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Case Report

Multiple Acyl-Coenzyme A Dehydrogenase Deficiency Leading to Severe Metabolic Acidosis in a Young Adult

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ABSTRACT

Background: Multiple acyl-coenzyme A dehydrogenase deficiency (MADD) is a rare metabolic disorder affecting fatty acid oxidation. Incidence at birth is estimated at 1:250 000, but type III presents in adults. It is characterized by nonspecific symptoms but if undiagnosed may cause ketoacidosis and rhabdomyolysis. A review of 350 patients found less than one third presented with metabolic crises. Our objective is to describe an adult with weakness after carbohydrate restriction that developed a pulmonary embolism and ketoacidosis, and was diagnosed with MADD type III.

Case Report: A 27-year-old woman with obesity presented to the hospital with fatigue and weakness worsening over months causing falls and decreased intake. She presented earlier to clinic with milder symptoms starting months after initiating a low carbohydrate diet. Testing revealed mild hypothyroidism and she started Levothyroxine for presumed hypothyroid myopathy but progressed. Muscle biopsy suggested a lipid storage myopathy. Genetic testing revealed a mutation in the *ETFDH* (electron transfer flavoprotein dehydrogenase) gene likely pathogenic for MADD; however, before this was available she developed severe ketoacidosis and rhabdomyolysis. She empirically started a low-fat diet, carnitine, cyanocobalamin, and coenzyme Q_{10} supplementation with improvement. Over months her energy and strength normalized.

Discussion: MADD may cause ketoacidosis and rhabdomyolysis but this is rare in adults. Diagnosis requires clinical suspicion followed by biochemical and genetic testing. It should be considered when patients present with weakness or fasting intolerance. Treatment includes high carbohydrate, low-fat diets, supplementation, and avoiding fasting.

Conclusion: There should be greater awareness to consider MADD in adults presenting with neuromuscular symptoms, if untreated it may cause severe metabolic derangements.

Introduction

Multiple acyl-coenzyme A dehydrogenase deficiency (MADD), also known as glutaric aciduria type II, is a rare, autosomal recessive, and clinically heterogenous inborn error of metabolism that affects fatty acid oxidation in turn affecting mitochondrial energy generation. Incidence at birth is estimated to be 1 in 250 000 individuals but its prevalence is unclear.[1] Pathogenic variants in *ETFDH* (electron transfer flavoprotein dehydrogenase), *ETFA* or *ETFB* lead to abnormal function of the electron transport flavoprotein complex and subsequent dysfunction of dehydrogenases involved in multiple biochemical pathways.[2] MADD may be classified as type I or type II with onset in the neonatal period, or type III with later onset. MADD type III is often characterized by nonspecific symptoms such as fatigue and muscle weakness, but if it is left undiagnosed it may lead to severe metabolic derangements. A literature review by Grünert (2014) of 350 patients with MADD type III found that less than 1 in 3 individuals presented with acute metabolic crises with metabolic acidosis, rhabdomyolysis, hypoglycemia, and/or transaminitis and almost 1 in 5 of those died of their condition.[3]

Abbreviations used: CK, creatine kinase; ETFA, electron transfer flavoprotein A; ETFB, electron transfer flavoprotein B; ETFDH, electron transfer flavoprotein dehydrogenase; MADD, multiple acyl-coenzyme A dehydrogenase deficiency; TSH, thyroid stimulating hormone.

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We present a case of a young adult with unsuspected MADD who presented initially with symptoms that suggested a broad differential diagnosis which worsened to the point of requiring admission to the intensive care unit for severe metabolic acidosis and myopathy.

Case Report

A 27-year-old woman presented to the hospital with severe fatigue and generalized muscle weakness that had progressively worsened over several months resulting in multiple falls and decreased oral intake. Her past medical history was pertinent for class III obesity (mass index, 40.0 kg/m^2). She presented 5 months earlier to neurology clinic with fatigue and proximal muscle weakness primarily affecting her lower extremities. This had developed over a period of 6 months after she started a low carbohydrate, calorie restricted diet for weight loss. She developed severe vomiting after a week of being on the diet and she stopped it after a month having already lost 20 lbs (9.07 kg). Testing revealed a slightly elevated thyroid stimulating hormone (TSH) at 5.45 μIU/mL (reference range: 0.550-4.780 μIU/mL) with elevated thyroid peroxidase antibodies and creatine kinase (CK) (588.0 units/L, reference range: 34.0-145.0 units/L). She was started on Levothyroxine 25 mcg daily for presumed hypothyroid myopathy but her symptoms continued to worsen and her TSH was still high at 4.17 μIU/mL (reference range: 0.358-3.740 μIU/mL). Antibody testing for myositis (PL-7, PL-12, Jo-1, EJ, OJ, SRP, MI-2, TIF1γ, MDA-5, NXP-2, PM/SCl, Ku, SS-A, U1-RNP, U2 snRNP, and U3 RNP antibodies; Esoterix Endocrinology), necrotizing myopathy (SRP IFA screen, HMG-CoA reductase antibody; Mayo Clinic Laboratories), myasthenia gravis (ACHR binding antibody, striated muscle antibody, Mayo Clinic Laboratories), and panel-based genetic testing for muscular dystrophies (Comprehensive Muscular Dystrophy Panel, Invitae) was normal. Electromyography suggested an inflammatory, genetic, or metabolic myopathy of her lower extremities. A vastus lateralis biopsy revealed vacuolated muscle fibers with lipid droplets suggestive of a lipid storage myopathy. A plasma acylcarnitine profile (Mayo Clinic Laboratories) revealed elevated small-, medium- and long-chain acylcarnitine species in a pattern suggestive of a defect in fatty acid oxidation. Urine organic acid analysis revealed elevated excretion of orotic acid (91 mmol/mol creatinine [Cr], reference range: <6 mmol/mol Cr) and 2-hydroxy glutaric acid (270 mmol/mol Cr, reference range: <50 mmol/mol Cr). Genetic testing was ordered; however, results were pending at the time of her presentation to the hospital.

She presented to the hospital with worsening weakness, multiple falls, and decreased oral intake. Neurological exam in the hospital revealed proximal greater than distal weakness of bilateral upper and lower extremities, neck weakness, and trace to absent lower extremity reflexes. She was also found to have a pulmonary embolism based on intraluminal filling defects in the segmental branches of the bilateral lower lobe pulmonary arteries. She was noted to have developed severe ketoacidosis with venous pH 7.00 (reference range: 7.32-7.43), beta hydroxybutyrate 5.67 nmol/L (reference range: 0.02-0.27 nmol/L), rhabdomyolysis with CK 4656 units/L (reference range: 34.0-145.0 units/L), and lactate peaking at 6.0 mmol/L (reference range: <1.3 mmol/L), prompting admission to the intensive care unit for treatment of acidosis. She was treated with sodium bicarbonate, normal saline, thiamine, dextrose, and heparin infusions, and improved within 24 hours. Her venous pH normalized to 7.45 (reference range: 7.32-7.43), CK improved to 245 units/L (reference range: 34.0-145.0 units/L), and lactate improved to 3.6 mmol/L (reference range: <1.3 mmol/L). She was empirically started on carnitine, riboflavin, cyanocobalamin, and coenzyme Q_{10} supplementation to treat a presumptive diagnosis of a riboflavin-responsive lipid storage myopathy such as MADD.[4] She did, however, continue to have objective weakness with proximal greater than distal weakness of bilateral upper and lower extremities on physical examination. Her genetic testing results while not immediately available were expedited and ultimately revealed a heterozygous frameshift mutation, c.51dup;p.(A18Cfs*5), in the *ETFDH* gene likely pathogenic for MADD.

After recovery from her acute illness she was discharged to inpatient rehabilitation for physical and occupational therapy. She was maintained on carnitine, riboflavin, cyanocobalamin, coenzyme Q_{10}, and thiamine supplementation along with a high carbohydrate, low-fat diet and discharged home to continue the same treatment. She was able to adhere to a diet with less than 25 g of fat per day and she was also advised to avoid prolonged fasting. Over the next few weeks she continued to have intermittent nausea requiring ondansetron, and neuropathic pain requiring pregabalin but overall her strength and energy started to improve. Her CK normalized, down to 36 units/L (reference range: 34.0-145.0 units/L) within 3 weeks after her presentation to the hospital (Fig. 1)

While her initial genetic testing revealed a single pathogenic variant in the *ETFDH* gene, she underwent additional testing including whole genome trio sequencing with no reportable sequence variants or copy number variants found that would be related to her condition (AR, ATN1, ATXN1, ATXN10, ATXN8OS, CACNA1A, CSTB, DIP2B, DMPK, FMR1, FXN, IL11RA, TBP, TCF4, Whole Genome Sequencing and Deletion/Duplication Trio Analysis, PerkinElmer Genomics), that is, did not find a second variant in the gene or evidence of genetic disorders that can mimic MADD. Karyotype and microarray revealed she was a carrier of a balanced translocation involving chromosomes 5 and 19; 46,XX,t(5;19)(p10;q10). Repeat plasma acylcarnitine profile on treatment showed a relative shift towards short- and medium-chain acylcarnitine species (Fig. 2). Repeat urine organic acid analysis was normal.

Over 4 months she gained nearly 30 lbs (13.61 kg) and metformin and eventually liraglutide were initiated in an attempt to help with weight loss. Her TSH was also noted to be as high as 21.58 μIU/mL (reference range: 0.550-4.780 μIU/mL) and her levothyroxine was increased slowly to 100 mcg daily. Nearly a year after her

Highlights

- Multiple acyl-coenzyme A dehydrogenase deficiency is a rare metabolic disorder.
- It presents with nonspecific symptoms but may cause severe metabolic derangements.
- It is easily treated with dietary modifications, supplements, and avoiding fasting.
- Inborn errors of metabolism like MADD should be considered in adults with weakness.

Clinical Relevance

There should be greater awareness to consider inborn errors of metabolism such as multiple acyl-coenzyme A dehydrogenase deficiency in adults presenting with nonspecific, neurological symptoms. While easily treated once diagnosed, multiple acyl-coenzyme A dehydrogenase deficiency if untreated may lead to severe metabolic deranagements.

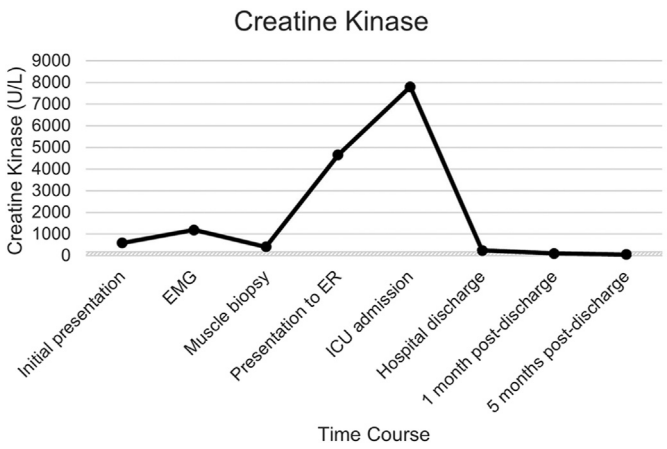

Fig. 1. Creatine kinase levels over the course of disease. Levels rose precipitously during hospital admission and normalized by discharge. (Gray shaded area corresponds to reference range: 34.0-145.0 units/L). *EMG* = electromyography; *ER* = extended release; *ICU* = intensive care unit.

hospitalization she continues to feel well with improved strength and energy.

Discussion

MADD is a rare, clinically heterogenous inborn error of metabolism often characterized by nonspecific symptoms such as fatigue and muscle weakness, but if left undiagnosed can lead to severe metabolic derangements such as rhabdomyolysis and metabolic acidosis.[5] While these complications most commonly occur in infancy, they have been rarely reported in adults. A review of 350 adult patients with MADD type III found that less than 1 in 3 presented with acute metabolic crises with ketoacidosis, rhabdomyolysis, hypoglycemia, and/or transaminitis, and almost 1 in 5 of those died of their condition.[3]

Adult-onset MADD can have an acute presentation mimicking Guillain-Barre syndrome with progressive ascending weakness and hyporeflexia.[6] It has been known to present in the setting of carbohydrate restriction.[7] Muscle biopsy exhibits cytoplasmic vacuoles on hematoxylin and eosin staining, plasma acylcarnitine analysis exhibits elevated acylcarnitines, and urine organic acid analysis exhibits elevated 2-hydroxy glutaric acid among others.[8] While fatigue and muscle weakness are nonspecific symptoms that can also be seen in other conditions such as inflammatory myopathies and muscular dystrophies, the above findings are all highly suggestive of a diagnosis of MADD, as in our patient.

Although only 1 heterozygous pathogenic variant was identified, her biochemical, clinical, and histopathological findings are consistent with MADD, and no alternative diagnosis was found on commercial genome sequencing. There are several reports of patients with a clinical-biochemical diagnosis of MADD where only 1 pathogenic variant is identified.[9-11] These patients are likely to have a second cryptic change in *ETFDH*, rather than representing carriers, as several variants that are hard to detect on commercial next-generation sequencing panels have been reported. These include synonymous variants, deep intronic variants, and pseudo-exon insertions.[12,13]

Treatment of MADD consists of avoidance of periods of prolonged fasting, restriction of fat and liberalization of carbohydrate intake, and supplementation with high-dose riboflavin, coenzyme Q_{10}, and levocarnitine.[1] Because fatty acid oxidation is critical to energy metabolism in the setting of prolonged fasting it is important that patients with MADD avoid fasting.[14] Riboflavin is a precursor to the coenzyme flavin adenine dinucleotide and this serves as a molecular chaperone that can help stabilize misfolded *ETFDH* proteins.[15] Coenzyme Q_{10} is known to be an important component of the electron transport chain in mitochondria. Misfolded *ETFDH* proteins lead to a secondary coenzyme Q_{10} deficiency.[16] Given the resulting accumulation of plasma acylcarnitines in these patients they may also become relatively carnitine deficient.[17] Surveillance of disease control in MADD involves monitoring plasma carnitine, acylcarnitine profile, CK, and urine organic acids;[1] however, it should be noted that the acylcarnitine profile and urine organic acids may sometimes be misleadingly normal in patients with MADD outside of periods of acute illness.[3]

In conclusion, there should be greater awareness to consider inborn errors of metabolism in the differential diagnosis of adults presenting with neurological symptoms.[18] While MADD is easily treated once diagnosed, it may lead to severe metabolic derangements as in our patient if undiagnosed. Therefore, a higher index of suspicion should be considered to diagnose MADD, especially when patients present with muscle weakness predominantly affecting the lower extremities, nausea and vomiting that develops after periods of fasting, intolerance of a low carbohydrate diet, or a metabolic acidosis of unclear etiology.

Disclosure

We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

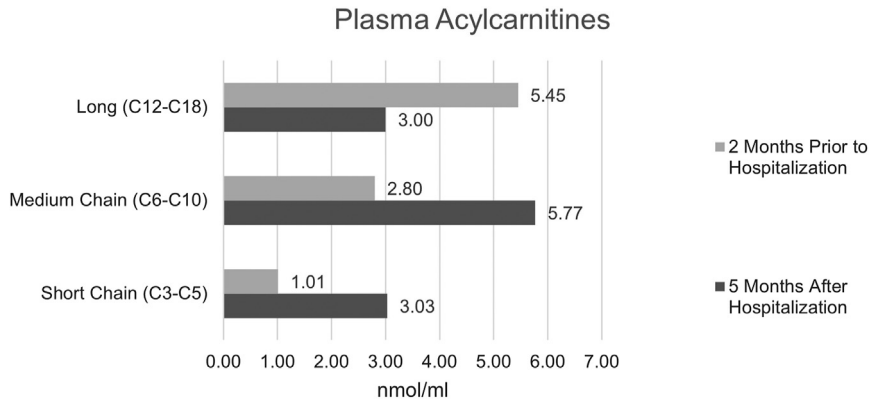

Fig. 2. Acetylcarnitine levels before and after treatment. Profile prior to treatment showed a trend toward elevation of long chain acylcarnitine levels that resolved after treatment (Flow Injection Analysis, Tandem Mass Spectrometry, Mayo Clinic Laboratories).

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