Acute Illness Protocol for Fatty Acid Oxidation and Carnitine Disorders

Saud H. Aldubayan, MD,† Lance H. Rodan, MD,* Gerard T. Berry, MD,* and Harvey L. Levy, MD**

Abstract: Inborn errors of metabolism (IEMs) are genetic disorders that disrupt enzyme activity, cellular transport, or energy production. They are individually rare but collectively have an incidence of 1:1000. Most patients with IEMs are followed by a physician with expertise in biochemical genetics (metabolism) but may present outside this setting. Because IEMs can present acutely with life-threatening crises that require specific interventions, it is critical for the emergency medicine physicians, pediatricians, internists, critical care physicians, and biochemical geneticists to be familiar with the initial assessment and management of patients with these disorders. Appropriate early care can be lifesaving. This protocol is not designed to replace the expert consultation of a biochemical geneticist but rather to improve early care and increase the level of comfort of the acute care physician with initial management of fatty acid oxidation and carnitine disorders until specialty consultation is obtained.

Key Words: inborn errors of metabolism, fatty acid oxidation, carnitine disorders

(*Pediatr Emer Care* 2017;33: 296–301)

SUMMARY OF THE PROTOCOL

Mitochondrial fatty acid β-oxidation (FAO) is an important source of energy for the liver, skeletal muscles, and cardiac muscle. It is also a major source of substrate for the production of ketone bodies, which are used as fuel by the brain when glucose is unavailable. Fatty acid β-oxidation and carnitine disorders are genetic disorders that impair mitochondrial FAO. They typically manifest with episodic metabolic decompensation provoked by poor caloric intake, emesis, prolonged fasting, intercurrent illness (eg, infection), medications (eg, valproic acid), and/or high fat intake. The clinical presentation of FAO and carnitine disorders can include hypoketotic hypoglycemia, liver dysfunction, and Reye-like syndrome. All patients with FAO and carnitine disorders are at risk for sudden death if not treated promptly and appropriately. Long-chain FAO disorders (FAODs; very long chain acyl-CoA dehydrogenase deficiency [VLCADD], long-chain hydroxyacyl-CoA dehydrogenase deficiency [LCHADD], and mitochondrial trifunctional protein [MTP] deficiency) and disorders of carnitine metabolism may additionally present with skeletal myopathy (including rhabdomyolysis), cardiomyopathy, and cardiac arrhythmia. All patients with poor oral intake should be promptly treated to avoid complications. The key to acute management consists of high dextrose intravenous (IV) infusion. Long chain disorders are additionally treated with medium-chain triglyceride (MCT) supplementation. Any underlying illness should be identified and treated. Of note, most of the patients with metabolic diseases carry emergency room letters that provide more individualized management recommendations, as well as the contact information of the patient's metabolic provider. Suggested management is summarized in Figures 1 (medium-chain acyl-CoA dehydrogenase [MCAD]) and 2 (long-chain FAO and carnitine disorders).

From the *Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA; and †Department of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

Disclosure: The authors declare no conflict of interest.

Reprints: Saud Aldubayan, MD, Harvard Medical School, Boston, MA (e-mail: saldubayan@partners.org).

ISSN: 0749-5161

BACKGROUND

Mitochondrial FAO is an important source of energy for the liver, muscle, and heart and becomes even more critical with prolonged fasting. It is also a major source of substrate for the synthesis of ketone bodies that are a crucial source of energy for the brain when glucose supply is reduced.[1] Fatty acids are classified by carbon chain length into short-, medium-, and long-chain fatty acids. Whereas short- and medium-chain fatty acids are thought to freely diffuse into the mitochondria, long-chain fatty acids require a 3-enzyme "carnitine shuttle" (Fig. 3). Within the mitochondria, FAO proceeds in a 4-step cycle with each step catalyzed by an enzyme that is chain-length specific for short-, medium-, or long-chain fatty acids.[1] Defects in almost every enzymatic step of FAO and the carnitine cycle have been described.[2]

Each FAO and carnitine disorder has a specific pattern of abnormalities on plasma acylcarnitine analysis as a result of the accumulation of specific chain length species of fatty acid carnitine esters. These plasma acylcarnitine abnormalities can facilitate the diagnosis of these disorders but generally do not inform acute management and so are not discussed further in this article (see Table 1 for a list of specific FAO and carnitine disorders, their acronyms, and characteristic acylcarnitine abnormalities).

Metabolic decompensation in FAO and carnitine disorders may be provoked by poor caloric intake, emesis, prolonged fasting, intercurrent illness/infection, medications (eg, valproic acid), and/or high fat intake.[3–5] Presenting features include hypoglycemia with insufficient ketosis (hypoketotic hypoglycemia) and liver dysfunction. Patients may also develop cerebral edema or a Reye-like syndrome (brain edema, metabolic acidosis, liver failure).[6–8] All patients with FAO and carnitine disorders presenting with poor oral intake are at risk for sudden death if not treated promptly and appropriately. Long-chain FAODs (VLCADD, LCHADD, and MTP deficiency) and carnitine disorders can additionally present with myopathy or rhabdomyolysis, cardiomyopathy, or arrhythmia.[9–11] Symptoms and signs of acute decompensation are summarized in Table 2.

The key to acute management in all FAO and carnitine disorders is high dextrose IV infusion. Long-chain disorders (VLCADD, LCHADD, and MTP deficiency) are also managed with diet modification, including restriction of long-chain triglycerides (eg, 8%–25% of daily calories) and supplementation with MCTs (eg, 10%–20% of daily calories).[12–14] Of note, MCT supplementation is contraindicated in short- and medium-chain FAODs.

MANAGEMENT

1. Laboratory Tests

The following tests should be performed when the patient presents with features of metabolic decompensation and/or acute

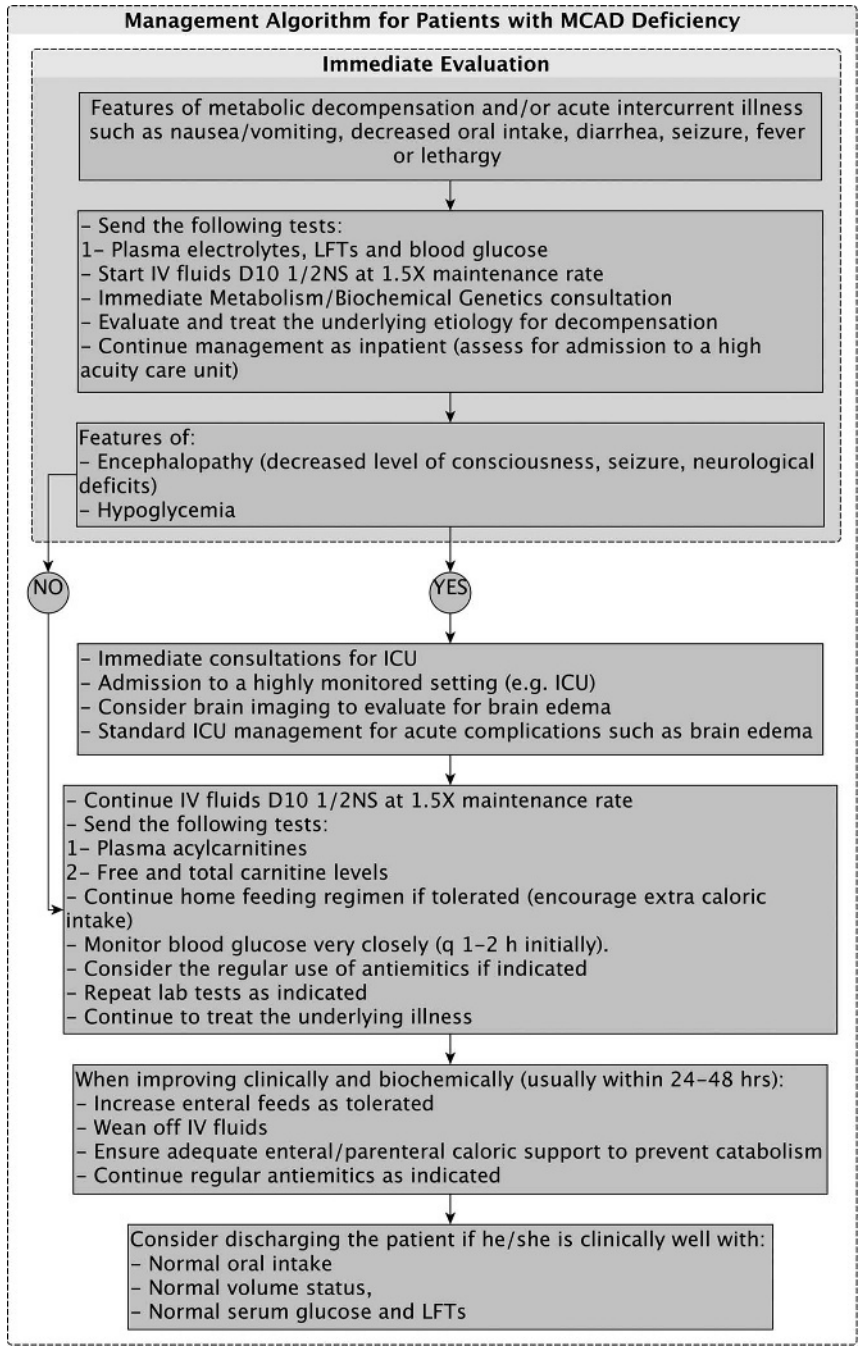

FIGURE 1. Medium-chain Acyl-CoA dehydrogenase deficiency treatment algorithm.

intercurrent illness: blood glucose, liver enzymes/liver function tests, creatinine kinase, chemistry panel, and ammonia if encephalopathic (see Table 3 for a list of the laboratory and imaging tests and their indications in patients with FAO or carnitine disorders).

2. IV Fluids

The key to acute management in all FAO and carnitine disorders is high dextrose IV infusion. Intravenous fluids should be initiated without delay not only in patients with metabolic decompensation but also if the patient has poor oral intake or emesis due to an intercurrent illness (eg, respiratory infection or gastroenteritis) to prevent a metabolic decompensation.[15]

Intravenous fluids containing 10% dextrose or greater combined with half or normal saline should be started at 1.5 times the maintenance rate for minimum glucose infusion rate of 8 to 10 mg/kg per minute.[2,3] Intravenous fluids containing 10% dextrose (or greater) should be used even if the blood glucose level is normal; patients with FAOD almost entirely depend on glucose for their energy needs and can deplete their glucose very rapidly. If the patient develops significant hyperglycemia (eg, blood glucose > 250 mg/dL) with glucosuria and has signs of a metabolic

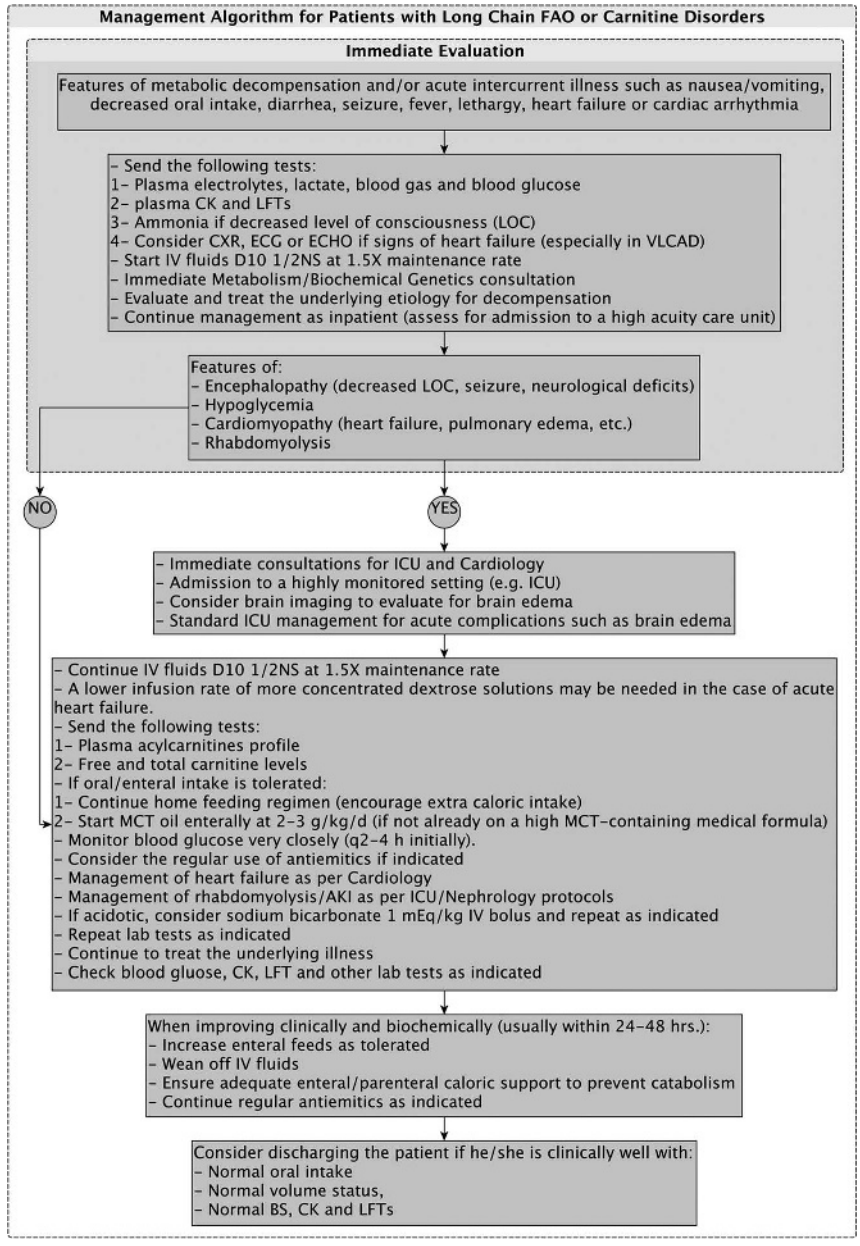

FIGURE 2. Long-chain FAODs and carnitine disorder treatment algorithm.

decompensation, then starting an insulin infusion should be considered in lieu of decreasing the glucose infusion rate to promote an anabolic state. The typical starting dose for insulin infusion is 0.01 IU/kg per minute. Insulin levels should be titrated to maintain blood glucose levels between 100 and 150 mg/dL.

Of note, the infusion of more concentrated dextrose solution (15%–25% dextrose) at a lower infusion rate using a central line may be required if there is poor cardiac function and/or in severe refractory decompensation. In addition, care should be taken when weaning IV fluids to decrease the rate slowly to avoid reactive hypoglycemia.

3. Diet

In addition to IV dextrose, the patient's oral/G-tube feeding may be continued as tolerated to provide additional calories. Antiemetics may be used to decrease emesis. If the patient is symptomatic, total daily calories (IV and enteral) should be 100% to 150% of maintenance calories.

Patients with MCAD deficiency generally follow a standard diet. Patients with VLCADD, LCHADD, and MTP deficiency generally follow a special diet that is high in MCTs and low in long-chain triglycerides. Infants and young children will be receiving a special metabolic infant formula as part of their diet (eg, Enfaport, Pregestimil, Lipistart). Older children and adults may be receiving an MCT supplement administered in multiple doses throughout the day. If the patient with confirmed VLCADD, LCHADD, or MTP deficiency is not normally receiving any MCT supplementation, he/she may be started on 2 to 3 g/kg per day of an MCT supplement divided every 6 to 8 hours.[12] This should be performed in consultation with a physician and a nutritionist with expertise in the management of patients with inborn errors of

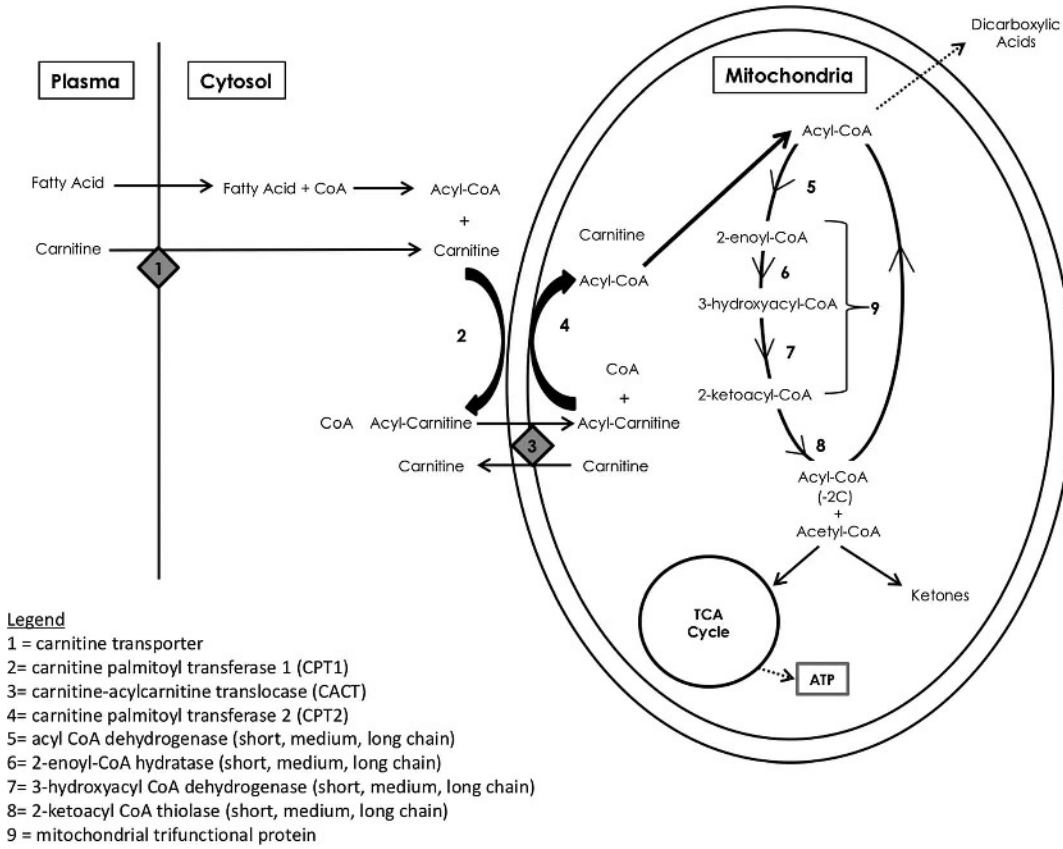

FIGURE 3. Fatty acid oxidation and carnitine cycles.

metabolism. Medium-chain triglyceride supplementation can produce diarrhea and gastrointestinal (GI) upset.

Medium-chain triglyceride supplementation is contraindicated in MCAD deficiency.

4. Medications to Avoid

Certain medications should be used with caution in those patients. For example, IV epinephrine will stimulate lipolysis and can exacerbate an FAOD. Valproic acid inhibits FAO and is relatively contraindicated.

5. Management of Complications

(i) Decreased level of consciousness

- Blood glucose should be remeasured to evaluate for symptomatic hypoglycemia.
- Ammonia should be measured to evaluate for Reye-like syndrome.
- Neuroimaging should be considered to evaluate for cerebral edema. If there is cerebral edema, standard neurocritical care principles should be followed (eg, hypertonic fluids, etc).
- Hemodialysis can be considered in consultation with the nephrology service if there is concern for a Reye-like

TABLE 1. FAO and Carnitine Disorders and the Acylcarnitine Abnormalities Seen in Them

Acronyms	Full Name	Acylcarnitine Profile
SCADD	Short-chain acyl-CoA dehydrogenase deficiency	Elevated C4
SCHADD	Short-chain hydroxyl-acyl CoA dehydrogenase deficiency	Elevated C4OH
MCADD	Medium-chain acyl-CoA dehydrogenase deficiency	Elevated C8 > C6 > C10
VLCADD	Very long chain acyl-CoA dehydrogenase deficiency	Elevated C14:1, C14
LCHADD	Long-chain hydroxyacyl-CoA dehydrogenase deficiency	Elevated C16OH, C18:1OH
MTP	Mitochondrial trifunctional protein	Elevated C16OH, C18:1OH
CPT1	Carnitine palmitoyltransferase 1 deficiency	Decreased C16, C18, C18:1, and elevated free carnitine (C0)
CAT	Carnitine-acylcarnitine transferase deficiency	Elevated C16, C18
CPT2	Carnitine palmitoyltransferase 2 deficiency	Elevated C16, C18

TABLE 2. Symptoms and Signs of Patients With FAODs or Carnitine Disorders During Acute Decompensation

Body System/Process	Symptoms and/or Signs*
Metabolic	Hypoketotic hypoglycemia (ie, hypoglycemia with insufficient increase in β-hydroxybutyrate or acetoacetate as measured in blood or urine), acidosis and hyperammonemia with Reye-like syndrome
Neurological	Encephalopathy, seizures, may have cerebral edema with Reye-like syndrome, myopathic symptoms (myalgia, rhabdomyolysis, and weakness). Note: patients with LCHADD and MTP deficiency may have baseline peripheral neuropathy and retinopathy.
GI	Nausea, vomiting, enlarged liver, elevated transaminases, very rare liver dysfunction/failure
Cardiovascular	Cardiomyopathy, arrhythmia

*Close relatives of affected individuals know the signs of decompensation in their relatives, and it is important to listen to their insight.

syndrome associated with severe electrolyte derangement, metabolic acidosis, and hyperammonemia.

(ii) Rhabdomyolysis (in long-chain FAO and carnitine disorders)
- Management is according to standard treatment.

(iii) Cardiomyopathy (in long-chain FAO and carnitine disorders)
- Patients should be monitored for arrhythmia and signs of cardiomyopathy.
- Consider early cardiology consultation for echocardiogram (ECHO) (cardiomyopathy in FAODs is dynamic, and a normal recent ECHO does not rule out cardiomyopathy).
- If cardiac function is severely impaired, the patient may require placement of a central line for infusion of a lower-volume, higher-concentration dextrose infusion.

6. Treatment of Underlying Etiology

Every effort should be made to identify and treat the underlying illness or metabolic stressor that triggered the decompensation. Infections such as gastritis/gastroenteritis, upper respiratory tract infection/bronchitis, and urinary tract infection are common causes for metabolic decompensations. These conditions should be managed according to standard recommendations. Commonly used antibiotics and antiemetics can be used safely in patients with FAO and carnitine disorders.

MONITORING

1. Strong consideration should be given to monitoring in an intensive care unit setting.
2. Neurological status should be monitored, with frequency indicated by clinical status.
3. Blood glucose should be repeated at least every 4 hours (more frequent if clinically indicated) and can be decreased in frequency if stable.
4. Creatinine kinase, liver enzymes/liver function, and chemistry panel should be evaluated on presentation and can be repeated as clinically necessary.
5. If the patient is encephalopathic, then plasma ammonia level should be measured.
6. In a patient with a long-chain FAO or carnitine disorder, consideration should be given to telemetry.
7. Patients with FAO and carnitine disorders usually need extended monitoring to ensure adequate oral/enteral intake before discharge. Early discharge after a successful trial of oral/enteral

TABLE 3. Laboratory Tests and Investigations That can Guide Clinical Care During Acute Metabolic Decompensations*

Laboratory Tests	Comments
Chemistry panel for bicarbonate level, anion gap, and blood glucose	To evaluate the degree of acidosis and hypoglycemia if present
CPK	To assess for rhabdomyolysis
Liver enzymes and function tests (albumin, bilirubin, and INR)	Liver disease can be seen in patients with severe metabolic decompensation.
Serum lactate	Can be elevated in hypovolemia
Plasma acylcarnitine analysis	Can be used to assess the severity of the disease
Plasma-free and total carnitine levels	To guide the dosing of carnitine supplementation
CK-MB and BNP	In long-chain FAO and carnitine disorders if CK elevated or signs of cardiomyopathy
CXR, ECG, and/or ECHO	In long-chain FAO and carnitine disorders if CK is significantly elevated or if there are signs of cardiomyopathy
Infectious work-up (CBC, cultures, CXR, urinalysis, etc)	To assess for the underlying etiology

*Sending laboratory tests should be guided by the clinical presentation of the patient. This is not an exhaustive list, and some of the tests listed here may not be indicated.

BNP indicates B-type natriuretic peptide; CBC, complete blood cell count; CK-MB, creatine kinase-MB; CPK, creatine phosphokinase; ECG, electrocardiogram; ECHO, echocardiogram.

feeding that is usually practiced for patients with GI diseases should be avoided in metabolic patients.

CONCLUSIONS

FAO and carnitine disorders are a heterogeneous group of metabolic disorders with a number of potential life-threatening acute complications. Early recognition of the risk factors for acute decompensation (eg, poor oral intake, emesis) is critical to prevent sudden death and ensure good outcome. The acute care physician is usually the first provider to evaluate the patient with FAODs and carnitine disorders and is in the unique position to improve patient outcome by instituting the appropriate early management while expert opinion from a biochemist geneticist is sought.

REFERENCES

1. Stryer L. *Fatty Acid Metabolism*. 4th ed. New York, NY: W.H. Freeman and Company; 1995.
2. Saudubray JM, John GB, Walter H. *Inborn Metabolic Diseases*. 5th ed. Berlin, Germany: Springer; 2012.
3. Arnold GL, Van Hove J, Freedenberg D, et al. A Delphi clinical practice protocol for the management of very long chain acyl-CoA dehydrogenase deficiency. *Mol Genet Metab*. 2009;96:85–90.
4. Vellekoop P, Diekman EF, van Tuijl I, et al. Perioperative measures in very long chain acyl-CoA dehydrogenase deficiency. *Mol Genet Metab*. 2011; 103:96–97.
5. Derks TG, van Spronsen FJ, Rake JP, et al. Safe and unsafe duration of fasting for children with MCAD deficiency. *Eur J Pediatr*. 2007;166: 5–11.
6. Iafolla AK, Thompson RJ Jr, Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. *J Pediatr*. 1994;124:409–415.
7. Lang TF. Adult presentations of medium-chain acyl-CoA dehydrogenase deficiency (MCADD). *J Inherit Metab Dis*. 2009;32:675–683.
8. den Boer ME, Wanders RJ, Morris AA, et al. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: clinical presentation and follow-up of 50 patients. *Pediatrics*. 2002;109:99–104.
9. Andresen BS, Olpin S, Poorthuis BJ, et al. Clear correlation of genotype with disease phenotype in very-long-chain acyl-CoA dehydrogenase deficiency. *Am J Hum Genet*. 1999;64:479–494.
10. Bonnet D, Martin D, De Lonlay Pascale, et al. Arrhythmias and conduction defects as presenting symptoms of fatty acid oxidation disorders in children. *Circulation*. 1999;100:2248–2253.
11. Hoffman JD, Steiner RD, Paradise L, et al. Rhabdomyolysis in the military: recognizing late-onset very long-chain acyl Co-A dehydrogenase deficiency. *Mil Med*. 2006;171:657–658.
12. Solis JO, Singh RH. Management of fatty acid oxidation disorders: a survey of current treatment strategies. *J Am Diet Assoc*. 2002;102: 1800–1803.
13. Gillingham MB, Scott B, Elliott D, et al. Metabolic control during exercise with and without medium-chain triglycerides (MCT) in children with long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiency. *Mol Genet Metab*. 2006;89:58–63.
14. Behrend AM, Harding CO, Shoemaker JD, et al. Substrate oxidation and cardiac performance during exercise in disorders of long chain fatty acid oxidation. *Mol Genet Metab*. 2012;105:110–115.
15. Dixon MA, Leonard JV. Intercurrent illness in inborn errors of intermediary metabolism. *Arch Dis Child*. 1992;67:1387–1391.