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## **Inborn Errors of Metabolism: Part 1: Overview**

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# Inborn Errors of Metabolism:

## Part 1: Overview

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**Author Disclosure**  
Dr Levy did not disclose any financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Objectives** After completing this article, readers should be able to:

1. Recognize the signs and symptoms that are suggestive of an inborn error of metabolism.
2. Describe the characteristics of different classes of metabolic syndromes.
3. Formulate a logical diagnostic approach to determining which specific condition is present when an inborn error of metabolism is suspected.
4. Delineate the value and scope of newborn screening programs.
5. Be aware of treatment modalities for inborn errors of metabolism.

### Introduction

As hospitalizations for traditional pediatric illnesses have declined during the last century, due primarily to improved treatment of infectious diseases, the contribution of other disorders has gained prominence. Biochemical genetics, with its various inherited metabolic disorders (inborn errors of metabolism), has become more important in the routine care of hospitalized pediatric patients. Newborn screening also is contributing to the increased awareness of inherited metabolic disorders. Only a few years ago, most states tested for only as many as eight disorders, generally including phenylketonuria, galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, sickle cell disease, hypothyroidism, and congenital adrenal hyperplasia. Recent changes in technology have permitted an increase in the number of disorders tested. A national panel has recommended expanding the testing to 29 disorders, but many states already have begun to screen for more than 40 different disorders with the new technology of tandem mass spectrometry. This expanding list includes amino acid disorders, organic acid disorders, urea cycle diseases, and fatty acid oxidation defects. Some states are working to add lysosomal storage diseases and peroxisomal disorders to their newborn screening panels.

Pediatricians need to recognize and become familiar with these diseases not only to help with the diagnosis but also to help educate parents and advocate for patients. Some patients may fall ill with inherited metabolic disorders not currently detected by newborn screening; others may have conditions that were missed on their newborn screens. Affected children may present at a few days to a few months of age with lethargy or vomiting and be thought to have sepsis or shock. Other disorders may present at a later age with a more indolent picture of developmental delay or regression.

Attempts have been made at developing a rational framework for conceptualizing inherited metabolic diseases, but there is no one simple method of categorizing all of the inherited metabolic diseases with their many different presentations and various ages of onset.

This review is in two parts. The article that appears in print offers a simplified approach to diagnosis and a discussion of the presentation of and testing for many groups of inherited metabolic disorders. The second part appears online only and provides a more detailed discussion of the various groups of inherited metabolic disorders.

### Abbreviations

<b>CDG:</b>	congenital disorders of glycosylation
<b>GSD:</b>	glycogen storage disease
<b>KGDH:</b>	alpha-ketoglutarate dehydrogenase
<b>MPS:</b>	mucopolysaccharidosis
<b>MRI:</b>	magnetic resonance imaging
<b>OXPPOS:</b>	oxidative phosphorylation
<b>PCD:</b>	pyruvate carboxylase deficiency
<b>PDD:</b>	pyruvate dehydrogenase deficiency

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Table 1. Inborn Errors of Metabolism Associated With an Acute Crisis

Diagnostic Clues		
Primary	Secondary	Suggested Disorders
Acidosis	± Hypoglycemia ± Lactic acidosis ± Ketosis ± Elevated ammonia Increased anion gap	Various organic acid disorders
	Significant lactic acidosis Normoglycemia	Mitochondrial disorders Pyruvate dehydrogenase deficiency Alpha-ketoglutarate dehydrogenase deficiency Pyruvate carboxylase deficiency
Hyperammonemia	Significant lactic acidosis Hypoglycemia Normal anion gap Normal lactate No ketosis	Glycogen storage type I Fructose-1,6-bisphosphatase deficiency Renal tubular acidosis
	Alkalosis or normal pH Normal lactate Reye-like illness (hypoglycemia, elevated liver transaminases, normal ketones)	Urea cycle disorders Fatty acid oxidation defects
Hypoglycemia	Acidosis ± Lactic acidosis ± Ketosis ± Hypoglycemia Increased anion gap	Various organic acid disorders
	Acidosis ± Ketosis ± Lactic acidosis ± Increased ammonia Increased anion gap Hepatomegaly ± Lactic acidosis	Various organic acid disorders Glycogen storage disorders
	No ketosis No acidosis Normal lactic acid	Hyperinsulinemia Fatty acid oxidation defects
	Hyponatremia Hypotension Signs of liver failure	Adrenal insufficiency Tyrosinemia Glycogen storage disease type IV Galactosemia Niemann Pick type C

### Approach to Diagnosis and Testing

In general, inherited metabolic disorders can be divided into two groups: disorders that can present with an acute crisis (Table 1), often with encephalopathy, and disorders that have a more chronic, indolent course (Table 2). Two authors have made significant contributions to help clinicians identify and diagnose inherited metabolic disorders. Jean Marie Saudubray (*The Molecular and Metabolic Bases of Inherited Disease*. 8th ed. New York, NY: McGraw Hill; 2001, updated online at [www.ommbid.com](http://www.ommbid.com)) and JTR Clarke (*A Clinical Guide to Inherited Metabolic Diseases*. 2nd ed. New York, NY: Cambridge

University Press; 2002) have described frameworks for the evaluation of these diseases. This review provides a simplified overview, but readers are encouraged to consult these references for additional assistance in diagnosing inherited metabolic disorders.

### Acute Presentation

Children who have inherited metabolic disorders almost always appear normal at birth because the metabolic intermediate that is responsible for the disorder frequently is a small molecule that can traverse the placenta and be eliminated by the mother's metabolism. Once the

**Table 2. Findings Suggestive of a Chronic Metabolic Disorder**

#### Neurologic

Developmental delay (especially with regression), seizures (myoclonic or partial complex), seizures resistant to anticonvulsant therapy, deafness, blindness, stroke, or movement disorder (dystonia, chorea)

#### Liver

Hepatosplenomegaly, cholestasis, liver failure ( $\pm$  cirrhosis), hypoglycemia

#### Heart

Cardiomyopathy (dilated or hypertrophic), arrhythmias

#### Kidney

Enlarged kidneys with microcysts, renal failure, tubular dysfunction, generalized amino aciduria, hypophosphatemia, rickets

#### Muscle

Peripheral muscle weakness, myoglobinuria

#### Eye

Cataracts, corneal opacities, lens dislocation, retinal abnormalities (cherry red spots, retinitis pigmentosa), ophthalmoplegia, strabismus

#### Dysmorphic Features

Macrocephaly, high forehead, large anterior fontanelle, coarsened facial features, large jaw, small jaw, large ears, abnormal fat distribution

infant is born, symptoms begin to appear after a variable period of time (days, weeks, months, or rarely, years) as the metabolite accumulates.

An acute presentation is most common in infants and young children. Infants have a limited repertoire with which to respond to an overwhelming illness. Generally, they manifest poor feeding and lethargy. Trying to distinguish a routine childhood illness from an inherited metabolic disorder can be difficult. Even if there is vomiting, respiratory distress, and eventually encephalopathy (coma), such symptoms most commonly are attributed to infection and sepsis, not to an inherited metabolic disorder. Routine blood tests, cultures, and chest radiographs yield unremarkable results. An important clue that should stimulate the clinician to look further is the lack of improvement with standard therapy.

Organic acidemias, urea cycle defects, and some disorders of amino acid metabolism can result in acute

encephalopathy. An inherited metabolic disorder always should be considered in the differential diagnosis, especially if there are no associated risk factors for infection. Consideration of these disorders may require some diagnostic suspicion, but identifying them requires only a few laboratory tests.

When presented with a child who has acute encephalopathy, the clinician must determine the pH, lactate value, electrolyte concentrations, liver function, and glucose status of the patient. Ammonia should be measured for any ill child who has unexplained lethargy or vomiting. The presence of ketones in the urine also may be important. The results of such tests can help to diagnose an underlying inherited metabolic disorder.

### Acidosis

The presence of acidosis (pH <7.30,  $P_{CO_2}$  <30 torr, and  $HCO_3^-$  <15 mEq/L [15 mmol/L]) indicates significant disturbance of normal metabolism and may result from infection, dehydration, intoxication, or anoxia as well as from an inborn error of metabolism. Organic acid disorders present with acidosis due to the accumulation of acidic metabolites. Hypoglycemia, lactic acidosis, ketosis, and a mild to moderately elevated ammonia value also may be present, either individually or together. The presence or absence of these other findings may help distinguish among different organic acidemias.

If hypoglycemia is present with lactic acidosis but no significant ketosis, disorders of gluconeogenesis should be investigated. Significant lactic acidosis may suggest the possibility of an energy production disorder, either a mitochondrial defect of oxidative phosphorylation (OXPHOS), pyruvate dehydrogenase deficiency (PDD), alpha-ketoglutarate dehydrogenase (KGDH) deficiency, or pyruvate carboxylase deficiency (PCD). Finally, acidosis without the elevation of lactate or the presence of ketosis and a normal anion gap suggests renal tubular acidosis.

**LACTIC ACIDOSIS.** Lactic acidosis often results from hypoxia or poor perfusion, which may be caused by dehydration. Glycogen storage diseases, pyruvate metabolism defects (PDD, PCD, KGDH), fructose-1,6-bisphosphatase deficiency, and mitochondrial OXPHOS abnormalities increase lactic acid production directly; organic acid disorders may cause a secondary rise in lactate. In many hospitals, it is relatively simple to measure lactic acid on a blood gas determination. Such testing is optimal because it provides both the pH and the lactate values quickly. Determination of the lactic

acid value helps with the diagnosis of organic acidurias and glycogen storage diseases.

For other disorders, it may be beneficial to measure pyruvate, but this determination is more difficult because the blood must be drawn and placed immediately into a special tube. Generally, the result is not available immediately. An increased lactic acid value with a lactic acid-to-pyruvate ratio of less than 25 is normal, but the elevated lactic acid suggests a defect in pyruvate dehydrogenase or an enzyme of gluconeogenesis (fructose-1,6-bisphosphatase or glucose-6-phosphatase). An increased ratio ( $>30$ ) suggests a deficiency of pyruvate carboxylase or KGDH or an OXPHOS defect. Determination of blood ketones (3-hydroxybutyrate and acetoacetic acid) helps to delineate the defect further. A ratio of 3-hydroxybutyrate-to-acetoacetic acid greater than 2:1 is suggestive of an OXPHOS defect.

**KETOSIS.** Ketosis is a normal physiologic response in some circumstances, but it is not normal when it is severe enough to cause acidosis. Neonates do not generate ketones well, so the presence of ketones in a newborn's urine is of concern. Many organic acidurias present with ketosis. Persistent ketosis with normal urine organic acids suggests a defect in one of two ketolytic enzymes.

**HYPERAMMONEMIA.** Ammonia values may be elevated in a number of disorders, including urea cycle defects, some organic acidemias, and fatty acid oxidation defects that may present with a Reye-like syndrome (vomiting, elevated liver transaminases, hyperammonemia, coma). The organic acid disorders can be distinguished by the presence of acidosis. Fatty acid oxidation defects generally create hypoglycemia, which the urea cycle defects do not.

**HYPOLYCEMIA.** When hypoglycemia is an isolated finding, hyperinsulinism should be considered. Hypoglycemia also can be associated with liver failure, so both metabolic disorders (tyrosinemia, glycogen storage disease [GSD] type IV, galactosemia, and Niemann-Pick disease type C) as well as congenital malformations and acquired conditions should be ruled out. If the hypoglycemia is associated with hepatomegaly ( $\pm$  lactic acidosis), glycogen storage diseases (GSD I, III, VI, and IX) and fructose-1,6-bisphosphatase deficiency are likely. When acidosis or ketosis is present with hypoglycemia, the organic acidurias are a likely cause. Hypoglycemia without ketosis (beyond the newborn period) should prompt investigation for a fatty acid oxidation defect. Lastly, hypoglycemia with hyponatremia and hypotension may

be a presentation of adrenal insufficiency, especially in patients who have been receiving steroids chronically.

### Treatment of Encephalopathy

Presentation of an infant or young child in an encephalopathic coma requires urgent treatment in an attempt to avert or mitigate neurologic sequelae and potential death from a treatable cause. Recognizing the possibility that an inborn error of metabolism may be responsible should prompt appropriate laboratory tests (ammonia, lactic acid, urine organic acids, plasma and urine amino acids, pH, glucose, liver function tests, pyruvate, acylcarnitine profile). The results of these tests may not be immediately available, but they should be completed in 48 to 72 hours. Treatment can begin before a definitive diagnosis is determined.

An elevated ammonia concentration without acidosis is presumed to be a urea cycle defect. Immediate arrangements for hemodialysis should be made and ammonia removal medications (sodium benzoate and sodium phenylacetate) and arginine administered. All protein intake should be halted if a urea cycle defect or a disorder related to protein "intolerance" such as an organic acidemia is suspected. Such protein deprivation cannot be undertaken without providing appropriate caloric intake from carbohydrate (10% glucose) and an intravenous fat emulsion. If the caloric intake is not sufficient, catabolism of the patient's protein occurs, raising ammonia concentrations in a urea cycle disorder or presenting substrate for the organic acidurias.

A number of inherited metabolic disorders respond to large ("mega") doses of the cofactors of their respective enzymes. Presumptively, a "cocktail" of such cofactors can be started for a possible inherited metabolic disorder. Vitamin B<sub>12</sub> (hydroxycobalamin) (1 mg/day intramuscularly), thiamine (50 mg orally BID), biotin (10 mg orally BID), riboflavin (50 mg orally BID), folic acid (10 mg orally BID), and carnitine (100 mg/kg per day orally divided QID) have been found to be effective for a number of disorders and should be administered. Patients who experience hypoglycemia should be given glucose to maintain normal plasma concentrations. Treatment can be tailored as the results of testing become available and a diagnosis is made.

### Chronic Disorders

The second group of metabolic disorders is characterized by a more chronic course. They are difficult to recognize and diagnose because their onset may be from birth to adulthood and they have myriad signs and symptoms. The presence of some clinical findings helps to organize

the group into more manageable subgroups. The first and largest subgroup is disorders that create neurologic abnormalities. Involvement of a specific organ system may suggest a specific inherited metabolic disorder and comprise the second subgroup. The third subgroup is defined by the presence of dysmorphic features, which although not common to many inherited metabolic disorders, can be a helpful distinguishing feature.

### Neurologic

Neurologic findings may include developmental or psychomotor delay, seizures, movement disorders, deafness, and blindness. Psychomotor or developmental delay is the most common clinical finding of inherited metabolic disorders. Not all children who exhibit developmental delay, however, have inherited metabolic disorders. Developmental delay due to an inherited metabolic disorder usually is global (rather than an isolated delay of speech, for example) and shows loss of milestones (regression) over time as the disease progresses.

Seizures, if they occur, are of various types, with electroencephalographic findings that may be difficult to classify into a specific seizure syndrome. Seizures (often myoclonic or partial complex) that are resistant to anti-convulsant therapy may suggest an underlying inherited metabolic disorder.

Movement disorders associated with inherited metabolic disorders include dystonias (abnormal muscle contractions that result in abnormal postures and involuntary torsional movements) and choreas (involuntary movements that can be athetotic and involve twisting or torsional movements).

Although there may be some overlap, involvement of either gray matter or white matter may help in narrowing the differential diagnosis of the underlying disorder. Disorders involving the cerebral gray matter tend to occur early in life. In addition to developmental delay, patients who have these conditions may exhibit seizures, a movement disorder (chorea or dystonia), hearing loss, or blindness (cortical or due to optic atrophy). Magnetic resonance imaging (MRI) findings may show only some cerebral atrophy or be read as normal. Neuronal lysosomal storage diseases can be considered in such patients as well as some of the mitochondrial disorders.

Disorders involving the cerebral white matter generally have abnormalities of tone (hypotonia or hypertonia) and motor difficulties (sometimes delayed or loss of motor milestones). This group includes the leukodystrophies, which, by definition, have abnormal white matter, and Canavan disease, Alexander disease, and some of the lysosomal storage disorders.

Some inherited metabolic disorders may result in neuronal migration defects. These conditions include peroxisomal disorders and some congenital disorders of glycosylation.

Stroke, an unusual finding in children, should suggest homocystinuria and the mitochondrial disorder MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes). Fabry disease and some forms of congenital disorders of glycosylation (CDG) also have been associated with stroke.

### Other Specific Organ System Involvement

**LIVER OR SPLEEN.** Liver involvement may lead to hypoglycemia, cholestasis, or liver failure with cirrhosis. Disorders that lead to cirrhosis include tyrosinemia, classic galactosemia, hereditary fructose intolerance, the Zellweger spectrum of peroxisomal disorders, CDG, alpha-1-antitrypsin deficiency, Wilson disease, and mitochondrial disorders. Hypoglycemia may result from a GSD or a fatty acid oxidation defect as well as some organic acidurias. Lysosomal storage diseases, especially the mucopolysaccharidoses (MPSs), are characterized by hepatosplenomegaly and also present with dysmorphic (coarsened) features, intellectual disability, and short stature.

**HEART.** Some fatty acid oxidation defects may present with severe cardiomyopathy. Other disorders that have significant cardiac symptoms include carnitine transport disorders, Pompe disease (GSD type II), Fabry disease, G<sub>M1</sub> gangliosidosis, CDG, and some mitochondrial diseases.

**KIDNEY.** Glutaric aciduria type II may cause enlarged kidneys that contain small microcysts and are detected at birth. Galactosemia and hereditary fructose intolerance with chronic exposure to fructose lead to proximal tubule dysfunction and kidney failure if left untreated. Tyrosinemia type I generally manifests tubular dysfunction, which results in hypophosphatemia and rickets. Cystinosis is associated with decreased glomerular function leading to end-stage renal failure. Fanconi syndrome (aminoaciduria) also may be caused by some mitochondrial diseases.

**MUSCLE.** Peripheral muscle weakness is characteristic of the muscle forms of GSD, generally appearing in older children and sometimes accompanied by myoglobinuria. Mitochondrial disease may cause muscle weakness with or without persistent lactic acidosis.

**EYE.** Ocular findings often provide a clue to an underlying inborn metabolic disorder. The presence of cataracts may suggest galactosemia, peroxisomal disorders, Lowe syndrome, alpha-mannosidosis, galactokinase deficiency, mitochondrial respiratory chain disorders, sialidosis, lysinuric protein intolerance, Sjögren-Larsson syndrome, and Wilson disease. In adults, patients who have Fabry disease or homocystinuria and carriers for both Lowe syndrome and galactosemia (galactose-1-phosphate uridylyltransferase deficiency and uridine diphosphate galactose-4-epimerase) also may develop cataracts.

Corneal abnormalities such as opacities can be seen in MPS I and VI, Wilson disease, galactosialidosis, cystinosis, Fabry disease, and tyrosinemia (ocular form). Homocystinuria and Marfan syndrome are associated with lens dislocation, as are molybdenum cofactor deficiency, sulfite oxidase deficiency, contractural arachnodactyly, and Marshall syndrome. Cherry red spots are found in a number of lysosomal storage diseases due to the accumulation of storage material in the retina, which causes paleness but a normal-appearing fovea, resulting in a central “spot.” This finding is associated with Tay-Sachs disease ( $G_{M2}$  gangliosidosis),  $G_{M1}$  gangliosidosis, sialidosis, Niemann-Pick disease, Farber disease, galactosialidosis, and metachromatic leukodystrophy.

Mitochondrial disease (Leigh syndrome, Kearns-Sayre syndrome), chronic progressive external ophthalmoplegia, and neurogenic weakness ataxia retinitis pigmentosa may be associated with retinitis pigmentosa as well as with weakness of the extraocular muscles leading to ophthalmoplegia. Other inherited metabolic disorders associated with retinitis pigmentosa include congenital disorders of glycosylation, ceroid lipofuscinoses, and peroxisomal disorders.

**SKIN.** Biotinidase deficiency often presents with alopecia and a rash (usually eczematike). Angiokeratomata characteristically are seen in Fabry disease, but also can be seen in fucosidosis, beta-mannosidosis, galactosialidosis, and aspartylglucosaminuria. Menkes syndrome is known for hair abnormalities (soft, pale, brittle, and wiry), but patients afflicted with arginosuccinic aciduria and citrullinemia also may have brittle hair.

Farber lipogranulomatosis (a sphingolipidosis) has unique periarticular subcutaneous nodules and also is characterized by joint swelling and contractures.

**DYSMORPHIC FEATURES.** Although not typical of most inherited metabolic disorders, dysmorphic features

can be a helpful diagnostic clue. The largest group of disorders associated with dysmorphic features is the lysosomal storage diseases. MPSs are the most identifiable members of this group and present with coarsened facial features, hepatosplenomegaly, and short stature. Other lysosomal disorders that present with dysmorphic features include some of the oligosaccharidoses (mannosidosis, galactosialidosis, aspartylglucosaminuria, sialidosis, and I-cell disease), which can involve features similar to those of the MPS disorders.  $G_{M1}$  gangliosidosis (a sphingolipidosis) also presents with MPS-like facial features. Farber lipogranulomatosis presents with dysmorphic features and characteristic periarticular subcutaneous nodules.

Only a few disorders present at birth or soon after with dysmorphic features: some of the lysosomal storage disorders, Sly syndrome, sialidosis, galactosialidosis,  $G_{M1}$  gangliosidosis, and Krabbe disease, as well as Pompe disease, which is a lysosomal disorder, although usually included with the GSDs. Peroxisomal disorders generally are associated with dysmorphic features characterized by the Zellweger spectrum (high forehead, flat occiput, large anterior fontanelle, hypoplastic supraorbital ridges, epicanthal folds, broad nasal bridge, anteverted nostrils, and micrognathia). Finally, many of the CDG exhibit dysmorphic features (large ears, strabismus, abnormal fat distribution).

## Evaluation

Evaluation for a possible inherited metabolic disorder in the chronic group begins with a developmental assessment and history. If an inherited metabolic disorder is suspected, a fairly extensive initial screen includes MRI of the brain; a skeletal survey; testing for plasma amino acids, urine organic acids, urinary mucopolysaccharides, and oligosaccharides; transferrin electrophoresis; measuring very long-chain fatty acids, pH, lactate, and ammonia; verifying results of the newborn screen; and obtaining an acylcarnitine profile and an ophthalmologic examination.

The MRI should help distinguish gray and white matter involvement as well as cerebellar hypoplasia (CDG) and neuronal migration defects (CDG and peroxisomal disorders). A skeletal survey may uncover evidence of dysostosis multiplex (lysosomal storage diseases). Urine testing for mucopolysaccharides and oligosaccharides may uncover many of the large group of lysosomal storage disorders. Measuring plasma amino

acids and urine organic acids is a good screen for disorders in these groups.

Transferrin electrophoresis helps with CDG, which are N-linked glycan synthesis disorders. Peroxisomal disorders can be screened for by measuring very long-chain fatty acids and phytanic acid. A pH and lactate measurement may reveal longstanding acidosis and elevated lactate values. Ammonia concentrations may be elevated with enzyme deficiencies of the urea cycle or some organic acid disorders. An acylcarnitine profile, similar to tandem mass spectrometry testing for newborn screens, can assist in the detection of fatty acid oxidation defects, carnitine transport defects, amino acid disorders, and organic acid disorders.

Results of the initial assessment (history and physical examination) can help to guide the evaluation, and some of these tests may be omitted. Positive results from such testing may lead to additional investigation and confirmatory testing by either an enzyme assay or DNA testing.

**EDITOR'S NOTE.** The second part of this article, which is published in the online edition of this issue, is a comprehensive overview of specific inborn errors of metabolism. Most readers will use this material as a reference resource. All readers are urged to familiarize themselves with this second portion of the article, which reflects a prodigious effort on the part of Dr Levy.

## PIR Quiz

Quiz also available online at [pedsinreview.aappublications.org](http://pedsinreview.aappublications.org).

5. On the second day after birth, an initially vigorous term infant begins to feed poorly, develops tachypnea, and becomes increasingly less responsive to stimulation. No other abnormal findings are detected on physical examination. Chest radiograph appears normal. Laboratory evaluation reveals a normal complete blood count; differential count; pH; and serum electrolytes, glucose, and lactate. Serum ammonia concentrations are high and urine ketones are absent. Of the following, the *most* likely explanation is:
  - A. Fatty acid oxidation defect.
  - B. Organic acidemia.
  - C. Renal tubular acidosis.
  - D. Sepsis.
  - E. Urea cycle defect.
  
6. On the second day after birth, an initially vigorous term infant begins to feed poorly, develops tachypnea, and becomes increasingly less responsive to stimulation. No other abnormal findings are detected on physical examination. Chest radiograph appears normal. The complete blood count and differential count are normal. The pH is low, serum ammonia value is high, sodium and chloride values are normal, potassium is elevated, bicarbonate is low, serum glucose is low, and serum lactate is slightly elevated. Ketones are present in the urine. Of the following, the *most* likely explanation is:
  - A. Fatty acid oxidation defect.
  - B. Organic acidemia.
  - C. Renal tubular acidosis.
  - D. Sepsis.
  - E. Urea cycle defect.



7. A previously healthy 2-month-old girl rapidly becomes comatose shortly after the onset of an apparent upper respiratory tract infection. Aside from clear nasal discharge and coma, findings on her physical examination are unremarkable. Chest radiography appears normal. Laboratory findings include a normal complete blood count and differential count, pH, serum electrolytes, and serum lactate. Serum ammonia values are high and serum glucose is low. There are no ketones in the urine. Of the following, the *most* likely explanation is:
  - A. Fatty acid oxidation defect.
  - B. Organic acidemia.
  - C. Renal tubular acidosis.
  - D. Sepsis.
  - E. Urea cycle defect.
  
8. A 12-month-old boy who has had progressive loss of developmental milestones over the past 6 months is found to have a cherry red spot on examination of each retina. He *most* likely suffers from a disorder of:
  - A. Glycoprotein synthesis.
  - B. Glycosylation.
  - C. Lysosomes.
  - D. Mitochondria.
  - E. Peroxisomes.
  
9. Physical examination of a newborn reveals a high forehead, flat occiput, large anterior fontanelle, hypoplastic supraorbital ridges, epicanthal folds, and micrognathia. The infant *most* likely has a disorder of:
  - A. Amino acid metabolism.
  - B. Fatty acid oxidation.
  - C. Glycogenolysis.
  - D. Lysosomes.
  - E. Peroxisomes.

### Correction

In the article “Adolescent Immunizations” in the February 2009 issue (*Pediatr Rev.* 2009;30:47–56), in Table 1, “group B *Streptococcus* (GBS)” is in error. The correct phrase is “Guillain-Barré syndrome (GBS)” and applies to both places where “GBS” is printed in that table. In addition, on page 55 of the article, the last sentence in the first paragraph of the section headed “Polio” should read: “Poliovirus, a member of the enterovirus family, perhaps is best known for causing a rapid onset of asymmetric acute flaccid paralysis with areflexia.”

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