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Children with Inborn Errors of Metabolism: Recognizing the Unusual and Life-threatening

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The child with an inborn error of metabolism often cannot be easily identified. Nonspecific symptoms and relative infrequent occurrence make diagnosis difficult and can lead to potential delays in both recognition and treatment. Newborn screening tests have been broadened to include more screens to allow for earlier identification and timely interventions. The clinician in the acute care setting must be aware of the possibility of metabolic disorders in the pediatric patient population in order to assure early identification and appropriate therapies, as well as avoidance of inappropriate interventions.

This review article highlights the changes in the newborn screening process in the United States, the subtle presenting signs and symptoms of a child with an undifferentiated metabolic disorder, and the initial testing to screen for a child with a potential metabolic disorder. General treatment guidelines also are reviewed, with an emphasis on initial stabilization and the involvement of a specialist in pediatric metabolic diseases. Finally, the testing indicated for a child who has unexpectedly died due to a possible inborn error is reviewed. A case-based format is used to allow for a practical approach to the care of the child with suspected metabolic disease.

— The Editor

Introduction

Identification of the child with an inborn error of metabolism can be difficult given the varied and subtle presentations. Most clinicians will infrequently care for a patient with a specific metabolic disease given the rarity of specific inborn errors

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of metabolism. Other diagnoses, such as sepsis, toxic ingestion, or non-accidental trauma, should be considered first as these are much more common to those working in an acute care setting. Most inborn errors are found in infants, but also can be first discovered when the patient is an adolescent or adult patient.

The diagnosis does not depend on the clinician's recall of the multiple metabolic pathways learned in his/her days in biochemistry or human development classes. However, the emergency medicine physician must maintain a heightened index of suspicion to allow for a proper and timely diagnosis. Successful treatment is dependent upon prompt therapy to correct the underlying metabolic imbalance.

Incidence

Although a specific inborn error of metabolism is rare, the aggregate incidence is estimated to be as high as one child in every 1,000 births.[1] More than 400 inborn errors of metabolism have been identified and characterized to date.[2] With the development of new technologies, more will undoubtedly be identified in the future.

Many of these disorders are inherited in an autosomal recessive pattern. Boys and girls are, therefore, equally affected. At first glance, family members may not have any symptoms if this type of inheritance is involved. Specific questions about similar symptoms in siblings or about previous unexplained infant deaths may lead to further support of the diagnosis of an inborn error of metabolism. Autosomal dominant and X-linked dominant modes of inheritance also are possible. A detailed family history may provide information for these types of inborn errors.[3] The majority of cases appear to be sporadic, however, and early recognition with the first birth is ideal.

Pathophysiology

Many times, children with these disorders will present in the newborn period because of the transition to a relatively catabolic state. The placenta serves as an effective filtering system for the elimination of toxic metabolites. Most infants with an inborn error are born in good condition and have normal birth weights. Children with disorders such as mucopolysaccharidoses or purine and pyrimidine disorders have slow progressive encephalopathies; therefore, these children will present later than the newborn period, as abnormal deposits build up over time.

Those disorders that give rise to toxic presentations include inborn errors of intermediary metabolism that lead to accumulation of toxic compounds proximal to the metabolic block. Examples of this group include aminoacidopathies like maple syrup urine disease, most organic acidemias like isovaleric acidemia, congenital urea cycle defects, and sugar intolerances like galactosemia. Children with these conditions often present with a symptom-free interval that is followed by clinical signs such as vomiting, lethargy, coma, or liver failure. These disorders require an early intervention to remove the toxin by special diets, exchange transfusion, peritoneal dialysis, or hemofiltration.

The disorders that involve energy metabolism involve either a deficiency in energy production or utilization resulting from a defect in the liver, myocardium, muscle, or brain. Defects in gluconeogenesis, fatty acid oxidation, and lactic acid production are included in this group and most often present with hypoglycemia. Other symptoms include failure to thrive, generalized hypotonia, cardiomyopathy, cardiac failure, sudden infant death, and dysmorphic features.

Another group of disorders involve disturbance in the synthesis or catabolism of complex molecules. Symptoms are permanent, progressive, independent of acute insults, and are not dependent on food intake. Lysosomal disorders, peroxisomal disorders, and inborn errors of cholesterol synthesis are included in this group and almost none are amenable to acute treatment.[4]

Case #1

An infant male is sent to your emergency department (ED) for further evaluation after an abnormal newborn screening test result comes back positive for suspected isovaleric acidemia. The primary care provider was contacted about the state screen results on day of life number 3. He is being sent to the ED for an overall assessment and for confirmatory testing.

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The infant was born at term after an unremarkable pregnancy to a healthy 21-year-old mother who had one previous spontaneous abortion. The child's birth weight was 3.015 kg. He is exclusively formula fed and has otherwise been doing well. He has had no fevers or change in his feeding or sleeping patterns. He awakens every two hours for feedings and has had no vomiting or diarrhea. He also has had no jaundice.

On physical exam, the child is vigorous and has no fever. His skin is clear of any rashes or abnormal markings. His heart exam shows a regular rate and rhythm without any murmurs. He has good pulses throughout and brisk capillary refill time. His lungs are clear and his work of breathing is normal. His abdominal exam revealed no tenderness, distension, or hepatosplenomegaly. He is a circumcised male with testes descended bilaterally. The baby cries vigorously during your exam and is easily consoled by his parents. He has good muscle strength and tone. His anterior fontanelle is soft and flat.

The medical geneticist on-call is contacted for any recommendations. They have asked that a urine sample be sent for confirmatory organic acid analysis. They also asked that plasma amino acids and acylcarnitines be obtained, along with serum electrolytes and blood glucose. They recommend that the child be started on simple electrolyte replacement solution overnight until a leucine-free diet can be started the next day if the testing confirms the diagnosis.

Newborn Screening for Metabolic Disorders. In an ideal world, all inborn errors of metabolism would be identified before any symptoms develop. If this were the case, children and their families could avoid delays in both diagnosis and treatment, as well as the potential for a catastrophic and possibly life-threatening event. Clinicians would be prepared, in advance, to care for these children earlier in their presentations and could potentially prevent extensive laboratory testing. Hospitalizations also could be avoided.

The initial newborn screening programs were instituted to identify those inborn errors of metabolism that benefited from early treatment. The classic example of such a disorder was phenylketonuria (PKU), in which avoidance of phenylalanine from early infancy prevented the development of developmental delays.[5] All 50 states screen newborns for PKU, congenital hypothyroidism, and galactosemia.[6]

With the advances in newborn screening techniques, more and more inborn errors of metabolism can now be identified before any signs or symptoms develop. Clinicians are reminded to check on the results of a patient's newborn screen at the time of their presentation for care. The results of the newborn screen are generally not available until after the child has been discharged from the newborn nursery. The testing done in each state continues to vary.[7,8] The most current information regarding newborn screening for each state can be accessed through the National Newborn Screening and Genetics Resource Center in Austin, Texas, at their web site (http://genes-r-us.uthscsa.edu).[9]

Tandem mass spectrometry (MS/MS) has become the standard for many state newborn screening programs.[10] This technology allows testing for a number of inborn errors of metabolism from a small blood sample. A neonate may be screened for up to 30 different disorders depending on the state in which they were born. Disorders that can be detected by this technology include organic acidemias, fatty acid oxidation defects, and urea cycle defects. The MS/MS technology also is more sensitive and specific than usual screening methods used for aminoacidemias. When MS/MS was compared with the usual fluorometric analysis for PKU detection, MS/MS not only confirmed all previous cases detected by the older methodology, but it also reduced the number of false-positive results from 91 to 3.[10]

Once a child is identified as having an inborn error of metabolism, he or she should be referred to a specialist in metabolic diseases. These specialists include medical geneticists, pediatric endocrinologists, and pediatric neurologists. The clinician should not hesitate to contact the patient's metabolic specialist whenever the child presents for care. Many of the families caring for these children will bring a copy of their child's care protocol or a recent hospital discharge summary with them when they present for care in the ED. Current medications, recommended testing and treatment, and contact information are clearly outlined on these care protocols. Some institutions also will have these care profiles compiled in a dedicated area of the medical record or in a separate care file. An emergency information form (EIF) for children with special health care needs also can be utilized for children with inborn errors of metabolism and is available through the American Academy of Pediatrics (AAP) and the American College of Emergency Physicians (ACEP).

Signs and Symptoms

Children with inborn errors of metabolism can present to the clinician in a variety of ways. The report of an abnormal newborn screening test before symptoms have had a chance to develop is the most desirable for both the parents and the clinician. Other children can present as intrauterine death or as sudden death at birth or in the first few days of life. In some cases, there is gradual deterioration of a newborn after a normal pregnancy and delivery.

There are some clinical presentations that are rather predictable of an inborn error of metabolism and should prompt the clinician to initiate prompt, appropriate testing and therapies. These include acute metabolic encephalopathy, hypoglycemia, cardiac disease, or sudden neonatal death. *(See Table 1.)*

The infant with acute neurologic decline may present with lethargy, poor feeding, vomiting with diarrhea and dehydration, or seizures. Calvo and colleagues[11] completed a retrospective review of 53 pediatric patients with a final diagnosis of an inborn error of metabolism who had previously required clinical attention at their ED over a 9-year period. They found a predominance of neurologic signs (85%), followed by digestive symptoms (58%), in this group of patients. Both of these signs were

Table 1. Signs and Symptoms of Inborn Errors of Metabolism

- ❑ Poor feeding/refusal to feed
- ❑ Periods of difficulty consoling
- ❑ Periods of difficulty awakening
- ❑ Vomiting
- ❑ Failure to thrive
- ❑ Hypotonia
- ❑ Hypertonia
- ❑ Tachypnea
- ❑ Tachycardia
- ❑ Hypoglycemia
- ❑ Acidosis
- ❑ Dehydration, especially if recurrent
- ❑ Apnea
- ❑ Seizures
- ❑ Altered mental status
- ❑ Sudden unexplained death
- ❑ Cardiomegaly
- ❑ Arrhythmia
- ❑ Shock
- ❑ Loss of thermoregulation

found in 51% of their patients. Only 7.5% of their patients presented without either neurologic or digestive signs. The neurologic signs included: tone abnormalities, lethargy, coma, seizures, irritability, and psychomotor delay. Only 36.4% of patients with an identified inborn error had previously been suspected of such a problem.

In terms of specific disorders, organic acidemias, urea cycle disorders, and disorders of amino acid metabolism can present with acute encephalopathy. As toxic metabolites accumulate in the central nervous system, the infant will demonstrate poor feeding and become progressively more lethargic. Other findings can include seizures, abnormal muscle tone, and intracranial hemorrhage. Most of these toxic metabolites cross the placenta and are cleared by the mother during gestation, allowing the child to appear normal at the time of birth. The interval between birth and the onset of symptoms varies and can range between hours and months.

Children with metabolic disorders may have sepsis associated with their initial presentation for care. Although clinicians generally think about one diagnosis as the cause for presenting symptoms, both sepsis and an inborn error of metabolism may be present in these children. The classic example of an inborn error of metabolism causing a predisposition to sepsis is galactosemia. Children with galactosemia are at greater risk of developing sepsis due to gram-negative organisms.[12]

In terms of age of presentation, the newborn period is certainly most common but the possibility of an inborn error of metabolism should be included in the differential diagnosis for a wide age range. If recurrent episodes of stupor, lethargy, or vomiting (especially with dehydration) occur, an inborn error should be suspected. Other situations suggesting an inborn error include: children with failure to thrive, dystonia, choreoathetosis, myoclonus, hypotonia, unexplained seizures, developmental delay, or cerebral palsy.

The history of a patient with an inborn error also may include an aversion to specific foods or an apparent extreme response to an illness that did not seem to have much effect on other family members.

Physical findings might include tachypnea, hepatomegaly, cataracts, jaundice, microcephaly, or an unusual odor. Galactosemia is the best known metabolic disease associated with jaundice. In this disorder, a deficiency of the enzyme galactose-1-phosphate uridyl transferase results in an accumulation of galactose-1-phosphate and other metabolites that are thought to have a directly toxic effect on the liver. Infants usually develop jaundice at the end of the first week or early in the second week of life. Indirect hyperbilirubinemia results from hemolysis secondary to high levels of galactose-1-phosphate in erythrocytes.

Cardiomegaly with congestive heart failure and hepatomegaly may be the clinical manifestations of children with glycogen storage disease type II or Pompe's disease. Unlike the other glycogen storage diseases, this disorder does not have hypoglycemia as a feature. Glycogen metabolism and release at the cytoplasmic level are normal in this disorder in which glycogen accumulates within lysosomes as a result of deficiency of the enzyme acid maltase. Macroglossia and hypotonia also can be prominent clinical features. Cardiomegaly, however, is the most striking feature and can be apparent even in the neonatal period. Congestive heart failure is the cause of death in most cases.[13]

Finally, unusual odors can lead to a suspicion of an inborn error of metabolism. Patients with maple syrup urine disease have urine that has a distinctive sweet odor similar to maple syrup or burnt sugar. Isovaleric acidemia and glutaric acidemia type II are associated with a pungent odor similar to the smell of sweaty feet.

Case #2

A 4-day-old female who was born at term after an uneventful pregnancy is brought to the ED when the mother noted the child had stopped breathing. They gave her several rescue breaths approximately 30 minutes earlier and the child began to cry afterward. They also report that the child has been difficult to arouse today. She has had no fevers, vomiting, diarrhea, cold symptoms, or cough. There are no other children at home, but the mother reports that their first two children died soon after birth. The child's birth weight was 8 pounds and 9 ounces. The mother noted that the child did not cry when she was born. She required some stimulation at birth and was observed in a NICU at another facility before being sent home on her second day of life. Since being home, the mother reported that the infant only

opened her eyes occasionally. The mother and grandmother reported that they felt the infant did not cry very much and was a "slow feeder." They state that the child has had frequent episodes of hiccups.

The child's temperature is 36.9 rectally. Her heart rate is 188, and respiratory rate is 32. Her oxygen saturation is 88% on room air. She has poor muscle tone and her respirations are irregular. She has no retractions, grunting, or wheezing. She has good peripheral pulses. Her anterior fontanelle is slightly sunken. Her sclerae are anicteric. Her mucous membranes are tacky. She has no detectable murmurs. Her abdomen is not distended and she has no hepatosplenomegaly, masses, or tenderness. Her skin is free of any petechiae, purpura, rashes, ecchymosis, or abrasions.

Supplemental oxygen is applied by simple mask, with improvement in her saturations but not in her respiratory effort. The infant does not withdraw from painful stimuli. She is noted to have rhythmic jerking movements of all four of her extremities for 1 to 2 minutes with no change in her vital signs. An intraosseous needle is used to obtain vascular access in her right tibia. Laboratory tests including electrolytes, glucose, and a blood culture are obtained. Her bedside glucose is 164. She is given a fluid bolus of normal saline with no change in her condition or vital signs.

She is given several 0.4 mg doses of lorazepam without any observed changes in vital signs or physical exam. She is given a 20 mg/kg loading dose of phenobarbital as well with no observable changes. She becomes completely apneic and is easily intubated using a 4.0 oral endotracheal tube. An indwelling urinary catheter is placed and a urine dipstick test is negative for nitrates, leukocytes, blood, ketones, or glucose. A urine culture is sent. A urine drug screen for drugs of abuse is negative.

A CT scan of her head reveals a small arachnoid cyst on the left side at the parietal-occipital area with a small area of surrounding hemorrhage. There is no evidence of cerebral edema or hydrocephalus.

CSF is obtained and the analysis shows 9 WBCs with 15% lymphocytes, 84% monocytes, and 12 RBCs. The Gram's stain on the CSF is negative. The protein is 77 and the glucose is 44. CSF culture and PCR testing for HSV infection also are sent. These were later found to be negative.

Ampicillin, cefotaxime, and acyclovir also were administered prior to the patient being admitted to the pediatric intensive care unit (PICU). Her urine and blood cultures were later found to be negative.

Both pediatric neurology and medical genetics are consulted. They recommend that additional testing be completed, including serum calcium, magnesium, phosphorous, ammonia, lactate, pyruvate, amino acid analysis, and chromosome testing. They also recommend urine studies for organic acids, and that the child not receive any protein until the ammonia level was known. Finally, they recommend that a plasma and CSF glycine level be obtained as well.

EEG monitoring is initiated soon after her arrival to the PICU. The EEG revealed that seizure activity is present in association with the infant's hiccups and head deviation. The patient is given further doses of phenobarbital until the seizure activity stops on the EEG monitor.

The patient's calcium, magnesium, phosphorous, and ammonia levels are normal. The plasma glycine level is 1,207 with a CSF glycine level of 304. As this CSF to plasma glycine level is much greater than 0.08, a diagnosis of nonketotic hyperglycinemia is made.

The patient was started on sodium benzoate, dextromethorphan, carnitine, and folinic acid as therapy. The child was eventually weaned off the ventilator over the following several days. Her diet was advanced as tolerated. She required placement of a gastrostomy tube for feedings as she did not show interest in her feedings offered orally. The child was discharged home to her mother and grandmother's care after a 4-week hospital stay.

Metabolic Disorders Associated with Seizures. A number of metabolic disorders are associated with isolated seizures, with or without progression to encephalopathy. Of the many inherited disorders, about 200 are associated with seizures and approximately 50 of these are known to present in infancy.[14] Seizures in infants may be difficult to recognize as their presentation can be subtle. Infants may demonstrate a sudden arrest of ongoing behavior, abruptly stop spontaneous movements, become pale or show mild circumoral cyanosis, or develop mild tachycardia. There may be no associated clonus, dystonia, or tonic posture. Simple, repetitive movements such as mouthing movements, lip-smacking, or bicycling leg movements can be seen. These movements may not be recognized or might be attributed to another cause. The observations of parents can be very helpful in the diagnosis of seizures in newborns. The parents are familiar with their child's typical behavior and will most likely be the first to notice changes that indicate seizure activity.

There appears to be no type of seizure activity that would specifically implicate an inborn error of metabolism as the underlying problem. Every manifestation of infantile seizure has been described, although myoclonus is the most commonly noted feature.[14] Intractable seizures also can be indicative of an underlying inborn error. In a practice parameter from the American Academy of Neurology published in 2006, studies for an inborn error of metabolism should be considered when the initial evaluation for status epilepticus reveals no etiology with the specific studies dependent upon the history and the clinical examination.[15] There was insufficient evidence to support or refute which studies should be done routinely and whether genetic testing should be done routinely in children with status epilepticus. The parameter was based upon a review of the literature, which found that 4.2% (range, 1.2 to 8.3%; median 4.0%; 95% CI, 2.9% to 5.8%) of children presenting with status epilepticus were diagnosed or had an inborn error of metabolism.

No antiepileptic medications are specifically preferred for seizures caused by metabolic defects. The approach to the child with seizures due to an underlying metabolic disorder should be the same as for any child presenting with status epilepticus. Support of airway, breathing, and circulation must take precedence, with attention given to identification and treatment of potentially reversible causes. Correction of underlying electrolyte or glucose abnormalities should be initiated. Hypoglycemia (glucose <50 mg/dL) should be corrected by administration of 0.5 gm/kg of dextrose (5 mL/kg of D 10 for an infant).[16] For those children with hypoglycemia refractory to dextrose infusions, glucagon can be considered in a dose of 1 mg via intramuscular injection. Hypocalcemia should be corrected using either 20 mg/kg (0.2 mL/kg) of 10% calcium chloride or 60-100 mg/kg (0.6-1 mL/kg) of 10% calcium gluconate through a slow IV/IO push.

Hypoglycemia is commonly seen in infants with disorders of carbohydrate metabolism or fatty acid oxidation. Children with hepatic glycogen storage diseases may also present with hypoglycemia. The hypoglycemia in these disorders is related to the inability of the liver to release glucose from glycogen and is most likely to be found during periods of fasting. Hypoglycemia, hepatomegaly, and lactic acidosis are prominent features of these disorders. Hypoglycemia also can be a prominent feature of galactosemia.

The seizures caused by an underlying metabolic disorder can be very difficult to control and may not respond to the usual antiepileptic therapies. Seizures may continue until appropriate treatment aimed at the underlying metabolic disorder is given. In the case of non-ketotic hyperglycinemia, there is loss of the inhibitory neurotransmitter, glycine, in the brainstem and spinal cord. Administration of sodium benzoate may lower the glycine and improve survival.[17]

Approximately two-thirds of patients who have non-ketotic hyperglycinemia exhibit symptoms in the first 48 hours of life. These children typically present with lethargy, apnea, profound hypotonia, feeding difficulties, hiccups, and intractable seizures. CSF and blood samples must be obtained simultaneously as they are needed for glycine analysis. A CSF-to-plasma glycine ratio of greater than 0.08 confirms the diagnosis.

Pyridoxine-dependent seizures also may be responsible for seizures refractory to usual treatment in the newborn period. These children often present with neonatal encephalopathy with hyper-alertness, irritability, and a sensitive startle reflex. They also can demonstrate respiratory distress, abdominal distension, and vomiting. Laboratory tests often reveal a metabolic acidosis. Structural abnormalities of the brain such as hypoplasia of the posterior part of the corpus callosum, cerebellar hypoplasia, or hydrocephalus should heighten suspicion for this deficiency and the need for treatment with pyridoxine to control seizure activity. Prompt resolution of seizure activity is seen within minutes after 100 mg of pyridoxine is given. The only way to confirm the diagnosis of pyridoxine-dependent epilepsy is to withdraw pyridoxine and demonstrate recurrence of seizures, followed by prompt resolution when pyridoxine is administered again.[17]

Laboratory Testing

Once an inborn error of metabolism is considered, laboratory tests optimally should be obtained prior to initiation of any therapy. Certainly, proper attention to the patient's airway, breathing, and circulation cannot be overlooked, as noted earlier. It may be helpful for the clinician to develop a department-wide protocol that includes laboratory testing for the pediatric patient who presents with various conditions that require emergent management and may be caused by an underlying metabolic disorder. The clinical condition of the patient at the time of their presentation to the ED provides a unique window of opportunity to obtain lab samples that could lead to a definitive diagnosis. Proper handling of the specimens is important to ensure accurate results.

Chemistries should include electrolytes, glucose, serum pH, lactate, liver enzyme tests, and ammonia levels. A urinalysis also will provide information about the production of ketones or reducing substances. Both plasma and urine for amino acids and urine for organic acids analysis can provide vital information to those who will provide further evaluation to determine if an inborn error of metabolism is indeed present.

Many of the children with inborn errors of metabolism demonstrate a metabolic acidosis during an acute episode of illness or upon initial presentation. Routine blood gases and electrolyte measurements will identify these abnormalities.

The group of inborn errors typically associated with metabolic acidosis is the group of organic acidemias (methylmalonic acidemia, propionic acidemia, and isovaleric acidemia). Plasma lactate often is elevated in organic acidemias as a result of interference with co-enzyme A (CoA) metabolism.[18] Neutropenia and thrombocytopenia also are often found and may lead the clinician to suspect sepsis instead of a metabolic disorder. Defects in pyruvate metabolism or in the respiratory chain may lead to primary lactic acidosis and metabolic acidosis. These disorders should be considered in those patients whose symptoms do not appear to be related to protein intake and those with lactic acidosis with normal urine organic acids.

Fatty acid oxidation disorders (such as medium-chain acyl-CoA dehydrogenase deficiency or MCAD) also are associated with a metabolic acidosis, along with a Reye syndrome-like presentation. Approximately 5-10% of unexplained sudden infant deaths may be attributed to these disorders.[19]

Table 2 outlines suggested initial laboratory testing for a child suspected of having an inborn error of metabolism.[18]

Case #3

A 2-year-old girl is brought to the ED for evaluation of "trouble walking." The parents note that she has been walking clumsily for the past few days. They initially thought that she was simply more tired than usual as she had been staying at

Table 2. Suggested Initial Laboratory Testing for a Child with Suspected Inborn Error of Metabolism

- ❑ Blood gases
- ❑ Blood glucose
- ❑ Plasma ammonia
- ❑ Plasma amino acids
- ❑ Serum electrolytes
- ❑ Serum liver function tests
- ❑ Blood lactate and pyruvate
- ❑ Complete blood cell count with differential
- ❑ Urinalysis
- ❑ Urine reducing substances
- ❑ Urine organic acids and amino acids

Note: Plasma and urine also should be frozen for assay of additional metabolites or hormones that might be present only during acute decompensation

her grandparents' home over the weekend while they were on a vacation. They became more concerned when she seemed to be confused, answered questions very slowly, and slept much longer than usual over the course of the past 24 hours. They were concerned that their daughter had possibly ingested a medication while at the grandparents' home; the grandmother takes several medications for hypertension and type II diabetes. The parents had called the grandmother, who tried to reassure them that all of the medication was accounted for and did not see how the child could have ingested anything over the weekend.

The patient had no recent fevers, cold symptoms, or cough. She had been eating and drinking as she normally did. Her urine output was good. She had no vomiting or diarrhea. The parents did report that she was a "picky eater" and had always been small for her age.

On physical exam, she is afebrile with normal vital signs. She is slow to answer questions and does not seem to focus well even with her parents. Her speech is difficult to understand. She has no evidence of trauma. Her pupils are equal, round, and reactive to light. Her mucous membranes are moist. Her sclerae are anicteric. Her skin is warm and dry with no rashes. Her lungs are clear. Her heart exam reveals no murmurs. Her pulses and perfusion are good. She has no joint swelling or extremity tenderness. She is only able to stand with support and she needed assistance with walking. Her gait is very wide-based.

A CT scan of her head is normal. Her electrolytes and blood glucose are within normal limits. A serum drug screen is negative. A urinalysis shows no glucose or ketones. Her lactate level also is normal. A lumbar puncture is completed and reveals no white blood cells or red blood cells and has normal glucose and protein levels. Her ammonia level is elevated at 267. Based upon her lack of acidosis in the setting of hyperammonemia, she is diagnosed with a urea cycle defect, ornithine transcarbamoylase deficiency (OTCD).

Hyperammonemia. Hyperammonemia is one of the possible underlying causes for the development of encephalopathy in children with an inborn error of metabolism. A plasma ammonia level should be obtained on any newborn presenting with encephalopathic symptoms, including unexplained vomiting or lethargy. Significant hyperammonemia is found in only a limited number of conditions; urea cycle defects and many of the organic acidemias are at the top of the list of these conditions. Newborns with an organic acidemia can be symptomatic within the first 24 hours of life but usually present beyond this time frame. Other potential causes for hyperammonemia in the newborn include sepsis, generalized infection with herpes simplex infection, or perinatal asphyxia.

The child with significant hyperammonemia (>400 mcmol/L and often >2000 mcmol/L) most often has a defect in the urea cycle. Infants with transient hyperammonemia of the newborn (THAN), organic acidemias (e.g., propionic, isovaleric, and methylmalonic acidemias), and fatty acid oxidation defects (e.g., carnitine uptake defect, carnitine palmitoyltransferase I deficiency) may have similar elevations in ammonia levels due to a secondary inhibition of the urea cycle by toxic metabolites.

The timing of the onset of symptoms may provide an important clue to the etiology for hyperammonemia. Patients with some type of organic acidemia, such as glutaric acidemia type II or with pyruvate carboxylase deficiency, may exhibit symptoms within the first 24 hours of life. Symptoms in the first 24 hours also may be characteristic of THAN, a condition that is not genetically determined. The typical patient with this disorder is a large, premature infant with a mean gestational age of 36 weeks. These children have symptomatic pulmonary disease from birth in addition to severe hyperammonemia. The condition also can occur in term infants without respiratory symptoms. Survivors do not have recurrent episodes of hyperammonemia and may or may not have neurologic sequelae depending upon the extent of the neonatal insult.[3,18]

Additional lab tests will help narrow the differential diagnosis for children with hyperammonemia. Urea cycle defects usually are not associated with significant metabolic acidosis or ketosis. Organic acidemias do cause these derangements; therefore, measurement of blood gases, electrolytes, and urine ketones can help distinguish between these two types of disorders. If tissue hypoxia is present in the critically ill infant, however, distinction between these two disorders may be difficult.

If hypoglycemia is found along with hyperammonemia, a fatty acid oxidation defect would be more likely.

The inheritance of these disorders is fairly straightforward. All of the conditions that cause hyperammonemia are transmitted through an autosomal recessive pattern, with the exception of ornithine transcarbamoylase deficiency (OTCD). Autosomal recessive traits are the result of two carrier parents and cause a

25% rate of recurrence. OTCD is inherited through variable X-inactivation, resulting in 50% of sons and 50% of daughters being affected and no male-to-male transmission occurring.

Newborns with hyperammonemia usually present in the first few days of life, with rapid deterioration in their mental status manifesting as repetitive vomiting and decreased interest in any feeding. Older children, such as the child in the case presentation, often have a history of repetitive vomiting episodes and may demonstrate avoidance of protein intake. They become symptomatic when being challenged with a protein meal or with an acute illness that other family members don't seem to be affected by to the same degree.

Treatment

Although treatment must be tailored to each of the inborn errors of metabolism, the initial approach should be stabilization of any child and must take first priority. Attention to vital signs and physical findings cannot be lost in an effort to obtain the correct type of sample, correct amount of sample, or correct sample collection method. Assessment of the child's general appearance and mental status is important to discover many of the metabolic disorders. The ability of the child to protect and maintain his/her own airway is still the paramount evaluation step, especially in those children with seizures or altered mental status. Evaluation of breathing effectiveness must be assessed and monitored over time as interventions are made and medications are given. Circulatory support may be necessary for the child with an inborn error who has poor perfusion due to an underlying disorder, dehydration, or concomitant sepsis. Figure 1 outlines an initial approach to the child with seizures, including special consideration for the child with a suspected inborn error of metabolism.

Adequate volume resuscitation with isotonic fluid therapy is indicated for those children with evidence of dehydration or shock. Correction of hypoglycemia also is important as part of the initial evaluation of the child with a suspected inborn error of metabolism. Attempts to obtain lab tests before any interventions again might be helpful. After adequate volume resuscitation, maintenance fluids of an appropriate type should be continued, with close attention given to changes in vital signs, mental status, perfusion, and urine output.

Other treatments are best initiated after consultation with a specialist in metabolic diseases if it is at all possible. The emergency physician should discuss with the specialist what specific testing, medication dosing, and type of feedings, if any, can take place to optimize testing without delays in treatment.

Experienced parents often are the best and most readily available resource for the emergency physician who is caring for a child with a known inborn error of metabolism. Frequently, they have been instructed to direct the evaluation and treatment for their son or daughter and may be a valuable resource. They should be questioned regarding previous episodes and of similarities to the current episode and previously effective treatments.

Figure 1. General Approach to the Child with Seizures *

ASSESS AIRWAY, BREATHING, AND CIRCULATION

Provide supplemental oxygen
Establish IV access
Place patient on cardiac monitor
Check patient's temperature
Check bedside glucose test

If blood glucose <50, give supplemental dextrose 0.5-1 gm/kg
Infant: 5 mL/kg of D 10
Toddler: 2-4 mL/kg of D 25
Adolescent: 1 mL/kg of D 50

If febrile, give rectal acetaminophen at 10-20 mg/kg

MEDICATION

Benzodiazepines (first-line choice)

Lorazepam 0.05-0.1 mg/kg IV

Buccal midazolam 0.2 mg/kg

IM midazolam 0.1 mg/kg

Rectal diazepam 0.3-0.5 mg/kg (may repeat X 2)

Obtain lab tests as indicated:
Blood cultures, urine cultures, and CSF if febrile for prolonged seizures with fever
Electrolytes if volume losses known or suspected ingestion
Toxicology screens
Anticonvulsant levels

Fosphenytoin (second-line choice)
10-20 mg PE/kg IV/IO/IM
Pay close attention to vital signs and cardiac rhythm during infusion

Phenobarbital (third-line choice)
(Be aware of risk for significant respiratory depression)
10-20 mg/kg IV/IO

If not already done so, strongly consider securing airway using rapid sequence intubation

ADDITIONAL LAB TESTS TO CONSIDER (CHILDREN < 1YR):

Blood gases
Plasma ammonia
Plasma amino acids
Serum liver function tests
Blood lactate and pyruvate
Complete blood cell count with differential

Urinalysis
Urine-reducing substances
Urine organic acids and amino acids
Check newborn screening results

(Involvement of pediatric neurology and metabolic specialist strongly encouraged)

SPECIAL CONSIDERATIONS:

Pyridoxine 100 mg IV (refractory seizures in children <1 yr or suspected isoniazid toxicity)

General anesthesia or barbiturate coma (requires EEG monitoring and PICU setting).

* Figure adapted from: Chiang VW. Seizures. In: *Textbook of Pediatric Emergency Medicine*. 5th ed. Lippincott Williams and Wilkins, 2006:629-636.

Treatment of hyperammonemia involves creation of alternative pathways for nitrogen excretion. Consultation with a metabolic specialist or geneticist should be made as soon as possible. In general, all oral intake should be stopped and ammonia should be cleared if significantly elevated. Concomitant hypoglycemia or acidosis also should be identified and treated. Airway protection, including intubation, may be necessary if the child's mental status is severely impaired. Peritoneal dialysis, continuous arteriovenous hemoperfusion, and exchange transfusion have been used to lower plasma ammonia levels, but these modalities are less effective than hemodialysis.[18] In those children with evidence of cerebral edema, dialysis is the treatment of choice rather than dietary manipulation, medications, or other less aggressive therapy. Sodium benzoate (500 mg/kg/day) given intravenously and sodium phenylbutyrate (600 mg/kg/day) either orally or intravenously are used to cause a drop in serum ammonia levels.[19] In patients suspected of having a urea cycle defect (i.e., significant hyperammonemia without acidosis), an infusion of 6 mL/kg of 10% arginine HCL can be given intravenously over 90 minutes.[18] Parenteral, high-energy, protein-free nutrition must be initiated, keeping in mind that fluid restriction may be necessary if there are signs of cerebral edema. Once the ammonia level is less than 150 mcmol/L, intravenous amino acids must be added and progressively increased. Only after the blood ammonia levels have stabilized, can enteral nutrition be restarted.

Case #4

A case report of a 19-year-old woman is made by Wilhelm.[22] She was brought to the ED by ambulance from another hospital for evaluation of new onset altered mental status. Her family and friends reported that she had been camping at a park for the weekend and she became ill on the second day of camping. The patient had consumed 6 or 7 shots of liquor and smoked marijuana during the afternoon and evening before becoming ill. The patient began to vomit on the morning of her ED visit. She became intermittently disoriented and drowsy. Her friends had taken her to the referring hospital. She received approximately one liter of D5 0.45 NS prior to transfer.

At the receiving hospital, the patient's family stated that she had no known medical problems and had taken Pepto-Bismol after becoming ill. They reported that she was allergic to aspirin but had no other medication allergies. When interviewed, the patient was oriented to person and place, was able to follow commands, and was speaking normally. She was afebrile. Her heart rate was 100 and her blood pressure was 70/20. Her respiratory rate was 20 and her oxygen saturation was 99% on room air. The patient had no evidence of trauma and she had no nuchal rigidity. The patient's motor strength was normal as were her reflexes, including her plantar reflexes. She was given a liter of normal saline and her blood pressure improved and remained above 100 mm Hg systolic. The patient was noted to have an ataxic gait.

Her evaluation included normal serum electrolytes except for a serum bicarbonate level of 18 mEq/L and an anion gap of 19. The blood glucose was 88. Her complete blood count was normal, as were her serum calcium and liver enzymes. Her blood urea nitrogen was elevated to 27 mg/dL. A urinalysis had a small amount of ketones present. A urine pregnancy test was negative. A computed tomography (CT) scan of the head was performed and was normal. A urine drug screen was later reported positive for marijuana, and the blood alcohol was negative.

The patient was admitted to the hospital at 5:30 a.m. At 9:30 a.m., she was found to be restless by nursing personnel. Fifteen minutes later, she was found to be pulseless and apneic. Cardiopulmonary resuscitation was begun, but was unsuccessful, and she was pronounced dead soon after the pulseless event.

A postmortem examination revealed macrovesicular steatosis or fatty changes of the liver. The neurologists caring for her recognized the similarity between the patient's clinical course and that of patients with chronic valproic acid toxicity. This led to analysis on premortem blood for plasma acylcarnitine profiling to determine the presence of a possible defect of fatty acid metabolism. This profile showed that octanyl carnitine was markedly elevated, indicating the presence of a genetic enzyme defect, medium chain acyl coenzyme-A dehydrogenase (MCAD) deficiency. A genetics laboratory was able to determine that the patient actually had two different mutations for the gene that codes for MCAD. One of the mutations was the most common mutation for MCAD.

The family was informed of the results of the complete postmortem examinations. They revealed that the patient had been hospitalized at age 2 years for a "Reye's syndrome-like illness."

MCAD Deficiency. MCAD deficiency is recognized as the most common inherited disorder of fatty acid oxidation. The inheritance pattern is autosomal recessive. If undiagnosed, MCAD deficiency has a reported mortality rate of up to 25%.[23] MCAD is necessary for the mitochondrial beta-oxidation of fatty acids; beta-oxidation is important in the energy production during fasting states as glycogen stores become depleted. In the absence of fasting, the patient appears to be well.

The most common presentation for a patient with MCAD deficiency is hypoglycemia without the compensatory production of ketones. Most patients will present within the first 2 years of life, with few presenting for care after age 4 years. Some children will present as a SIDS (sudden infant death syndrome) or a near-SIDS episode. Any fasting state, febrile illness, or alcohol consumption may lead to decompensation, including progressive lethargy, seizures, or coma. The patient's altered mental status may be caused by hypoglycemia, hyperammonemia, or increased toxic fatty acid intermediates.

An increased anion gap may be present due to the increased free fatty acids. The patient's blood glucose usually will be low due to impaired gluconeogenesis and depletion of glucose production. There also may be elevation in the serum ammonia

Table 3. Postmortem Samples for Evaluation of Possible Inborn Error of Metabolism

WHOLE BLOOD
5 mL in an ethylenediamine tetraacetic acid tube for DNA analysis (refrigerated at 4°C)
URINE
5 mL or more for amino acid and organic acid profiles, acylglycines, and orotic acid (frozen)
CSF
1-3 mL for amino acid analysis (frozen)
Consult with metabolic expert before obtaining unless sample already obtained
SKIN
3 X 2 mm full thickness collected under sterile conditions into tissue culture medium or saline (do NOT use iodine-containing preparations)
LIVER AND MUSCLE BIOPSIES
For electron microscopy, histopathology, and enzymology
Collect within 2-4 hours of death
Flash frozen in liquid nitrogen or on dry ice

and liver function tests. Urine ketones may be absent due to diminished production from the normal oxidation of fatty acids.

For those clinicians who have been in practice for a longer period of time, the case presentation above might be reminiscent of patients they have diagnosed with Reye's syndrome. Some authors now feel that many cases of Reye's syndrome were actually presentations of underlying metabolic disorders such as MCAD deficiency.[24] The number of cases of Reye's syndrome has decreased significantly in the past 20 years, and at the same time an increased number of cases of metabolic disorders, including MCAD deficiency, have been reported.[25]

This case also highlights the need to keep inborn errors of metabolism in mind for the older patient population as well. The clinician should especially be concerned if a patient has presented with repeated episodes of acidosis in the setting of stressors as mentioned above. MCAD deficiency is phenotypically heterogeneous. Patients can present in a variable fashion, with some patients never demonstrating any illness.[26]

The importance of a postmortem exam also is highlighted in this case presentation. An accurate diagnosis is vital so that families can receive appropriate genetic counseling about risk of recurrence and the need to screen other family members who may be potentially affected. Although sometimes a difficult subject to address after a child has died, the clinician is in a unique role to stress the importance of perimortem sample collection to provide appropriate information to the family members.

The clinician also might provide valuable information to the medical examiner to raise the concern about possible underlying metabolic disorders. Timely and appropriate handling of specimen samples is necessary to perform appropriate testing in these unusual circumstances. Consultation with a specialist in metabolic diseases also can be helpful to ensure that samples are obtained in an acceptable manner and in an appropriate time frame.

Table 3 indicates the type of samples that are helpful for a "metabolic autopsy."[27,28]

Conclusion

The child with an inborn error of metabolism can be difficult to identify unless a high index of suspicion is maintained by the emergency medicine physician. Nonspecific symptoms such as vomiting, poor feeding, or poor weight gain should be seen as clues to the diagnosis of an inborn error. More overt symptoms such as an acute life-threatening event, cardiovascular collapse, or status epilepticus also should raise concerns for these disorders. As for all children presenting for care, the emergency physician should pay close attention to the airway, breathing, and circulation of the patient with an inborn error as they seek a diagnosis. The expansion of the newborn screening technologies to include tandem mass spectrometry will allow for a more rapid diagnosis of a greater number of these disorders before symptoms develop. Involvement of specialists in metabolic disorders should be sought when these patients present for care. Initial screening laboratory tests will help guide the diagnosis as well as the treatment of many of these disorders. Postmortem analysis can be initiated for the child who suddenly dies to evaluate for the possibility of an underlying inborn error as well.

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CME Questions

91. Which of the following can be found in a child with an inborn error of metabolism?
    A. A normal exam
    B. Poor feeding
    C. Vomiting
    D. All of the above

92. Which of the following laboratory findings would be consistent with an inborn error of metabolism?
    A. Hyperglycemia
    B. Metabolic acidosis
    C. Anemia
    D. Elevated CSF protein

93. Which of the following statements regarding the inheritance pattern of an inborn error of metabolism is true?
    A. They are mainly autosomal recessive diseases.
    B. Girls are affected more often than boys.
    C. A detailed family history will always uncover a familial predisposition.
    D. Newborn screening will determine the inheritance pattern.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a credit letter. When your evaluation is received, a credit letter will be mailed to you.

CME Objectives

The CME objectives for *Pediatric Emergency Medicine Reports* are to help physicians:

a.) Quickly recognize or increase index of suspicion for specific conditions;

b.) Describe the epidemiology, etiology, pathophysiology, historical and physical examination findings associated with the entity discussed;

c.) Correctly formulate a differential diagnosis and perform necessary diagnostic tests;

d.) Apply state-of-the-art therapeutic techniques (including the implications of pharmacologic therapy discussed) to patients with the particular medical problems discussed;

e.) Provide patients with any necessary discharge instructions.

94. Which of the following is true regarding newborn screening programs in the United States?
    A. The programs are the same in all states.
    B. The results are now available before an infant is discharged from the hospital.
    C. Tandem mass spectrometry can be used to screen for organic acidemias, fatty acid oxidation defects, and urea cycle defects.
    D. The programs now reliably identify all inborn errors of metabolism.

95. Of the following disorders, which one is *not* associated with metabolic acidosis?
    A. Methylmalonic acidemia
    B. Medium chain acyl-CoA dehydrogenase deficiency
    C. Urea cycle defect
    D. Isovaleric acidemia

96. Which of the following hyperammonemia-causing disorders is *not* inherited through an autosomal recessive pattern?
    A. Ornithine transcarbamoylase deficiency
    B. Urea cycle defect
    C. Organic acidemia
    D. Fatty acid oxidation defects

97. Which of the following is true about MCAD deficiency?
    A. It is the least common inherited disorder of fatty acid oxidation.
    B. It has an autosomal dominant inheritance pattern.
    C. It presents within the first 5 years of life.
    D. The most common presentation is that of hypoglycemia without ketone production.

98. Which of the following is important in the postmortem evaluation of a child with a suspected inborn error of metabolism?
    A. Whole blood
    B. Urine
    C. Skin, liver, and muscle biopsies
    D. All of the above

99. Which of the following statements is true regarding the management of seizures in children with an inborn error of metabolism?
    A. Benzodiazepines are not helpful in their management.
    B. A variety of seizure types are associated with an inborn error of metabolism.
    C. Pyridoxine will most likely be necessary to control seizures caused by an inborn error of metabolism.
    D. The degree of hypoglycemia caused by an inborn error of metabolism will *not* lead to seizure activity.

100. Which of the following laboratory test is least likely to be abnormal in a child with a suspected inborn error of metabolism?
    A. Serum ammonia
    B. Serum electrolytes
    C. Serum glucose
    D. Serum amylase

Answers: 91. D; 92. B; 93. A; 94. C; 95. C; 96. A; 97. D; 98. D; 99. B; 100. D

Correction

An incorrect answer was noted to CME question in the July 2008 issue on common ENT infections. The correct answer to question number 66 should have been "maxillary." It should have read:

66. Within the first 2 years of life, the location for an acute sinusitis is most commonly confined to which of the following sinuses?
    A. Ethmoid
    B. Sphenoid
    C. Frontal
    D. Maxillary

Answer: D

In Future Issues:

Pediatric Procedural Sedation

PEDIATRIC Emergency Medicine Reports
The Practical Journal of Pediatric Emergency Medicine

Inborn Errors of Metabolism

Signs and Symptoms of Inborn Errors of Metabolism

- ❑ Poor feeding/refusal to feed
- ❑ Periods of difficulty consoling
- ❑ Periods of difficulty awakening
- ❑ Vomiting
- ❑ Failure to thrive
- ❑ Hypotonia
- ❑ Hypertonia
- ❑ Tachypnea
- ❑ Tachycardia
- ❑ Hypoglycemia
- ❑ Acidosis
- ❑ Dehydration, especially if recurrent
- ❑ Apnea
- ❑ Seizures
- ❑ Altered mental status
- ❑ Sudden unexplained death
- ❑ Cardiomegaly
- ❑ Arrhythmia
- ❑ Shock
- ❑ Loss of thermoregulation

Suggested Initial Laboratory Testing for a Child with Suspected Inborn Error of Metabolism

- ❑ Blood gases
- ❑ Blood glucose
- ❑ Plasma ammonia
- ❑ Plasma amino acids
- ❑ Serum electrolytes
- ❑ Serum liver function tests
- ❑ Blood lactate and pyruvate
- ❑ Complete blood cell count with differential
- ❑ Urinalysis
- ❑ Urine reducing substances
- ❑ Urine organic acids and amino acids

Note: Plasma and urine also should be frozen for assay of additional metabolites or hormones that might be present only during acute decompensation

General Approach to the Child with Seizures *

ASSESS AIRWAY, BREATHING, AND CIRCULATION

Provide supplemental oxygen
Establish IV access
Place patient on cardiac monitor
Check patient's temperature
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Anticonvulsant levels

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If not already done so, strongly consider securing airway using rapid sequence intubation

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(Involvement of pediatric neurology and metabolic specialist strongly encouraged)

SPECIAL CONSIDERATIONS:

Pyridoxine 100 mg IV (refractory seizures in children <1 yr or suspected isoniazid toxicity)

General anesthesia or barbiturate coma (requires EEG monitoring and PICU setting).

* Figure adapted from: Chiang VW. Seizures. In: *Textbook of Pediatric Emergency Medicine*. 5th ed. Lippincott Williams and Wilkins, 2006:629-636.

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CSF

1-3 mL for amino acid analysis (frozen)
Consult with metabolic expert before obtaining unless sample already obtained

SKIN

3 X 2 mm full thickness collected under sterile conditions into tissue culture medium or saline (do NOT use iodine-containing preparations)

LIVER AND MUSCLE BIOPSIES

For electron microscopy, histopathology, and enzymology
Collect within 2-4 hours of death
Flash frozen in liquid nitrogen or on dry ice

Supplement to *Pediatric Emergency Medicine Reports*, October 2008: "Children with Inborn Errors of Metabolism: Recognizing the Unusual and Life-threatening. *Author:* **Mark S. Mannenbach, MD,** Assistant Professor, Department of Pediatric and Adolescent Medicine, Mayo College of Medicine, Rochester, MN.