Fatty Acid Beta-Oxidation Disorders: A Brief Review

Vijay A. Vishwanath

Division of Pediatric Neurology, Department of Neurology, Albany Medical Center, Albany, N.Y., USA

Key Words

Mitochondrial fatty acid β -oxidation disorders · Fatty acid β -oxidation disorder · MCAD deficiency

Abstract

Background: Mitochondrial fatty acid β -oxidation disorders (FAODs) are a heterogeneous group of defects in fatty acid transport and mitochondrial β -oxidation. They are inherited as autosomal recessive disorders and have a wide range of clinical presentations. **Summary:** The background information and case report provide important insight into mitochondrial FAODs. The article provides a wealth of information describing the scope of these disorders. **Key Messages:** This article presents a typical case of medium chain acyl-CoA dehydrogenase deficiency and summarizes the pathophysiology, clinical presentation, diagnosis and treatment of mitochondrial FAODs.

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Introduction

Mitochondrial fatty acid β -oxidation disorders (FAODs) are a group of about 20 defects in fatty acid transport and mitochondrial β -oxidation that are inherited as autosomal recessive disorders. FAODs have a varied presentation, with either neonatal onset with hyperammonemia, transient hypoglycemia, metabolic acido-

sis, cardiomyopathy and sudden death or late onset with neuropathy, myopathy and retinopathy [1]. Most cases with FAODs are now identified using newborn screening by mass spectrometry (MS/MS) of blood spots. Pregnancies of mothers heterozygous for FAOD have been associated with development of severe pre-eclampsia, acute fatty liver of pregnancy and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) in mothers and intrauterine growth retardation in infants [2].

Case Report

A 5-year-old girl is brought in by the emergency medical services to the pediatric emergency room for sudden loss of consciousness in school. She was found to have blood glucose level of 66 and was started on a bolus of intravenous fluids on the way to the hospital. Her mom insisted that patient be given a bolus of D10 initially and she also brought in extensive medical records that indicate that she has a FAOD. Her birth history was as follows: a 6 lbs 3 oz baby girl was born to a 32-year-old G1P0 mom at 39 weeks gestational age with APGAR scores of 8 and 8 after 16 h of labor via spontaneous vaginal delivery without further instrumentation after artificial rupture of membranes. Baby was placed on hypoglycemia protocol for initial low blood glucose levels by finger sticks, but recovered after being given formula feeds in the nursery. Mom had requested that baby be exclusively breastfed after the first couple of days when she started producing sufficient breast milk. The baby developed hyperbilirubinemia on day 4 of life and was transferred to NICU for mild respiratory distress (not requiring intubation), phototherapy and management of transient hypoglycemic episodes in spite of ad-

Fig. 1. Long chain fatty acid oxidation. The different sites of deficiencies causing FAODs are listed: (1) long-chain fatty acid transport or binding effect, (2) carnitine uptake defect, (3) CPT I deficiency, (4) CACT deficiency, (5) CPT II deficiency, (6) VLCAD, MCAD and SCAD deficiencies.

equate breastfeeding time. The baby's hyperbilirubinemia and hypoglycemic episodes resolved by day 8 of life and baby was discharged home on breastfeeds after follow-up was advised with a hospital-based pediatrician. The newborn screen was drawn during the NICU stay on full feeds and was sent to the State labs for processing. By the end of the first month of life, the parents and the pediatrician received a letter from the State requesting for additional testing as the baby was found to have a FAOD on the newborn screen. The baby remained asymptomatic and continued to meet adequate milestones in the first 3 months of life. On further testing, the baby was found to have medium chain acyl-CoA dehydrogenase (MCAD) deficiency. Since the age of 4 months, the patient had been hospitalized multiple times for episodes of hypoglycemia.

Clinical Case: MCAD Deficiency

MCAD deficiency presents with an incidence of approximately 1:10,000 in Europe, Australia and the USA [3]. Patients with MCAD deficiency may be normal at birth and only present with the classic clinical features when exposed to periods of stress such as prolonged fasting or vomiting precipitated by active infection. These typically present in the first 2 years of life with transient episodes of hypoglycemia and sometimes with seizures or coma during periods of acute decompensation related to changes in diet when weaning the infant off breastfeeding or off nighttime feeds or during infections like upper respiratory tract infections or viral gastroenteritis. Patients may also present with cardiomegaly (usually hypertrophic), arrhythmias or myopathy. The cardiac presentation typically occurs within weeks while myopathy typically occurs after infancy. The most common mutation associated with MCAD deficiency is the K304E mutation of the *ACADM* gene [4]. Initial labs may indicate transaminitis, increased CPK and hypoglycemia [5]. Blood C8 carnitine level is a highly specific marker, but may only be moderately elevated in mild phenotypes [3]. The excretion of hexanoylglycine in urine is pathognomonic for MCAD; however, it is not detectable in

milder phenotypes [3]. A definitive diagnosis is made if there is an elevation of C₈, C_{8:1} and C_{10:1} esters. Acute episodes are managed with intravenous fluids (containing 10% dextrose and bicarbonate) and therapy with carnitine. Patients are advised to avoid periods of catabolic stress and seek rapid intervention in periods of illness [6].

Discussion

Overview of FAODs

Fatty acids represent an important source of energy in periods of catabolic stress related to increased muscular activity, fasting or febrile illness, where as much as 80% of the energy for the heart, skeletal muscles and liver could be derived from them [7]. They play an important role in the neonate due to the limited glycogen reserves and high metabolic rate. Fatty acid oxidation produces acetyl-CoA, which supplies energy to other tissues when glycogen stores are depleted. The medium- and short-fatty acids are transported directly into the cytosol and mitochondria. The long-chain fatty acids are conjugated to carnitine and transported across the mitochondrial membrane and released as acyl-CoA to be used in the β -oxidation pathways (fig. 1) [7].

Mitochondrial fatty acid oxidation disorders comprise 4 groups: (1) disorders of the entry of long-chain fatty acids into mitochondria, (2) intramitochondrial β -oxidation defects of long-chain fatty acids affecting membrane bound enzymes, (3) β -oxidation defects of short- and medium-chain fatty acids affecting enzymes of the mito-

Table 1. Classification of FAODs

The different fatty acid oxidation disorders [6] could be classified as follows:	
(1) Disorders of plasma membrane functions	
Carnitine uptake defect	
Long-chain fatty acid transport/binding defect	
(2) Disorders of fatty acid transport across the mitochondrial membranes	
CPT I deficiency	
CACT deficiency	
CPT II deficiency	
(3) Disorders of long-chain fatty acid β -oxidation	
VLCAD deficiency	
Trifunctional protein deficiency and isolated long-chain L3-hydroxyl-CoA dehydrogenase deficiency	
(4) Disorders of medium-chain fatty acid β -oxidation	
MCAD deficiency	
Medium- and short-chain L3-hydroxyl-CoA dehydrogenase deficiency	
Medium-chain 3-ketoacyl-CoA thiolase deficiency	
(5) Disorders of short-chain fatty acid β -oxidation: SCAD deficiency	

chondrial matrix and (4) disorders of impaired electron transfer to the respiratory chain from mitochondrial β -oxidation [3].

FAODs may involve any part of the mitochondrial β -oxidation pathway affecting the plasma membrane functions, mitochondrial fatty acid transport or the short-, medium- or long-chain fatty acid β -oxidation pathways. Carnitine palmitoyltransferase I (CPT I), carnitine–acylcarnitine translocase (CACT) and carnitine palmitoyltransferase II (CPT II) represent different enzymes of the carnitine cycle that help transport the long-chain fatty acids across mitochondrial membranes and may be deficient causing impairments in transport of the fatty acids across mitochondrial membranes. Very long-chain acyl-CoA dehydrogenase (VLCAD), MCAD and short-chain acyl-CoA dehydrogenase (SCAD) are responsible for metabolism of acyl-CoAs of chain lengths C_{12–18}, C_{6–10} and C_{4–6}, respectively. Other deficiencies in the fatty acid oxidation cycle that may cause clinical symptoms include tri-functional protein deficiency, isolated long-chain L3-hydroxyl-CoA dehydrogenase deficiency, medium- and short-chain L3-hydroxyl-CoA dehydrogenase deficiency and medium-chain 3-ketoacyl-CoA thiolase deficiency (table 1) [7].

Clinical Features

There may be a range of clinical presentations ranging from mild liver dysfunction, cardiomyopathy and/or skeletal myopathy to severe liver disease that may present with a recurrent Reye-like syndrome that may start in the in-

fantile period with hepatic steatosis, unexplained hepatic failure and non-ketotic hypoglycemia [8]. Stressors such as fasting may exacerbate the hepatic disease. Figure 2 shows both general and specific manifestations of FAODs.

Diagnosis

Prenatal Diagnosis

FAODs are diagnosed prenatally by biochemical or molecular methods following chorionic villus sampling or amniocentesis. Mutation analysis is the preferred technique, if the molecular defect is known in the index case [9]. Prenatal diagnosis becomes necessary when there is a history of maternal liver disease complicating pregnancies [1].

Diagnosis in Newborns

FAOD is screened as part of the newborn screen based on acylcarnitine profiling of blood spots using tandem mass spectrometry. The following FAODs are diagnosed by newborn screening: CACT deficiency, CPT II deficiency (neonatal and late onset), VLCAD deficiency, MCAD deficiency, SCAD deficiency and a few other disorders like electron transport flavoprotein-ubiquinone oxidoreductase (ETF-QO) deficiency, α -ETF deficiency and β -ETF deficiency [10].

Diagnosis in Children and Adults

The main laboratory studies include routine labs (CBC, BMP, hepatic panel, ammonia, lactate and CPK), acylcarnitine levels, MS/MS analysis of organic acids,

Fig. 2. Clinical manifestations of FAODs [11].

plasma carnitine, acylcarnitines and urine acylglycine analysis, with a definitive diagnosis based on mutation analysis or measurement of specific enzyme activity [10]. Fatty acid transport studies using fibroblasts reveal possible fatty acid transporter defects. Liver biopsy may be necessary if patient present with primarily hepatic dysfunction and may reveal steatosis [8]. The diagnosis of FAODs even postmortem may help in genetic counseling and evaluation of siblings [3].

Treatment

Acute Presentation

The goal would be to reverse hypoglycemia and to treat comorbidities. The current treatment would include administering intravenous fluid bolus with 10% dextrose at 2 ml/kg in neonates or larger boluses in older children followed by D10 maintenance fluids. Some sources have used 12–15 mg/kg/min of glucose. It is important to not use intralipids in the acute presentation [6].

Long-Term Therapy

The goal would be to stop fat catabolism by preventing further fatty acid oxidation. The initial steps would be the prevention of hypoglycemia in periods of cata-

bolic stress by using frequent feeds and clinical supervision during periods of illnesses. A low fat, high carbohydrate diet is recommended. Dietary fat restriction is not indicated in MCAD deficiency and mild long-chain FAODs recently identified by newborn screening. Long-chain fat, however, needs to be restricted in severe long-chain FAODs and substituted by medium-chain triglycerides [3]. Hospital admission is recommended for procedures that would require the patients to take nothing orally for >8 h, especially if less than 1 year of age. Carnitine is undisputedly effective in patients with carnitine transporter deficiency [3]. Liver transplantation may be the ultimate consideration if there is no evidence of neurological disease or other systemic involvement that may impair recovery and return to baseline function [8].

Contribution Information

V.A. Vishwanath, MD, PhD, contributed to the structure design, literature review, research of the patient case and write-up of the manuscript. Dr. V.A. Vishwanath reports no disclosures and will comply with Committee of Medical Journal Editor's uniform requirements.

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