiring dialysis and ultimately renal transplantation. Females may develop renal insufficiency on average about 10 years later than males, although some females have few symptoms and may not develop kidney disease. Other associated features include reduced sweating, angiokeratomas of the skin, early atherosclerosis and stroke, and cardiac hypertrophy. Diagnosis can be made by demonstration of low  $\alpha$ -galactosidase enzyme activity in males. DNA testing can also be helpful, particularly in females in whom enzyme testing is not useful because they may show near-normal enzyme activity. ERT is available for treatment.

Gaucher disease type 1 is due to lysosomal  $\beta$ -glucocerebrosidase deficiency. The condition results in massive accumulation of glucocerebroside in the liver, spleen, and bone marrow. Gaucher is more common in individuals of Ashkenazi Jewish descent. Features include anemia and thrombocytopenia due to marrow obliteration and splenic sequestration, hepatosplenomegaly, and bone pain. The brain is not affected, although Parkinsonism has been recently shown to be associated with Gaucher disease. (11) ERT and substrate inhibitors are available for treatment. Neuropathic variants (types 2 and 3) also exist. Type 2 is associated with early onset, rapid, and severe neurodegeneration in childhood, and type 3 is associated with ocular and neuromotor dysfunction, often with severe visceral signs of Gaucher disease in childhood.

Krabbe disease is due to deficiency in the lysosomal enzyme galactosylceramidase. The condition results in infantile neurodegeneration. Infants present in the first few postnatal months with increasing muscle tone and profound irritability. Recurrent fevers without source can be seen. The infant develops seizures, vision loss, and developmental regression, with death often occurring before 12 months of age. Diagnosis is by enzyme assay or DNA analysis. Cerebrospinal fluid protein is often markedly

elevated. HSCT has been used in Krabbe disease with mixed results. Milder, late-onset forms of Krabbe disease also exist.

Pompe disease (GSD II) is due to a deficiency in the enzyme acid  $\alpha$ -glucosidase (GAA) that results in accumulation of glycogen in the lysosome of muscle cells. Classically, this condition presents in early infancy with hypertrophic cardiomyopathy, shortened P-R interval on electrocardiography, and skeletal and respiratory muscle weakness. CK values are elevated. Heart failure, respiratory insufficiency, and death occur without treatment. ERT is available and is most efficacious if started before cardiac function deteriorates. Therefore, Pompe disease is being added to NBS. Milder forms of the condition may present with muscle weakness and elevated CK values later in childhood or adulthood. Diagnosis is by demonstration of GAA enzyme deficiency on blood spot or fibroblasts or by DNA analysis.

## PEROXISOMAL DISORDERS

The peroxisome is a cellular organelle with disparate functions, including oxidation of very long-chain fatty acids (VLCFAs). Defects in peroxisomal function or assembly can result in several severe neurodegenerative disorders. These conditions are not included in NBS and may present with severe infantile hypotonia, skeletal dysplasia, sensory deficits (hearing and vision loss), hepatomegaly, or neurologic regression in childhood. Zellweger syndrome results from near or complete absence of peroxisomes. Affected infants present with dysmorphic facial characteristics, seizures, liver disease, characteristic bone involvement, profound hypotonia, and hearing and vision deficits. Magnetic resonance imaging of the brain shows a leukodystrophy (abnormal myelination). The condition is usually fatal in infancy.

Adrenoleukodystrophy is an X-linked condition that results from a deficiency in peroxisomal oxidation of VLCFAs. It presents with developmental regression, white matter disease, new-onset spasticity, and adrenal failure typically in school-age boys, although there is a broad spectrum of phenotypes. Onset occurs after a period of normal growth and development. Initial screening for both of these conditions is by plasma VLCFA analysis. HSCT may halt progression in some patients (12).

## MITOCHONDRIAL DISORDERS

Mitochondrial disorders are complex multisystemic conditions that result from mutations in the mitochondrial

genome or nuclear genes required for mitochondrial function (13). Point mutations in the mitochondrial genome are transmitted via maternal inheritance, deletions or duplications in the mitochondrial genome are usually sporadic, and mutations in nuclear genes required for mitochondrial function are inherited in a mendelian pattern, usually autosomal recessive. The mitochondria have several important functions but most important is the production of cellular energy in the form of adenosine triphosphate via the respiratory chain. Genetic alterations that diminish the mitochondria's ability to produce energy result in dysfunction in tissues with the highest energy demands. Therefore, mitochondrial disorders preferentially affect the brain, skeletal and cardiac muscles, and the eye. Muscle biopsy may show ragged red fibers on light microscopy. Strategies for diagnosing mitochondrial diseases vary and are beyond the scope of this review, but they include next-generation DNA sequencing of multigene panels for nuclear gene mutations, sequencing of the mitochondrial genome, and specific assays of muscle respiratory chain activity. Because plasma lactate is neither a sensitive nor specific marker of mitochondrial disease, the decision to evaluate a patient for mitochondrial disease should rely on the clinical phenotype.

MELAS (mitochondrial encephalomyopathy, lactic acid, and stroke-like episodes) is one common mitochondrial disorder that is usually due to a maternally inherited mutation in the mitochondrial tRNA for leucine. Symptoms often present in adolescence with diabetes mellitus, recurrent stroke-like episodes, migraine headaches, and hearing loss. Kearns-Sayre syndrome usually results from sporadic (non-inherited) partial deletions of the mitochondrial genome. Common features include cardiac conduction abnormalities, cardiomyopathy, lactic acidosis, and progressive external ophthalmoplegia. Respiratory chain disorders are usually inherited in an autosomal recessive pattern and are related to mutations in nuclear genes important for assembly, maintenance, or production of the respiratory chain (but may also be maternally inherited due to mitochondrial point mutations). These conditions usually present in infancy with hypotonia, muscle weakness, global developmental delays, lactic acidosis, and seizures. Neuroimaging may show basal ganglia lesions consistent with Leigh syndrome.

## CONCLUSION

Metabolic disorders can be difficult to understand due to their rarity and the multiplicity of conditions. Applying context to this group of conditions can aid in the initial

evaluation. Disorders of energy sources can largely be screened for by a few simple tests. Amino acidopathies can be evaluated via PAA and UOA analysis; organic acidemias via electrolytes, urine ketones, UOA analysis, and PAC profile; urea cycle disorders via UOA and PAA analysis and ammonia; and FAOD via UOA, PAC profile, urine ketones, blood glucose, and plasma carnitine. In addition, NBS allows for the early recognition of many, but not all of these disorders. Therefore, clinicians should consider these conditions in the differential diagnosis, even for a child who has a negative NBS result. The lysosomal disorders are more difficult to diagnosis via routine screening tests, but the clinical features (eg, visceromegaly, developmental regression, coarse facial features) should alert the clinician to the possibility.

## Summary

By their very nature, rare inborn errors of metabolism challenge the generation and application of evidence-based medicine.

- On the basis of limited research evidence as well as consensus, newborn screening for select metabolic disorders, including phenylketonuria, medium-chain acyl CoA dehydrogenase

deficiency, and glutaric acidemia type I, may improve long-term outcomes for affected children. (4)(8)(9)

- On the basis of primarily consensus, due to lack of relevant clinical studies, inborn errors due to defects in the metabolism of energy sources (protein, fatty acids, and carbohydrates) may present in infancy with overwhelming metabolic decompensation, and initial laboratory evaluations may reveal hyperammonemia, nonketotic hypoglycemia, or a metabolic acidosis with an elevated anion gap, depending on the disorder.
- On the basis of primarily consensus, due to lack of relevant clinical studies, specific laboratory testing for inborn errors of metabolism should include plasma amino acids, urine organic acids, plasma carnitine, and plasma acylcarnitine profile.
- On the basis of primarily consensus, due to lack of relevant clinical studies, disorders of cellular organelles, such as lysosomal and peroxisomal disorders, may present with progressive organomegaly, developmental regression, dysmorphic facial characteristics, or sensory loss.

*CME quiz and references for this article are at <http://pedsinreview.aappublications.org/content/37/1/3>. Access this and all other PIR CME quizzes available for credit at: <http://www.aappublications.org/content/pediatrics-review-quizzes>.*

## Parent Resources from the AAP at HealthyChildren.org

- Organic Causes of Weight Gain and Obesity: <https://www.healthychildren.org/English/health-issues/conditions/obesity/Pages/Organic-Causes-of-Weight-Gain-and-Obesity.aspx>

## PIR Quiz

There are two ways to access the journal CME quizzes:

1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: <http://www.aapublications.org/content/journal-cme>.

1. You are working in the pediatric emergency department when parents bring in their 12-day-old male infant. They assert he has not been waking to feed over the past 24 hours. He normally breastfeeds every 3 hours for 20 minutes and now he sleeps almost continuously. They state he has had a cough and runny nose for the past few days with a temperature of 38.1°C (100.5°F) and has been "floppy" for the past several hours. On physical examination, he is difficult to wake. His respiratory rate is 36 breaths/min, heart rate is 120 beats/min, blood pressure is 57/35 mm Hg, and temperature is 38.0°C (100.4°F). His lungs are clear and cardiac examination reveals regular rate and rhythm without murmur. His abdomen is soft. He has poor capillary refill (4-5 sec) and markedly decreased tone. You suspect infection or a metabolic disorder. Which of the following is the initial laboratory test in the evaluation of a metabolic disorder?
  - A. Blood glucose.
  - B. Liver panel.
  - C. Plasma amino acids.
  - D. Serum ketones.
  - E. Urine organic acids.
2. An 8-day-old female infant is admitted to the general pediatric ward with a 2-day history of lethargy and vomiting. She was born at 38 weeks' gestation via repeat cesarean section and did well. She was discharged home on postnatal day 3. She has been breastfeeding every 3 hours with supplemental 20-cal/oz formula. Since last evening, she has become difficult to arouse and has had multiple episodes of vomiting. She is not febrile and does not have cough, rhinorrhea, diarrhea, or a rash. There have been no ill contacts. She is started on ampicillin and gentamicin after obtaining blood, urine, and cerebrospinal fluid for culture. The third-year medical student on the service raises his hand and says he has been researching a differential diagnosis. He states that urea cycle defects can present in this manner and perhaps plasma ammonia should be assessed. Which of the following is true when evaluating plasma ammonia?
  - A. A capillary specimen is more reliable than a venous specimen.
  - B. Elevated results require a repeat specimen sent the following day, after initiation of therapy.
  - C. The specimen should be placed on ice at bedside and immediately sent to the laboratory.
  - D. The specimen should be tested within 3 hours.
  - E. Venous compression from tourniquet use may cause a falsely low result.
3. You are seeing a 17-year-old girl in the adolescent medicine clinic for the first time. She states that she was diagnosed with phenylketonuria as an infant. She also mentions she has been sexually active for the past 3 years and believes she is currently pregnant. Although her primary physician has repeatedly counseled her to maintain a strict phenylalanine-free diet, she has been noncompliant. You explain to her the risks to the fetus associated with elevated phenylalanine levels, which includes which of the following?
  - A. Craniosynostosis.
  - B. Hepatoblastoma.
  - C. Intellectual disability.
  - D. Renal insufficiency.
  - E. Skeletal dysplasia.
4. As the intern covering the pediatric ward, you check on a 5-day-old infant who was recently admitted for a sepsis evaluation. His babysitter felt he had been lethargic, with three episodes of emesis over the previous 12 hours. You note he has been started on antibiotics, but you decide to obtain an ammonia assessment, which is reported as

**REQUIREMENTS:** Learners can take *Pediatrics in Review* quizzes and claim credit online only at: <http://pedsinreview.org>.

To successfully complete 2016 *Pediatrics in Review* articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

1,742.3  $\mu\text{g}/\text{dL}$  (1,244  $\mu\text{mol}/\text{L}$ ) 20 minutes later. You review the initial management of urea cycle defects. Which of the following is most accurate in the treatment of a urea cycle defect?

- A. All US states screen for ornithine transcarbamylase deficiency.
  - B. Fever and common childhood illnesses do not play a role in exacerbations in infants with urea cycle disorders.
  - C. Hemodialysis is commonly required to lower plasma ammonia concentrations and nephrology should be consulted upon diagnosis.
  - D. Liver transplantation does not improve the long-term management of hyperammonemia due to urea cycle defects.
  - E. Other dietary strategies, rather than removing protein from the diet, are recommended by experts to avoid hyperammonemic crises.
5. You are preparing a lecture for pediatric residents on inborn errors of metabolism. Your goal is to provide the information they need to immediately identify infants who may present with a metabolic disorder and to begin management of these infants. Which of the following acute treatments is most useful in the emergent management of suspected metabolic disorders?
- A. Dextrose-containing fluids with salt.
  - B. Dextrose-containing fluids without salt.
  - C. Hypertonic saline bolus (3 mL/kg).
  - D. Hypertonic saline bolus (10 mL/kg).
  - E. Normal saline bolus (10 mL/kg).

## **Inborn Errors of Metabolism (Metabolic Disorders)**

Gregory M. Rice and Robert D. Steiner

*Pediatrics in Review* 2016;37;3

DOI: 10.1542/pir.2014-0122

### **Updated Information & Services**

including high resolution figures, can be found at:  
<http://pedsinreview.aappublications.org/content/37/1/3>

### **References**

This article cites 13 articles, 2 of which you can access for free at:  
<http://pedsinreview.aappublications.org/content/37/1/3.full#ref-list-1>

### **Permissions & Licensing**

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<https://shop.aap.org/licensing-permissions/>

### **Reprints**

Information about ordering reprints can be found online:  
<http://classic.pedsinreview.aappublications.org/content/reprints>





## **Inborn Errors of Metabolism (Metabolic Disorders)**

Gregory M. Rice and Robert D. Steiner

*Pediatrics in Review* 2016;37;3

DOI: 10.1542/pir.2014-0122

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pedsinreview.aappublications.org/content/37/1/3>

Pediatrics in Review is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1979. Pediatrics in Review is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0191-9601.

# American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

