FULMINANT LIPID STORAGE MYOPATHY DUE TO MULTIPLE ACYL-COENZYME A DEHYDROGENASE DEFICIENCY

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ABSTRACT: Introduction: The lipid storage myopathies, primary carnitine deficiency, neutral lipid storage disease, and multiple acyl coenzyme A dehydrogenase deficiency (MADD), are progressive disorders that cause permanent weakness. These disorders of fatty acid metabolism and intracellular triglyceride degradation cause marked fat deposition and damage to muscle cells. Methods: We describe a rapidly progressive myopathy in a previously healthy 33-year-old woman. Over 4 months, she developed a proximal and axial myopathy associated with diffuse myalgia and dysphagia, ultimately leading to respiratory failure and death. Results: Muscle biopsy showed massive accumulation of lipid. Plasma acylcarnitine and urine organic acid analysis was consistent with MADD. This was confirmed by molecular genetic testing, which revealed 2 pathogenic mutations in the ETFDH gene. Conclusions: This report illustrates a late-onset case of MADD and reviews the differential diagnosis and evaluation of patients with proximal myopathy and excessive accumulation of lipid on muscle biopsy.

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CASES OF THE MONTH

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Fatty acid oxidation (FAO) provides a major source of energy in muscle when physiological demand exceeds glycolytic production. Disorders of fatty acid metabolism and intracellular triglyceride degradation result in fat deposition and damage to muscle cells.1,2 Lipid storage myopathies are progressive disorders that cause permanent weakness. They include the following diseases: primary carnitine deficiency; neutral lipid storage disease; and multiple acyl-coenzyme A dehydrogenase deficiency (MADD).3 MADD is an autosomal recessive disorder of fatty acid, amino acid, and choline metabolism, which results from deficiency of the electron transfer flavoprotein–electron transfer flavoprotein–ubiquinone oxidoreductase (ETF-QO).4

MADD is subdivided based on severity of the mutation and age of onset as follows: type I, neonatal onset with congenital anomalies; type II, neonatal onset without congenital anomalies; and type III, late onset. The neonatal-onset cases are usually fatal and are characterized by severe non-ketotic hypoglycemia, metabolic acidosis, multisystem involvement, and excretion of large amounts of fatty acid and amino acid–derived metabolites.5

Late-onset MADD is highly variable in age and symptoms at onset. Recurrent episodes of lethargy, vomiting, hypoglycemia, metabolic acidosis, and hepatomegaly, often preceded by metabolic stress, may be seen along with muscle pain and progressive proximal muscle weakness with increased lipid deposition in muscle tissue.6 We present the case of a 33-year-old woman who developed a rapidly progressive proximal myopathy due to MADD, and we review the clinical and laboratory evaluations of patients with a lipid storage myopathy.

CASE REPORT

A 33-year old, right-handed woman presented with a 3-month history of progressive proximal muscle weakness. Initially, her symptoms were restricted to the lower extremities with proximal leg weakness and associated low back and posterior thigh pain. She noticed difficulty rising from a low-seated position and climbing stairs. Over the following weeks, she began to experience weakness of the arms with difficulty raising her arms to brush her hair or place objects in upper cabinets. Her walking was limited to short distances due to fatigue and muscle soreness. A few days before presentation, she developed difficulty holding her head upright, problems chewing, and dyspnea with exertion. She denied diplopia, eyelid ptosis, dysarthria, dysphagia, numbness, paresthesias, or incontinence.

Work-up before her presentation included the following: creatine kinase 178 U/L (24–173 U/L); aspartate aminotransferase (AST) 109 U/L (10–50 U/L); alanine aminotransferase (ALT) 76 U/L (10–50 U/L); and calcium 10.3 mg/dl (8.4–10.2 mg/dl); and normal or negative erythrocyte sedimentation rate, complete blood count, Lyme, antinuclear antibodies, ceruloplasmin, C-reactive protein, hepatitis panel, parathyroid hormone, thyroid-stimulating hormone, electrolytes, blood

Abbreviations: acyl-CoA, acyl-coenzyme A; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CoQ10, coenzyme Q10; CPT, carnitine palmitoyltransferase; ETF, electron transfer flavoprotein; ETF-QO, electron transfer flavoprotein–ubiquinone oxidoreductase; FAO, fatty acid oxidation; MADD, multiple acyl-CoA dehydrogenase deficiency; MRC, Medical Research Council

Key words: electron transfer flavoprotein; electron transfer flavoprotein–ubiquinone oxidoreductase; fatty acid oxidation disorders; lipid storage myopathy; multiple acyl-CoA dehydrogenase deficiency

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Lipid Storage Myopathy
urea nitrogen, creatinine, glucose, and cortisol. Her brain MRI study showed a pineal cyst, and her lumbosacral spine MRI was unremarkable. Her initial electromyogram demonstrated normal insertional activity, no abnormal spontaneous activity, and early recruitment of low-amplitude, brief duration motor unit action potentials in proximal muscles, suggestive of a myopathy. Quadriceps muscle biopsy showed minimal variation in muscle fiber diameter in the absence of inflammation or necrosis.

Her past medical history was remarkable for anxiety and depression. She denied any prior history of exercise intolerance or muscle weakness. She was taking citalopram 20 mg/day and hydrocodone/ibuprofen 7.5 mg/200 mg as needed for pain. Her family history was negative for neuromuscular or neurological disease. Her mother had rheumatoid arthritis and bipolar disorder, and her father had diverticulosis.

On physical examination her blood pressure, pulse, and respiratory rate were 110/80 mm/Hg, 100 beats/min, and 18 breaths/min, respectively; her height was 67 in, and her weight was 205 lbs. Mental status testing was normal. Cranial nerve examination was normal. Motor examination showed weakness of neck flexors and extensors, and of proximal greater than distal limb muscles. The Medical Research Council (MRC) muscle strength scores were as follows (bilaterally symmetric): arm abductors 2/5; arm flexors 4/5; arm extensors 4/5; wrist extensors 5/5; wrist flexors 5/5; finger extensors 5/5; finger flexors 5/5; intrinsic hand muscles 5/5; hip flexors 3/5; hip adductors 4/5; hip abductors 4/5; knee extensors 5/5; knee flexors 5/5; foot dorsiflexors 5/5; and plantarflexors 5/5. She used her arms to push off from a low seated position in order to stand. Sensation and coordination were normal. She needed assistance with ambulation.

Two weeks after initial presentation, her symptoms had progressed and required hospital admission for pain management. She described the pain as constant muscle soreness, which was concentrated along the back and proximal extremities. Gabapentin 300 mg 3 times daily and hydrocodone/ibuprofen combination were prescribed, which reduced the severity of her pain by approximately 50%. Her laboratory evaluation showed elevated creatine kinase of 350 U/L, AST 112 U/L, and ALT 160 U/L. Muscle biopsy of the left deltoid was consistent with a lipid storage myopathy (Fig. 1). Serum lactate and pyruvate levels were mildly elevated, and serum carnitine levels were reduced (total 8 μmol/L, range 31–67 μmol/L; free 7 μmol/L, range 25–55 μmol/L). She was placed on supplemental carnitine 1 mg 4 times daily.

Three weeks later, she was readmitted for evaluation and treatment of muscle pain and weakness, mild to moderate dysphagia, and moderate dyspnea on exertion. She was restricted by pain more than weakness and needed assistance with her daily activities at home. She revealed that she had recently restricted her intake of carbohydrates in order to lose weight. On admission, her forced vital capacity was 1.4 L (35% predicted), prompting nocturnal non-invasive ventilation. Her creatine kinase was elevated at 3127 U/L. Her serum transaminases values were increased with AST of 531 U/L and ALT of 225 U/L. The following tests were requested: urine organic acids; plasma acylcarnitines; and free and total carnitine. Her carnitine dose was doubled to 4 mg twice daily. Coenzyme Q₁₀ (CoQ₁₀) 150 mg twice daily and riboflavin 100 mg twice daily were added. She had a rapid decline in respiratory function over the next several days. Given the severity of her condition and lack of response to therapy, she was placed on comfort measures and died the following day. The results of laboratory testing were reported the week after her death. Her plasma acylcarnitine levels showed increased long and very-long-chain acylcarnitine species (C₁₂–C₁₈), and her urinary organic acid profile demonstrated significant changes.
elation of several organic acids, including glutarate, 2-hydroxyglutarate, 3-hydroxyglutarate, gluconate, suberylglycine, hexanoylglycine, isovalerylglycine, isobutyrylglycine, 5-hydroxyhexanate, and dicarboxylic acids, consistent with the diagnosis of MADD. Molecular genetic testing revealed 2 mutations in the ETFDH gene, c.245>T (p.Ser82Phe) and c.524G>A (p.Arg175His), encoding the enzyme ETF-QO, both previously described pathogenic mutations (Denver Genetic Laboratories, Aurora, Colorado).7,8

**DISCUSSION**

Lipid is stored predominantly in oxidative muscle fibers as triacylglycerol, where it occupies approximately 0.2% of the fiber volume under normal conditions.9 This storage is the result of fatty acid uptake rather than biosynthesis and provides an energy source, as triacylglycerol may be readily hydrolyzed to free fatty acids that enter the mitochondria for β-oxidation. Circulating fatty acids in the plasma enter by facilitated diffusion and are converted to acyl-CoA before entry into the mitochondria for β-oxidation or conversion to lipid metabolites.10

A long-chain acyl-CoA requires conversion to a long-chain acylcarnitine to enter the mitochondria (Fig. 2). This reaction in reverse allows carnitine to regulate CoA concentration in the cell; therefore, carnitine may be depleted when accumulation of acyl-CoA occurs.11 Each cycle of β-oxidation produces NADH, FADH2, and acetyl-CoA. The first reaction requires a chain-length-specific acyl-CoA dehydrogenase (Fig. 3). Electrons from this reaction are transferred to ETF, ETF-QO, and ubiquinone. This creates a proton gradient that generates 2 adenosine triphosphate molecules (Fig. 4).12

Abnormal storage of triacylglycerol in muscle can result from disorders of either endogenous or exogenous fatty acid metabolism. Lipid storage myopathies with massive accumulation of lipid on muscle biopsy and progressive weakness include primary carnitine deficiency, neutral lipid storage disease with ichthyosis, neutral lipid storage disease with myopathy, and MADD.13

MADD, also known as glutaric aciduria type II, is a condition that leads to abnormal fatty acid, amino acid, and choline metabolism. It is the result of a deficiency of either ETF or ETF-QO, the 2 electron transfer flavoprotein enzymes responsible for the transfer of electrons from acyl-CoA dehydrogenases to the respiratory chain. ETF is encoded by 2 genes, ETF and ETFB, and ETF-QO is encoded by 1 gene, ETFDH.14 These compounds couple β-oxidation reactions to ubiquinone of the respiratory chain. The electron transfer flavoproteins are also required by the mitochondrial enzymes isovaleryl-CoA and glutaryl-CoA dehydrogenase. Therefore, MADD affects oxidation of long-, medium-, and short-chain fatty acids and the metabolism of lysine and leucine. The presentation, based on severity of mutation, is divided into the following 3 types: type I, neonatal with congenital abnormalities and cystic renal dysplasia; type II, childhood with hypoglycemia, encephalopathy, muscle weakness, or cardiomyopathy; and type III, adult with progressive weakness or rhabdomyolysis episodes, which in some cases are riboflavin-responsive. Urine organic acids show C5–C10 dicarboxylic aciduria and acylglycine derivatives, and plasma acylcarnitines demonstrate elevation in all chain lengths, C4–C18:1. Plasma total and free carnitine levels are low. Most of the myopathic forms of MADD are related to mutations in the ETFDH gene. The late-onset myopathic form may be triggered by infections, fasting, pregnancy, or surgery.15

Evaluation of patients who present with a progressive myopathy and extensive lipidosis on muscle biopsy begins with measurement of plasma total and free carnitine, plasma acylcarnitines, and urine organic acids. Carnitine values are frequently lowered in the FAO disorders; however, levels are always decreased dramatically in patients with primary carnitine deficiency. Plasma acylcarnitines are generally elevated in disorders of FAO. Specific elevations of acylcarnitines correspond to chain length of the deficient dehydrogenase. As each dehydrogenase is dependent on ETF and ETFDH, indiscriminant elevations of acylcarnitines of all chain lengths are seen in the plasma analysis of patients with MADD. The urinary organic acid profile is most often normal or non-specific in adult...
In MADD, this study is markedly abnormal with excretion of high levels of 2-hydroxyglutaric acid with or without acylglycine derivatives. The levels of carnitine, plasma acylcarnitines, and urine organic acids are normal in the neutral lipid storage diseases, as the defect is in endogenous metabolism of triacylglycerol. The biochemical profile used to diagnose these conditions may be confirmed by molecular genetic testing.

The clinical presentation of type III, late-onset MADD is typically a 3–6-month history of exercise intolerance and proximal weakness affecting predominantly hip and shoulder girdle muscles. Weakness of the neck flexor muscles occurs frequently. Muscle weakness may fluctuate and often worsens during intermittent infections, fasting, catabolic stress, or pregnancy. Episodes of hepatopathy, vomiting, and somnolence or stupor (Reyes syndrome–like crises) are common, but muscle weakness and exercise intolerance usually precede these events. Some patients have respiratory failure that requires assisted ventilation. The organic aciduria is often intermittent and only evident during periods of illness or catabolic stress.

**FIGURE 3.** β-oxidation. Each cycle of β-oxidation produces 1 acetyl-CoA, NADH, and FADH₂. Acetyl-CoA may enter the tricarboxylic acid cycle. NADH and FADH₂ transfer electrons for oxidative phosphorylation. The length of the acyl-CoA molecule is reduced by 2 carbons with each cycle. The initial reaction is catalyzed by an acyl-CoA dehydrogenase specific to the fatty acyl-CoA length. There are 4 dehydrogenases: very-long-chain acyl-CoA dehydrogenase (VLCAD); long-chain acyl-CoA dehydrogenase (LCAD); medium-chain acyl-CoA dehydrogenase (MCAD); and short-chain acyl-CoA dehydrogenase (SCAD).

**FIGURE 4.** Electron transport system. Electron transfer flavoprotein (ETF) and electron transfer flavoprotein–ubiquinone oxidoreductase (ETF-QO) function as electron acceptors for all 4 acyl-CoA dehydrogenases, transferring the electrons to ubiquinone (Q) of the electron transport system. This process creates a proton gradient responsible for generating 2 ATP molecules via the enzyme ATP synthase.
Riboflavin treatment has been shown to improve the symptoms and metabolic profiles in MADD patients, particularly those with type III. Riboflavin (vitamin B2) is the precursor of the coenzyme flavin adenine dinucleotide, which is the redox prosthetic group of the acyl-CoA dehydrogenases and ETF and ETF-QO. Coenzyme Q10 (ubiquinone) and carnitine should be added, as secondary deficiencies of these are frequently seen in MADD. In general, a high-carbohydrate, low-fat diet (70–75% complex carbohydrates and 10–15% fats) is recommended in FAO disorders. To avoid fasting, patients are given uncooked cornstarch snacks (1.5–2.0 g/kg per dose) during the day.

Riboflavin therapy was given to our patient late in her disease course. She had suffered severe muscle and liver injury, which was considered irreversible by the treating physicians and led to the family’s decision to withdraw support. If this treatment was initiated earlier in the disease course, it is possible that further muscle and liver damage could have been prevented.

In conclusion, lipid storage myopathies are rare conditions seen more often in children. They are characterized by progressive muscle weakness and changes on muscle biopsy. When lipid accumulation is large, 3 disorders should be considered in the differential, primary carnitine deficiency, neutral lipid storage disease, and MADD. The diagnosis of MADD is confirmed with plasma acylcarnitine, urine organic acid analysis, and molecular genetic testing showing 2 pathogenic mutations in the ETFDH gene. Late-onset cases of MADD are uncommon and more prevalent in mainland China, where 148 cases have been described since 2009, resulting from mutations in the ETFDH gene. In southern China, the carrier frequency of a common mutation (c.250G>A) is estimated to be 1.35%. Muscle biopsy is essential, as it shows excessive lipid droplets in type 1 fibers in all cases, including those that are milder and riboflavin-responsive. Confirmatory genetic testing is commercially available. MADD should be considered in patients who present with lipid storage myopathy, because riboflavin treatment has been shown to improve the symptoms and metabolic profiles if offered early in the disease course.

REFERENCES

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