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An 18-Month-Old Child with a Previously Undiagnosed Fatty Acid Oxidation Disorder

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CASE PRESENTATION

History

An 18-month-old child was brought by her parents to the emergency department (ED) because of persistent vomiting and dehydration. She had been sick for 2 to 3 days with what was believed to be a viral illness. She had an occasional nonproductive cough, loose stools, and low grade fevers, with a maximum temperature of 38.2°C (100.8°F) axillary. Her parents had been in constant communication with their pediatrician and were managing her at home with oral rehydration therapy. Although they had been fairly successful for the first couple of days using small amounts of fluid at frequent intervals, her parents were concerned that she was becoming increasingly somnolent. Her parents also noted that her urinary frequency had decreased, and her urine appeared to be more concentrated. She had no history of rash, and no known infectious contacts. She had been previously healthy, without any prior hospitalizations or major illnesses. She took no medications, and she had no known drug allergies. There were no known toxic exposures. There was no family history of unusual metabolic or infectious diseases, and no family history of any unusual or unexplained deaths occurring in children.

Key Point

Children with viral illnesses frequently have some degree of vomiting. It is generally not a major concern as long as hydration is able to be maintained. In this case, however, vomiting was associated with a decreased frequency of urination, indicating dehydration and possible shock. In addition, the child had become increasingly somnolent. Somnolence is a much more ominous sign that may be associated with a variety of life-threatening conditions, including overwhelming infection, central nervous system disorder, or serious metabolic dysfunction.

Physical Examination

On arrival to triage, the child was noted to be unresponsive and apneic. She was immediately brought to a treatment room and resuscitated. She received bag-mask ventilation with 100% oxygen, but there were no pulses, and chest compressions were initiated. She was intubated and placed on a monitor that revealed asystole. Breath sounds were clear to auscultation during manual ventilation, but there were no spontaneous respirations. There were no heart tones or central pulses, and chest compressions were continued. Pupils were fixed and dilated bilaterally. Her abdomen was slightly distended and her liver was palpable 3 fingerbreadths below the right costal margin. No bowel sounds were heard, and no other organomegaly or masses were appreciated. Extremities were cool and pulseless. Oxygen saturation by pulse oximetry was undetectable. Rectal temperature was 36.1°C (97.0°F).

Key Point

This child obviously had arrested at some point in time between leaving the home and arriving at triage. Her pupils were fixed and dilated, her extremities were cool, and her core body temperature was below normal. All of these findings indicate that her metabolic rate had been diminished—or that she had been without spontaneous circulation—for some period of time.

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Clinical Course

As resuscitative efforts continued, an intraosseous line was inserted and the patient was given multiple doses of epinephrine per the Pediatric Advanced Life Support (PALS) guidelines. A fingerstick blood glucose level was obtained and was less than 20 mg/dL, and she was given 2 mL/kg body weight of 25% dextrose solution. She received 2 fluid boluses of normal saline solution, 20 mL/kg each. She received subsequent doses of atropine, sodium bicarbonate, hydrocortisone, and calcium gluconate. There was no return of spontaneous circulation after one-half hour, and the resuscitation was stopped. Post-mortem examination revealed massive cerebral edema, fatty enlargement of the liver, and elevation of urinary organic acids (mono- and dicarboxylic acid metabolites).

- **What is the differential diagnosis for a child with vomiting and dehydration who presents in extremis with profound hypoglycemia?**

Table 1. Differential Considerations for Hypoglycemia in Children

Idiopathic ketotic hypoglycemia
Toxic ingestions
Common: ethanol, salicylates, oral hypoglycemics, insulin
Uncommon: isoniazid, propranolol, pentamidine, quinine, disopyramide, unripe ackee fruit
Hepatic dysfunction
Reye syndrome, hepatitis, cirrhosis
Sepsis
Inborn errors of metabolism
Organic acidurias
Urea cycle defects
Fatty acid oxidation disorders
Endocrinopathies
Hyperinsulinism, adrenal insufficiency, hypopituitarism, hypothyroidism

DIFFERENTIAL DIAGNOSIS

Clinically significant hypoglycemia is defined as a blood glucose of less than 40 mg/dL. The list of differential considerations for hypoglycemia in children is large and includes idiopathic ketotic hypoglycemia, toxic ingestions, sepsis, liver dysfunction, inborn errors of metabolism, and endocrinopathies (**Table 1**).

Idiopathic ketotic hypoglycemia is perhaps most common cause and occurs in children under the age of 5 years who become hypoglycemic after prolonged fasting or intercurrent illness. One of the body's normal responses to decreased substrate availability is to convert fat into glucose, thus resulting in the formation of ketone bodies, which are excreted and detected as urinary ketones. Although these children may become quite symptomatic and develop a decreased level of consciousness, normal mentation rapidly returns with supplemental glucose, and the condition itself is not life-threatening.

Toxic ingestions are probably the next most common cause of hypoglycemia in children and include a wide variety of substances. In the ED, the most common occurrences are seen with ethanol (children drinking out of parents' glasses the morning after a party), salicylates, insulin, and oral hypoglycemic agents. Other less common toxins include isoniazid, propranolol, pentamidine, quinine, disopyramide, and unripe ackee fruit ("Jamaican vomiting sickness").

Hypoglycemia may occur with certain forms of hepatic dysfunction, such as hepatitis and cirrhosis. Reye syndrome has been associated with similar clinical presentations. This child, however, had no exposures to salicylates. In addition, many people now believe that the majority of the cases initially attributed to Reye syndrome actually may have been fatty acid oxidation (FAO) disorders.[1] Sepsis also may be associated with hypoglycemia; however, the hypoglycemia is not usually as severe as that seen in the case patient. In addition, sepsis would be less likely in the absence of other signs of infection.

A few endocrine disorders also should be considered, including acute adrenal insufficiency, hypopituitarism, and hypothyroidism. Although children with these disorders can be precipitated into crisis by an intercurrent illness or infection, the episode is usually not as rapid or as dramatic as in this case. Transient neonatal hyperinsulinism occurs in macrosomic infants of diabetic mothers but is limited to the neonatal period.

Three classes of inborn errors of metabolism may be associated with hypoglycemia and an acutely altered mental status: FAO disorders, organic acidurias, and urea cycle defects (**Table 2**). FAO disorders most commonly present with hypoketotic hypoglycemia, altered mental status, seizures, and some degree of hyperammonemia. Organic acidurias most commonly present with severe ketoacidosis and a high anion gap. Patients with urea cycle defects primarily present with marked hyperammonemia, often with levels greater than 1,000 µmol/L.

Urea cycle defects and organic acidurias tend to manifest themselves earlier (roughly 50% in the first month of life and 90% within the first year), whereas

Table 2. Common Presentations of Inborn Errors of Metabolism Associated with an Acutely Toxic Appearance

Inborn Error	Summary of Presentation	Glucose	Ketosis	Anion Gap	Ammonia
Organic acidurias	Ketoacidosis with high anion gap	Variable	High	High	Normal to very high
Fatty acid oxidation disorders	Hypoketotic hypoglycemia	Low	Low (abnormally low for level of hypoglycemia)	Normal to slightly elevated	Normal to moderately high
Urea cycle defects	Normoglycemic with marked hyperammonemia	Variable	Normal (normal to slightly elevated)	Normal to slightly elevated	Very high (often > 1000 μmol/L)

Adapted from Hostetler MA, Arnold GL, Mooney R, et al. Hypoketotic hypoglycemic coma in a 21-month-old child. Ann Emerg Med 1999;34:396, with permission from Elsevier Science.

disorders of FAO tend to present somewhat later (roughly 50% in the first year and 90% by the age of 3 years).[2–4] These are only general guidelines, however, and it is important to remember that inborn errors may present at any age, even in adults.[5–8] It is sometimes difficult to distinguish between specific disorders during the acute presentation because of the considerable variability that may occur within and among disorders. Nevertheless, this particular presentation in this age group warrants strong consideration of a FAO disorder.

- **What are the most commonly involved enzymes in FAO disorders?**
- **What is the pathogenesis of acute episodes?**
- **How are children with FAO disorders managed?**

FATTY ACID OXIDATION DISORDERS

Definition

FAO disorders involve defects in the mitochondrial oxidation of fatty acids, specifically, the enzymes responsible for beta oxidation (the conversion of fatty acids into ketone bodies). At least 10 inherited defects have been identified in humans. Three of the more commonly involved enzymes include very-long-, medium-, and short-chain acyl-CoA dehydrogenase (VLCAD, MCAD, and SCAD). Other, less common defects include carnitine palmitoyltransferase (CPT) I; CPT II; carnitine/acylcarnitine translocase; 2,4-dienoyl-CoA reductase; mitochondrial trifunctional protein; and long- and short-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD and SCHAD).

Epidemiology and Screening

MCAD deficiency is the most common of the FAO disorders and is inherited as an autosomal recessive trait. Its frequency has been estimated to be as high as 1 in every 8000 to 15,000 live births.[8–10] The true prevalence, however, remains unknown, as it still is not universally screened for during routine neonatal screening. MCAD is a logical choice for screening in that it is relatively prevalent and has significant morbidity and mortality if not detected.[11–17] Recent studies have indicated that most patients with symptomatic MCAD deficiency can be detected by newborn screening.[9–10] In addition, morbidity and mortality rates improve significantly if patients are detected prospectively.[2,6,18]

MCAD deficiency has an approximately equal gender distribution. The gene responsible for the enzymatic defect found in MCAD has been mapped to locus 1p31. In the most common mutation, guanine is substituted for adenine at the 985th residue (A985G) resulting in a lysine to glutamate substitution.[10] It is most common in people of northern European descent. More than 80% of clinically diagnosed patients with MCAD deficiency are homozygous for A985G, and between 15% and 18% are compound heterozygotes.[8–10,19]

Current evidence suggests that approximately 6% of children presenting with sudden unexpected death before the age of 1 year,[13,14,16] and up to 30% of children presenting with unexplained hypoglycemia[20] have laboratory findings consistent with a FAO disorder. Most of these are based on retrospective studies, however, and further prospective studies are needed to determine whether more widespread screening of at-risk or symptomatic children in the ED would be helpful. Interestingly, the exact prevalence rates of FAO disorders in symptomatic children presenting to the ED with hypoglycemia have never been investigated.

Pathogenesis of Acute Episodes

Even metabolically normal children occasionally become hypoglycemic when stressed by fasting or serious

Figure 1. Age at onset and incidence of mortality among 104 children with MCAD deficiency. Each square represents 1 patient. MCAD = medium-chain acyl-CoA dehydrogenase. (Adapted with permission from Roe CR, Coates PM. Mitochondrial fatty acid oxidation disorders. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. 7th ed. New York: McGraw-Hill; 1995:1501–34. © 1995 The McGraw-Hill Companies, Inc.)

illness. When stressed, most children can respond by increasing their reliance on ketone bodies (fatty acids) for energy. As their cells use beta oxidation to extract energy from fatty acids, the accompanying formation of acetoacetate and β-hydroxybutyrate (ketone bodies) occurs. Occasionally, children with diminished fat stores become obtunded owing to their relative hypoglycemia; however, these children do become ketotic, and they usually return to a normoglycemic state immediately after supplemental glucose has been provided.

When FAO is impaired, ketone body production is limited, and the child becomes profoundly hypoglycemic. There is a corresponding relative lack of ketosis; in addition, toxic intermediates of FAO accumulate. Affected infants, therefore, present with hypoketotic hypoglycemia, severe metabolic acidosis, and a characteristic organic aciduria. The combination of hypoglycemia, accumulation of toxic intermediary metabolites, and hyperammonemia combine to cause cerebral edema, obtundation, coma, and—if not reversed—death. Children with FAO disorders may remain obtunded for prolonged periods of time despite provision of adequate glucose, often for several days.

Clinical Presentation of FAO Disorders

History. FAO disorders are characterized by periodic episodes of hypoketotic hypoglycemia and hepatic encephalopathy triggered by periods of catabolic stress, most often occurring between the ages of 3 months and 6 years.[4,6,18] These children are at risk for a wide variety of presentations, including vomiting, hypoglycemia, lethargy, encephalopathy, hepatomegaly, seizures, coma, cardiopulmonary arrest, and sudden death.[4,6,15,17,18] Long-term complications include developmental and behavioral disturbances, failure to thrive, and chronic muscle weakness.[4,6,18]

FAO disorders may not present during early infancy because most infants are fed regularly and frequently. As the amount of time extends between feedings, however, the need for fatty acid catabolism increases. For this reason, toddlers are particularly at risk. In retrospect, many children have a history of unusual dehydration or lethargy associated with previous viral illnesses that have required either treatment in the ED or admission to the hospital.[6,18]

For children with undiagnosed MCAD, the mortality rate is 20% to 25%; among those that survive, approximately 30% have irreversible neurological damage.[2,18] Almost all deaths occur in previously undiagnosed cases. **Figure 1** provides a graphic illustration of mortality data from one of the largest case series published, and compares the age of onset (diagnosis) and mortality. It should be noted, however, that some persons with the genetic defect remain asymptomatic throughout life.[7]

Physical examination. Although early development is usually normal, children are frequently small for their age. Their degree of development also depends on the number and severity of prior hypoglycemic episodes. Children who have had unrecognized periods of hypoglycemia usually experience some degree of adverse effect on growth and development, including the central nervous system.

During periods of wellness, the physical examination is essentially normal. During acute episodes, however, children are tachypneic and tachycardic out of proportion to the severity of their illness. They are usually somnolent or lethargic and may even be comatose. Of note clinically, their obtundation is usually not immediately reversed with supplementation of glucose. Children with FAO disorders also may present with cardiac failure resulting from cardiomyopathy (either hypertrophic or dilated) or skeletal muscle pain or weakness, with or without rhabdomyolysis. Cardiac dysfunction has been observed in as many as 50% of patients.[4] Children appear flaccid with somewhat decreased reflexes. The results of the neurologic examination are otherwise nonspecific, without localizing signs. Marked hepatomegaly is often present; however, true hepatic failure is rare and occurs in fewer than 10% of patients.[4]

Diagnosis of FAO Disorders

The hallmark of FAO disorders is hypoketotic hypoglycemia. Serum ammonia level may be mildly to moderately elevated. Serum electrolytes may show a low bicarbonate level and elevated anion gap; however, it is generally not as marked as that seen with organic acidurias.

Definitive diagnosis is confirmed by testing the urine for organic acids and the serum for amino and organic acids. MCAD deficiency is characterized by urinary excretion of high amounts of dicarboxylic acids, including adipic, suberic, sebacic, and dodecanedioic acids.[21,22] The diagnostic metabolites, however usually only accumulate during periods of fasting, when the beta oxidation pathway is being stressed. As these toxic metabolites continue to accumulate, the body attempts to conserve free CoA by substituting carnitine. Substitution results in a relative carnitine deficiency, and excessive urinary excretion of acyl-carnitine compounds.[23,24] If a FAO disorder is suspected, acute samples should be obtained while in the ED. The single best test for detecting FAO disorders is a urine test for organic acids. This test should be done in the ED, and not deferred to the pediatrician's office or well visit check-up, because the organic acid levels may be completely normal if checked during periods of normal dietary intake. The diagnosis also may be confirmed by skin biopsy and fibroblast culture[16]; however, they are much more difficult and costly and are available at only a few select tertiary centers.

FAO disorders are genetic diseases, so prenatal testing is an important option for families with affected children. Genetic counseling is particularly important in order to identify other members who may be at risk of sudden death.[6] The possibility of an FAO disorder also should be considered in families in which there has previously been a sudden unexpected death, particularly if the autopsy revealed evidence of fatty liver degeneration or cerebral edema. The outcome for siblings with FAO disorders that are diagnosed prospectively is very good.[6]

Key Point

Convalescent specimens obtained during states of wellness may not reveal the characteristic metabolites necessary to make the diagnosis. If the diagnosis is suspected, specimens should be sent during the acute phase of the illness and not delayed or deferred until later points in time.

Treatment During Acute Episodes

Children with a toxic appearance present a challenge as the differential diagnosis is broad, and immediate action is critical. An organized clinical and diagnostic approach is key (**Figure 2**). Management begins with attention to the ABCs—airway, breathing, and circulation. This step is followed by a systematic determination of basic metabolic parameters, including rapid determination of glucose and serum electrolyte levels, urinalysis, and blood pH testing. In cases of unexplained illness, prolonged obtundation, severe hypoglycemia, or acidosis, we recommend adding tests for serum ammonia and urine organic acids. The estimated cost for both tests compares favorably with routine comprehensive toxicology screening and complete sepsis evaluations.[15]

Hypoglycemia is treated with 2 to 4 mL/kg of 25% dextrose solution. Isotonic fluid boluses (20 mL/kg each)are given until euvolemia is achieved. Acute adrenal insufficiency is a reasonable concern, and therefore hydrocortisone (2 mg/kg intravenously) is recommended. Severe acidemia may be treated with either sodium bicarbonate, or tris-hydroxymethyl-aminomethane, provided that adequate ventilation is ensured.

Toxic-appearing children are at risk for sepsis and, therefore, specimens should be obtained for a full sepsis evaluation including complete blood count, blood culture, urinalysis, urine culture, and cerebrospinal fluid analysis for cell count, Gram stain, and culture. Broad spectrum antibiotics should be promptly given. Reasonable choices include ampicillin and gentamicin for neonates younger than 6 weeks, ampicillin and ceftriaxone for infants between the ages of 6 weeks and

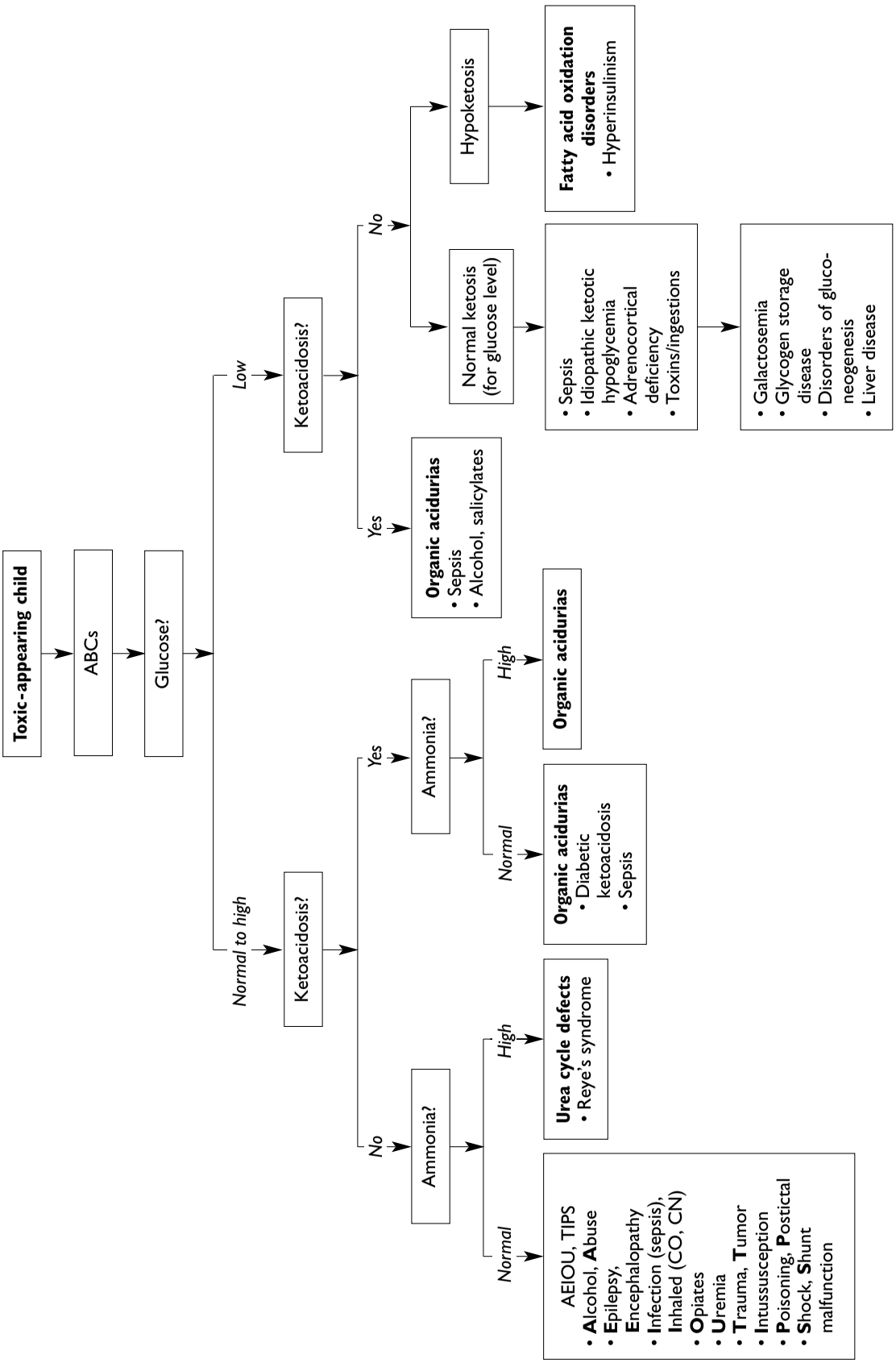

Figure 2. Clinical and diagnostic approach to a toxic-appearing child. (Adapted from Hostetler MA, Arnold GL, Mooney R, et al. Hypoketotic hypoglycemic coma in a 21-month-old child. Ann Emerg Med 1999;34:397, with permission from Elsevier Science.)

3 months, and ceftriaxone for children older than 3 months. In addition, vancomycin can be added if the child is particularly ill or if penicillinase-resistant streptococci are a concern.

Long-Term Outpatient Therapy for FAO Disorders

Once the diagnosis of FAO disorders has been made, the mainstay of long-term outpatient therapy involves dietary supplementation and prevention of catabolism. The composition of the diet should be adjusted to provide the greatest caloric density in carbohydrates and proteins, while at the same time minimizing lipids and ensuring that no periods of fasting occur that last for more than 4 to 5 hours. Children are at greatest risk during periods of intercurrent illness. During acute illnesses, a continuous glucose energy source should be provided to prevent catabolism and production of intermediary metabolites. An infusion of 10% dextrose in normal saline at 1.5 times maintenance provides the required 8 to 10 mg/kg of glucose per minute to prevent catabolism.

Once the diagnosis has been made, the diet adjusted, and close attention has been paid to preventing catabolism during fasting or intercurrent illness, few children have any further episodes of encephalopathy, morbidity, or death.[6,18] Strict avoidance of fasting, particularly during intercurrent illnesses, appears to be very effective in reducing serious morbidity and mortality.[18]

Beta oxidation of fatty acids involves a complex mitochondrial pathway that relies on adequate cytosolic levels of carnitine. Supplemental administration of carnitine is recommended by many specialists in inherited metabolic diseases based upon the theory that carnitine provides conjugation and excretion of the toxic intermediary metabolites, and many children have a relative carnitine deficiency.[3,23] In addition, adequate amounts of both riboflavin and nicotinamide are recommended to facilitate electron transport and assist in the production of adenosine triphosphate.[22]

CONCLUSION

FAO disorders are an important consideration for acutely ill children presenting with hypoglycemia. Children frequently have milder sentinel events in which they present with dehydration and lethargy that in retrospect, is out of proportion to normal chronology of the illness. Affected children may remain unrecognized until they are severely ill, at which point sudden death may occur.

Laboratory testing for FAO disorders is cost-efficient, but should be performed during the acute phase of illness. Heightened suspicion and early recognition by the primary care or emergency physician for the possibility of a FAO disorder may prevent subsequent morbidity and mortality. **HP**

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