Inborn Errors of Metabolism in Infancy: A Guide to Diagnosis

Barbara K. Burton, MD

ABSTRACT. Recent advances in the diagnosis and treatment of inborn errors of metabolism have improved substantially the prognosis for many of these conditions. This makes it essential that the practicing pediatrician be familiar with the clinical presentation of these disorders. A practical clinical approach to the recognition of inborn errors of metabolism in the young infant is presented in this review. Indications for specific laboratory studies are discussed. Guidelines are provided for the stabilization and emergency treatment of critically ill infants. This approach will identify those infants who will benefit from additional evaluation and specific treatment.

Many of the inborn errors of metabolism, including urea cycle defects, organic acidemias, and certain disorders of amino acid metabolism, present in the young infant with symptoms of an acute or chronic metabolic encephalopathy. Typical symptoms include lethargy, poor feeding, apnea or tachypnea, and recurrent vomiting. Metabolic acidosis and/or hyperammonemia are observed in many of these conditions, but there are notable exceptions, including nonketotic hyperglycinemia and molybdenum co-factor deficiency. Therefore, appropriate laboratory testing for metabolic disorders should be performed in any infant who exhibits these findings. Although sepsis may be the initial consideration in a neonate with these symptoms, inborn errors of metabolism should always be in the differential diagnosis, particularly in a full-term infant with no specific risk factors.

Hypoglycemia may be the predominant finding in a number of inborn errors of metabolism, including glycogen storage disorders, defects in gluconeogenesis, and fatty acid oxidation defects. The latter disorders, among the most common encountered, exhibit marked clinical variability and also may present as a sudden death, a Reye’s-like episode, or a cardiomyopathy. Jaundice or other evidence of hepatic dysfunction is the mode of presentation of another important group of inborn errors of metabolism including galactosemia, hereditary tyrosinemia, neonatal hemochromatosis, and a number of other conditions. A subset of lysosomal storage disorders may present very early with coarse facial features, organomegaly, or even hydrops fetalis. Specific patterns of dysmorphic features and congenital anomalies characterize yet another group of inherited metabolic disorders, such as Zellweger syndrome and the Smith–Lemli–Opitz syndrome. Each of these symptom complexes, and the appropriate evaluation of the affected infants, is discussed in more detail in this review. Pediatr. 1998; 102(6). URL: http://www.pediatrics.org/cgi/content/full/102/6/e69; inborn errors of metabolism, inherited metabolic disorders.

ABBREVIATIONS. CNS, central nervous system; THAN, transient hyperammonemia of the newborn; OTC, ornithine transcarbamylase; CoA, co-enzyme A; PDH, pyruvate dehydrogenase; GSD, glycogen storage disease.

The number, complexity, and varied clinical presentation of inborn errors of metabolism present a formidable challenge to the practicing pediatrician. Yet, in many cases, prevention of death or permanent neurologic sequelae in patients with these disorders is dependent on early diagnosis and institution of appropriate therapy. It is therefore incumbent on the pediatrician to be familiar with the major signs and symptoms of inborn errors of metabolism and with the basic laboratory studies necessary to arrive at an initial diagnosis. Although the pediatrician may rarely be called on to be the sole provider of long-term care to patients with these complex disorders, he or she will be responsible for the emergency care and stabilization of the infants and children affected and should be familiar with the fundamental aspects of such care.

It is the purpose of this review to define the constellation of findings in the young infant that should alert the pediatrician to the possibility of inherited metabolic disease. The discussion is confined to those disorders that typically present in early infancy and have potential life-threatening consequences. The many disorders that typically present in later childhood, such as most lysosomal storage disorders, are not included. The laboratory tools used to evaluate infants suspected of having metabolic disease are described. Treatment of important groups of metabolic disorders is addressed, focusing on the stabilization and acute management of patients with these conditions. A more comprehensive discussion of each of these topics can be found in recent editions of reference textbooks.1,2

CLINICAL MANIFESTATIONS OF INBORN ERRORS OF METABOLISM

Acute Metabolic Encephalopathy

Several groups of inherited metabolic disorders, most notably the organic acidemias, urea cycle defects, and certain disorders of amino acid metabolism, typically present with acute life-threatening symptoms of an encephalopathy. These symptoms are the result of toxic effects of accumulating metabolites on the central nervous system (CNS). Because
most of these metabolites cross the placenta and are cleared by the mother during gestation, affected infants usually appear normal at birth. The interval between birth and onset of clinical symptoms ranges from hours to months. The initial findings are usually those of lethargy and poor feeding, as seen in almost any sick infant. Although sepsis is often the first consideration in infants who present in this way, these symptoms in a full-term infant with no specific risk factors strongly suggest a metabolic disorder. Infants with inborn errors of metabolism may become debilitated and septic rather quickly, and it is therefore important that the presence of sepsis not exclude consideration of other possibilities. If untreated, the lethargy associated with these conditions may progress to coma. Other signs of CNS dysfunction, such as seizures and abnormal muscle tone, also may be noted. Evidence of cerebral edema may be observed, and intracranial hemorrhage occasionally occurs.

An infant with an inborn error of metabolism who presents more abruptly or in whom the lethargy and poor feeding go unnoticed may first come to attention because of apnea or respiratory distress. The apnea is typically central in origin and a symptom of the metabolic encephalopathy, but tachypnea may be a symptom of an underlying metabolic acidosis, as occurs in the organic acidemias. Infants with urea cycle defects and evolving hyperammonemic coma initially exhibit central hyperventilation, which leads to respiratory alkalosis.

Vomiting is a striking feature of many of the inborn errors of metabolism associated with protein intolerance, although considerably less common in the newborn than in the older infant. If persistent vomiting occurs in the neonatal period, it usually signals significant underlying disease. Inborn errors of metabolism should always be considered in the differential diagnosis. It is common for an infant to be diagnosed as having a metabolic disorder after having undergone surgery for suspected pyloric stenosis. Formula intolerance is frequently suspected, and many affected infants have numerous formula changes before a diagnosis is finally established.

The basic laboratory studies that should be obtained for an infant who has symptoms of a metabolic encephalopathy consistent with an inborn error of metabolism are listed in Table 1.

### TABLE 1. Laboratory Studies For an Infant Suspected of Having an Inborn Error of Metabolism

<table>
<thead>
<tr>
<th>Test</th>
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<tr>
<td>Complete blood count with differential</td>
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<tr>
<td>Urinalysis</td>
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<tr>
<td>Blood gases</td>
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<tr>
<td>Serum electrolytes</td>
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<tr>
<td>Blood glucose</td>
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<td>Plasma ammonia</td>
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<tr>
<td>Urine reducing substances</td>
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<tr>
<td>Urine ketones if acidosis or hypoglycemia present</td>
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<tr>
<td>Plasma and urine amino acids, quantitative</td>
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<td>Urine organic acids</td>
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<tr>
<td>Plasma lactate</td>
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**Hyperammonemia**

Among the most important laboratory findings associated with inborn errors of metabolism presenting with an acute encephalopathy is hyperammonemia. A plasma ammonia level should be obtained for any child with unexplained vomiting, lethargy, or other evidence of an encephalopathy. Significant hyperammonemia is observed in a limited number of conditions. Inborn errors of metabolism, including urea cycle defects and many of the organic acidemias, are at the top of the list. Also in the differential diagnosis in the neonate is a condition referred to as transient hyperammonemia of the newborn (THAN), whereas in the older infant, fatty acid oxidation defects may be considered. Ammonia levels in newborns with these conditions frequently exceed 1000 μmol/L. The finding of marked hyperammonemia provides an important clue to diagnosis and indicates the need for urgent treatment to reduce the ammonia level. The degree of neurologic impairment and developmental delay observed subsequently in affected infants has been shown to be dependent on the duration of the neonatal hyperammonemic coma.

A flowchart for the differentiation of conditions producing significant hyperammonemia in the newborn is presented in Fig 1. The timing of the onset of symptoms may provide an important clue. Patients with some of the organic acidemias, such as glutaric acidemia type II or with pyruvate carboxylase (PC) deficiency, may exhibit symptomatic hyperammonemia during the first 24 hours. Symptoms in the first 24 hours also are characteristic of THAN, a condition that is poorly understood but apparently not genetically determined. The typical patient with this disorder is a large, premature infant (mean gestational age of 36 weeks) who has symptomatic pulmonary disease, often from birth, and severe hyperammonemia. The condition can occur in full-term infants, however, including those without respiratory symptoms. Survivors do not have recurrent episodes of hyperammonemia and may or may not exhibit neurologic sequelae, depending on the extent of the neonatal insult.

Infants who develop severe hyperammonemia after 24 hours of age usually have a urea cycle defect or an organic acidemia; infants with organic acidemias typically exhibit a metabolic acidosis as well. Urine organic acid analysis should always be obtained, regardless of whether acidosis is present. Metabolic acidosis is not a typical feature of the urea cycle defects. Plasma amino acid analysis is helpful in the differentiation of the specific defects in this group. In addition, carbamyl phosphate synthetase deficiency and ornithine transcarbamylase (OTC) deficiency may be differentiated by measuring urine orotic acid, which is low in the former and elevated in the latter. Although the family history is often negative, a positive history of early male deaths or females with episodic illness in the family of a male infant with hyperammonemia suggests ornithine transcarbamylase deficiency, the only one of the urea cycle defects with a sex-linked mode of inheritance.

Less significant elevations of plasma ammonia...
than those associated with inborn errors of metabolism and THAN can be observed in a variety of other conditions associated with liver dysfunction, including sepsis, generalized herpes simplex infection, and perinatal asphyxia. Liver function studies should be obtained in evaluating the significance of moderate elevations of plasma ammonia. However, even in cases of severe hepatic necrosis, it is rare for ammonia levels to exceed 500 μmol/L.4 Mild transient hyperammonemia with ammonia levels as high as twice normal is relatively common in the newborn, especially in the premature infant, and is usually asymptomatic. It appears to be of no clinical significance, and there are no long-term neurologic sequelae.

Metabolic Acidosis

The second important laboratory feature of many of the inborn errors of metabolism during acute episodes of illness is metabolic acidosis with an increased anion gap, readily demonstrable by measurement of arterial blood gases or serum electrolytes and bicarbonate. A flowchart for the evaluation of infants with this finding is presented in Fig 2. An increased anion gap (≥16) is observed in many inborn errors of metabolism and in most other conditions producing metabolic acidosis in the neonate. In contrast, the differential diagnosis of metabolic acidosis with a normal anion gap is essentially limited to two conditions, diarrhea and renal tubular acidosis. Among the inborn errors, the largest group typically associated with overwhelming metabolic acidosis in infancy is the group of organic acidemias, including such entities as methylmalonic acidemia, propionic acidemia, and isovaleric acidemia.

In addition to specific organic acid intermediates, plasma lactate often is elevated in organic acidemias as a result of secondary interference with co-enzyme A (CoA) metabolism. Neutropenia and thrombocytopenia are commonly observed and further underscore the clinical similarity of these disorders to neonatal sepsis. Hyperammonemia, sometimes as dramatic as that associated with urea cycle defects, is commonly but not uniformly seen in clinically ill infants with organic acidemias.

Defects in pyruvate metabolism or in the respiratory chain may lead to primary lactic acidosis presenting as severe metabolic acidosis in infancy.5 Unlike most of the other conditions presenting acutely in the newborn, clinical features of these disorders

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Fig 1. Flowchart for differentiation of conditions associated with neonatal hyperammonemia. ASA, indicates argininosuccinic acid; CPS, carbamyl phosphate synthetase.
are unrelated to protein intake. Disorders in this group should be considered in patients with lactic acidosis who have normal urine organic acids. Differentiation of the various disorders in this group can be facilitated by measuring plasma pyruvate and calculating the lactate/pyruvate ratio. A normal ratio (≤25) suggests a defect in pyruvate dehydrogenase (PDH) or in gluconeogenesis, and an elevated ratio (≥25) suggests PC deficiency, a respiratory chain defect, or a mitochondrial myopathy.

Not all infants with life-threatening metabolic disease have metabolic acidosis or hyperammonemia. For example, nonketotic hyperglycinemia typically presents in the neonatal period with evidence of severe and progressive CNS dysfunction, but with neither metabolic acidosis nor hyperammonemia. The same is true of molybdenum co-factor deficiency, which on the surface may be virtually indistinguishable from hypoxic–ischemic encephalopathy. Even patients with galactosemia may rarely present with symptoms of CNS toxicity, which may progress to cerebral edema, when galactose-1-phosphate levels rise precipitously. Therefore, the series of laboratory studies listed in Table 1 should be obtained for any infant with clinical findings suggesting an inborn error of metabolism, even if metabolic acidosis and hyperammonemia are not present. Most of the tests on this list are self-explanatory. Although not available in many hospital laboratories, amino acid and organic acid analysis can be obtained in any part of the country through reference laboratories or through referral of samples to medical center genetics units. It is important to insist that any reference laboratory used for this purpose provide prompt test results and reference ranges and provide interpretation of abnormal results.

A summary of the inborn errors of metabolism most likely to be associated with symptoms of an acute encephalopathy is presented in Table 2. The typical laboratory findings in each condition or group of conditions are also listed.

**Emergency Treatment of the Infant With an Acute Metabolic Encephalopathy**

When an inborn error of metabolism, such as an organic acidemia or urea cycle defect, is suspected in a critically ill infant, immediate treatment should be initiated, even if a definitive diagnosis may not yet be established. Within 48 to 72 hours, the results of amino acid and organic acid analysis should be available, allowing diagnostic confirmation in most cases. Appropriate and aggressive treatment before the confirmation of a diagnosis may be life-saving and may avert or reduce the neurologic sequelae of some of these disorders. The immediate treatment of infants with disorders in this group has two primary goals. The first is the removal of accumulating metabolites such as organic acid intermediates or ammonia. At the first suspicion of a disorder associated with protein intolerance, protein intake should be discontinued immediately. In critically ill infants with hyperammonemia, arrangements should be made for hemodialysis. Although peritoneal dialysis, continuous arteriovenous hemoperfusion, and ex-
change transfusion all have been used in the past to lower plasma ammonia levels, all are substantially less effective than hemodialysis. In infants who are comatose or ventilator-dependent, or who exhibit evidence of cerebral edema, dialysis should be instituted immediately without waiting to determine whether there is a response to dietary manipulation, medication, or other less aggressive therapy. Maximal supportive care should be provided simultaneously. In patients suspected of having a urea cycle defect because of significant hyperammonemia without acidosis, an infusion of 6 mL/kg of 10% arginine HCl (0.6 g/kg) can be given intravenously over 90 minutes. In patients with citrullinemia and argininosuccinic aciduria, this often results in a precipitous drop in the plasma ammonia level. An intravenous arginine preparation is available commercially and should be readily accessible to any hospital pharmacy.

If an organic academia is suspected, vitamin B12 (1 mg) should be given intramuscularly in case the patient turns out to have a B12-responsive form of methylmalonic academia. Biotin (10 mg) should be given orally or by nasogastric tube, because some patients with multiple carboxylase deficiency are biotin-responsive. If acidosis exists, intravenous bicarbonate should be administered liberally. Calculations of bicarbonate requirements appropriate for the treatment of other conditions are rarely adequate in these disorders because of ongoing production of organic acids or lactate. The acid-base status should be monitored frequently, with therapy adjusted accordingly. Dialysis should be considered for severely acidic neonates with organic acidemias, regardless of whether hyperammonemia is present.

After removing toxic metabolites, the second major goal of therapy in infants with inborn errors of metabolism should be to prevent catabolism. Intravenous glucose should be administered liberally to provide as many calories as possible. Intravenous lipids can be given to infants with urea cycle defects and other disorders in which dietary fat plays no role. Protein should not be withheld indefinitely. If clinical improvement is observed and a final diagnosis has not been established, some amino acid intake should be provided after a maximum of 2 to 3 days of complete protein restriction. Essential amino acids or total protein can be provided orally or intravenously at an initial dose of 0.5 g protein/kg/24 hours. This should be increased incrementally to 1.0 g/kg/24 hours and held at that level until the diagnostic evaluation is complete and plans can be made for definitive long-term therapy. Therapy should be planned in conjunction with a geneticist or specialist in metabolic disease. Until then, supplemental calories and nutrients can be provided orally using protein-free diet powder (product 80056, Mead Johnson, Evansville, IN or Prophree, Ross Laboratories, Columbus, OH). Once a definitive diagnosis is established, commercial products formulated for individual diseases can be instituted.

**Hypoglycemia**

Hypoglycemia and its associated symptoms occasionally may be seen in infants with disorders of protein intolerance, but it is seen more commonly in disorders of carbohydrate metabolism or fatty acid oxidation. Among the best known inborn errors of metabolism associated with hypoglycemia are the hepatic glycogen storage diseases (GSD). The hypoglycemia in these disorders is related to the inability of the liver to release glucose from glycogen, and it is most profound during periods of fasting. Hypoglycemia, hepatomegaly, and lactic acidosis are prominent features of these disorders. Hypoglycemia is not a feature of GSD type II (Pompe disease) because cytoplasmic glycogen metabolism and release are normal in this disorder in which glycogen accumulates within lysosomes as a result of deficiency of the enzyme acid maltase. Clinical manifestations of this disorder include macroglossia, hypotonia, cardiomegaly with congestive heart failure, and hepatomegaly. Cardiomegaly is the most striking feature and may be apparent in the neonatal period. Congestive heart failure is the cause of death in most cases. Hypoglycemia may be a prominent feature of both galactosemia and hereditary fructose intolerance, although symptoms of the latter disorder occur only after fructose (sucrose) has been introduced in the diet.

A number of inherited defects in fatty acid oxidation have been identified in infants presenting with
hypoglycemia. These disorders are important because of their apparent frequency and because of the variability of the initial presentation. Infants affected have an impaired capacity to use stored fat for fuel during periods of fasting and readily deplete their glycogen stores. Despite the development of hypoglycemia, acetyl CoA production is diminished, and ketone production is impaired. The hypoglycemia occurring in these conditions is typically characterized as nonketotic, although small amounts of ketones may be produced. Hypoglycemia may occur as an isolated finding or may be accompanied by many of the other biochemical derangements typically associated with Reye syndrome, such as hyperammonemia, metabolic acidosis, and elevated transaminases. Hepatomegaly may or may not be present. Any infant presenting with findings suggesting Reye syndrome should be evaluated for fatty acid oxidation defects. Because the incidence of true Reye syndrome has decreased, most children presenting at any age with this constellation of findings have an inherited metabolic disorder.

The most common of the fatty acid oxidation defects is medium-chain acyl CoA dehydrogenase deficiency. In addition to presenting as nonketotic hypoglycemia or a Reye’s-like syndrome, it may present as sudden death or an acute life-threatening event. Many reports of infants diagnosed as having medium-chain acyl CoA dehydrogenase deficiency have described a history of a sibling who died of SIDS. Fat accumulation in the liver or muscle of any infant dying unexpectedly should suggest strongly the possibility of this or a related disorder of fatty acid oxidation. Very long-chain fatty acyl CoA dehydrogenase deficiency is associated with similar clinical findings, although there also may be evidence of a cardiomyopathy. Infants with this and several other fatty acid oxidation defects may present with cardiac arrhythmias or unexplained cardiac arrest.

The accumulation of fatty acyl CoAs in patients with fatty acid oxidation defects leads to a secondary carnitine deficiency, probably as a result of excretion of excess acylcarnitines in the urine. Urine organic acid analysis, measurement of serum carnitine, and analysis of the plasma acylcarnitine profile are the most helpful laboratory studies in the initial screening for defects in fatty acid oxidation. These studies are sufficient to establish the diagnosis of medium-chain acyl CoA dehydrogenase deficiency, which is associated with the presence of a characteristic metabolite, octanoylcarnitine, on the acylcarnitine profile. Enzymatic assays may be necessary for the definitive diagnosis of some of the fatty acid oxidation defects. As is true for the defects in carbohydrate metabolism leading to hypoglycemia, treatment of the fatty acid oxidation defects involves avoidance of fasting and provision of adequate glucose. Restriction of dietary fat intake and supplemental L-carnitine therapy are recommended.

### Table 3. Inborn Errors of Metabolism Associated With Neonatal Liver Disease and Laboratory Studies Useful in Diagnosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Laboratory Studies</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Galactosemia</td>
<td>Urine reducing substances; RBC galactose-1-phosphate uridytransferase</td>
<td>13</td>
</tr>
<tr>
<td>Hereditary tyrosinemia</td>
<td>Plasma quantitative amino acids; urine succinylacetone</td>
<td>14</td>
</tr>
<tr>
<td>α₁-Antitrypsin deficiency</td>
<td>Quantitative serum α₁-antitrypsin; protease inhibitor typing</td>
<td>15</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
<td>Serum ferritin; liver biopsy</td>
<td>16</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td>Plasma very long-chain fatty acids</td>
<td>17</td>
</tr>
<tr>
<td>Niemann–Pick disease type C</td>
<td>Skin biopsy for fibroblast culture; studies of cholesterol esterification and accumulation</td>
<td>18</td>
</tr>
<tr>
<td>GSD type IV (brancher deficiency)</td>
<td>Liver biopsy for histology and biochemical analysis or skin biopsy with assay of branching enzyme in cultured fibroblasts</td>
<td>19</td>
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urine, galactose-containing feedings should be discontinued immediately and replaced by soy formula or other lactose-free formula pending the results of an appropriate enzyme assay on erythrocytes to confirm the diagnosis. Untreated infants with galactosemia, if they survive the neonatal period, have persistent liver disease, cataracts, and severe mental retardation. Many affected infants die of *Escherichia coli* sepsis in the neonatal period, and the early onset of sepsis may alter the presentation of the disorder. Although many states have newborn screening programs for galactosemia, clinical manifestations of the disorder may appear before the results of screening studies are available, and it is therefore critical that physicians remain alert to this possibility.

Another disorder that may be associated with neonatal jaundice is α₁-antitrypsin deficiency, a common condition with clinical manifestations that may be identical to those of traditional neonatal or giant cell hepatitis. A determination of serum α₁-antitrypsin should be a part of the initial evaluation of all children presenting with this syndrome. Hereditary tyrosinemia also should be considered in any child who presents with liver disease in early infancy. The biochemical hallmarks of this disorder include marked elevations of plasma tyrosine and methionine and generalized aminoaciduria with a disproportionate increase in the excretion of tyrosine. However, these findings are relatively nonspecific and may be observed as a secondary phenomenon in other forms of liver disease. Determination of succinylacetone in the urine is a helpful diagnostic test for the disorder.

A recently described and poorly understood disorder, neonatal hemochromatosis, may be the most common cause of congenital cirrhosis. Its fulminating course distinguishes it from many of the other metabolic disorders associated with neonatal liver disease. In addition to being associated with severe liver failure from birth, the disorder is characterized by distinctive hepatic morphology and hepatic and extrahepatic parenchymal iron deposition. Serum ferritin and iron are typically elevated, whereas total transferrin is low, but these findings are not diagnostic. The definitive diagnosis is established by liver biopsy or autopsy. Most infants affected succumb to the disorder during the early weeks of life.

Less common metabolic causes of neonatal liver dysfunction include Niemann–Pick disease type C and GSD type IV. Infants with Niemann–Pick disease type C exhibit cholestatic jaundice that typically resolves by several months of age. They are then clinically normal for a period of months to years before developing findings of a degenerative neurologic disorder. Infants with GSD type IV accumulate an abnormal form of glycogen in the liver as a result of a deficiency of the glycogen branching enzyme. This leads to progressive cirrhosis and generalized hepatic dysfunction. Hypoglycemia is not a prominent feature as it is in some other forms of GSD. Zellweger syndrome, another cause of neonatal jaundice and hepatic dysfunction, is usually recognizable clinically because of the associated hypotonia and dysmorphic features. It is the prototype of the peroxisome assembly disorders and is associated with generalized peroxisomal dysfunction.

In contrast to disorders in which there is an elevation of the direct-reacting bilirubin, a persistent elevation of indirect bilirubin beyond the limits of physiologic jaundice, without evidence of hemolysis, suggests the diagnosis of Crigler–Najjar syndrome. The hyperbilirubinemia in this disorder is related to a partial or complete deficiency of glucuronyl transferase, the liver enzyme responsible for the normal conjugation of bilirubin to bilirubin diglucuronide. In patients with this disorder, the standard modalities of phototherapy and exchange transfusion may prevent the development of kernicterus in the neonatal period.

**Finding Suggestive of a Storage Disease**

Many of the well-known lipid storage diseases do not typically present in early infancy. Among those that occasionally may be associated with hepatosplenomegaly in the first few months of life are GM₁-gangliosidosis type I, Gaucher disease, Niemann–Pick disease, and Wolman disease. The GSDs may be associated with hepatomegaly in the newborn period. Infants with the most common mucopolysaccharidoses, such as the Hurler and Hunter syndromes, uncommonly exhibit clinical abnormalities in the first few months of life. Newborns with the typical features of these syndromes, such as coarse facial features, hepatosplenomegaly, skeletal abnormalities, and hernias, are more likely to have GM₁-gangliosidosis or a mucolipidosis, such as I-cell disease. β-Glucuronidase deficiency, classified as mucopolysaccharidosis type VII, may present in the neonatal period with features virtually indistinguishable clinically from those seen later in Hurler and Hunter syndromes. An infantile form of sialidosis is typically associated with findings at birth. Indeed, the clinical manifestations of several of these conditions may be so severe in utero that fetal hydrops develops.

If one of these disorders is suspected, urine screening tests for mucopolysaccharides and oligosaccharides should be performed. These can be helpful diagnostically, but negative results do not rule out the possibility of a storage disorder. In addition, false-positive mucopolysaccharide test results are commonly observed in neonates. The definitive diagnosis of most lysosomal storage disorders is made by appropriate biochemical studies on leukocytes or cultured skin fibroblasts.

**Abnormal Odor**

Abnormal body or urinary odor, more commonly observed by nurses or mothers rather than by physicians, is an important but often overlooked clue to the diagnosis of several of the inborn errors of metabolism and may be the most specific clinical finding in these patients. In the acutely ill infant with an abnormal odor, isovaleric acidemia, glutaric acidemia type II, and maple syrup urine disease are the most likely entities to be encountered. In maple syrup urine disease, the urine has a distinctive sweet odor, said to be reminiscent of maple syrup or burnt
sugar. The odor associated with isovaleric acidemia and glutaric acidemia type II is pungent and unpleasant and similar to that of sweaty feet.

Dysmorphic Features

There formerly appeared to be a clear distinction between inborn errors of metabolism and dysmorphic syndromes, both of which may be inherited in a similar manner. Infants with inherited metabolic disease were thought to be phenotypically normal at birth, with no evidence of major or minor structural anomalies. It is now apparent, however, that inherited metabolic disorders may be associated with consistent patterns of birth defects, suggesting that metabolic derangements in utero may disrupt the normal process of fetal development.

This phenomenon is illustrated clearly by the group of disorders associated with multiple defects in peroxisomal enzymes, including those involved in fatty acid oxidation and plasmalogen synthesis. These include Zellweger syndrome and neonatal adrenoleukodystrophy and several variant conditions, all of which are associated with congenital hypotonia and dysmorphic features such as epicantal folds, Brushfield spots, large fontanels, simian creases, and renal cysts. Patients with glutaric acidemia type II have a characteristic phenotype including a high forehead, hypertelorism, low set ears, abdominal wall defects, enlarged kidneys, hypospadias, and rocker bottom feet. An energy-deficient mechanism, similar to that postulated for maternal diabetes mellitus, has been suggested to explain these findings. Several of the other organic acidemias, such as mevalonic aciduria and 3-OH-isobutyric aciduria, as well as PDH deficiency, have been associated with multiple dysmorphic features. The dysmorphic findings in PDH deficiency may strongly resemble those observed in fetal alcohol syndrome, and it has been suggested that this resemblance is explained by a common mechanism in the two disorders. It has been postulated that in fetal alcohol syndrome, acetaldehyde from the maternal circulation may inhibit fetal PDH, thus leading to malformations.

The Smith–Lemli–Opitz syndrome is an autosomal recessive disorder associated with a wide range of malformations including dysmorphic facies, cleft palate, congenital heart disease, hypospadias, polydactyly, and syndactyly. Recent observations have revealed that this disorder is an inborn error of cholesterol biosynthesis associated with decreased levels of plasma cholesterol and markedly elevated levels of the cholesterol precursor 7-dehydrocholesterol. The defect in cholesterol synthesis associated with this condition presumably leads to abnormal development in many different organ systems.

Isolated malformations may be even more commonly associated with inherited metabolic disorders than are specific malformation patterns. Patients with nonketotic hyperglycinemia frequently have agenesis of the corpus callosum and may have gyral malformations related to defects in neuronal migration. Agenesis of the corpus callosum also is seen in PDH deficiency. It is not uncommon for patients with almost any of the inborn errors of metabolism to exhibit one or more dysmorphic features or anomalies that are nonspecific. The observation of dysmorphic features in an infant should in no way preclude consideration of an inherited metabolic disorder. In selected circumstances, it may heighten the clinical suspicion.

Abnormal eye findings typically are associated with many of the inborn errors of metabolism, although they are not always found at the time of initial presentation. Cataracts may be observed in galactosemia, Zellweger syndrome, Lowe syndrome, and a number of other conditions. Dislocated lenses, seen in homocystinuria, molybdenum co-factor deficiency, and sulfite oxidase deficiency, may be found as early as the first month of life and are an important clue to the diagnosis. Retinal degenerative changes are typical of the peroxisomal disorders and are observed in several other conditions as well. Other abnormalities that may be associated with inborn errors of metabolism include corneal clouding and congenital glaucoma. A careful eye examination by an ophthalmologist should be performed whenever an inherited metabolic disorder is suspected.

Samples to Obtain From a Dying Child With a Suspected Inborn Error of Metabolism

If death appears imminent in a child suspected of having an inborn error of metabolism, it is important to obtain the appropriate samples for postmortem analysis. This is critical for resolution of the cause of death and is essential for subsequent genetic counseling and prenatal diagnosis. The following samples should be collected and stored: urine, frozen; plasma, separated from whole blood and frozen; and a small snip of skin obtained using sterile technique and stored at room temperature or 37°C in tissue culture medium, if available, or sterile saline. If an autopsy is performed, a sample of unfixed liver tissue should be obtained as soon as possible after death and frozen at −20°C for subsequent biochemical studies. Additional tissue should be preserved for electron microscopy. If consent for autopsy is denied, consent for a postmortem needle biopsy of the liver can be requested. The liver tissue should be frozen in total or in part if histologic studies appear to be indicated. As soon as possible after death, the case should be reviewed with a metabolic specialist and plans made for the transport of samples to the appropriate laboratory.

SUMMARY

Recent advances in diagnosis and treatment have improved significantly the prognosis for many infants with inborn errors of metabolism. Early clinical diagnosis is essential in ensuring that affected infants will receive the benefits of these advances. It is hoped that the guidelines presented in this review will assist the physician in the recognition of infants who may have an inborn error of metabolism and in the initial evaluation and stabilization of these patients.

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Pediatrics 1998;102:e69
DOI: 10.1542/peds.102.6.e69

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/content/102/6/e69.full.html