Medium-chain acyl-CoA dehydrogenase deficiency: Sudden and unexpected death of a 45 year old woman

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Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common fatty acid oxidation disorder. The clinical phenotype is heterogeneous and includes acute liver dysfunction, hypoglycemic coma, and sudden unexpected death.[1] Most patients first present between birth and 15 months of age, with few reports after 4 years of age. It has been hypothesized that some affected cases may not manifest any significant problem throughout life, resulting in clinical under-ascertainment.[2-3] To our knowledge, the oldest patient with fatal onset of symptoms to be reported previously was a 16 year old girl.[4]

A 45 year old Caucasian female was hospitalized for distal colectomy to remove a biopsy-proven adenocarcinoma found at 60 cm on colonoscopy. Her past medical history revealed an allergy to compazine, no previous surgeries or significant illnesses, and a recent weight loss of approximately 5 pounds. She was not taking any medications. With the exception of positive fecal occult blood test and nonspecific abdominal symptoms (cramping, pain, diarrhea), her physical examination on the day of admission was reported to be negative. In retrospect, however, she complained of nausea and discomfort after a routine overnight fasting in preparation for a colonoscopy.

Preoperative plasma fasting glucose and aspartate amino transferase (AST) were 91 mg/dL (70–110) and 25 U/L (15–37), respectively. The patient underwent a left colon resection and tolerated the procedure well without complications. Of note, the direct examination of the liver was reported to be normal. The patient was kept NPO and was prescribed 2 L of intravenous Ringer's lactate solution (glucose-free) over a 2 day period. On the morning of the third postoperative day, the patient complained of nausea and drowsiness. At that time, her plasma glucose (68 mg/dL) and AST (58 U/L) were marginally abnormal. Her mental status continued to deteriorate and became unresponsive by early afternoon. A CT scan of the head was read as negative. She was admitted to the intensive care unit where a transient improvement in alertness was noticed, possibly secondary to the administration of parenteral fluids. However, several hours later she went into respiratory arrest and could not be resuscitated.

Postmortem examination was significant for a prominent yellow fatty appearance of the liver and kidneys, with diffuse macro- and microvesicular fatty infiltration confirmed by oil-red-O staining. For this reason, biochemical investigations in postmortem liver and plasma were pursued.[1,5] In the liver, octanoic acid (0.106 μmol/100 mg protein; controls: 0.01–0.08) and cis-4-decenoic acid (0.047 μmol/100 mg protein; controls: <0.001) were elevated, glucose was not detectable (controls: 0.20–8.5 μmol/100 mg protein). Plasma AST was 147 U/L, total and free carnitine were 38 μmol/L (35–84) and 13 μmol/L (24–63), respectively; the esterified/free carnitine ratio was elevated (2.0; controls: 0.1–0.8). The acylcarnitine profile of the same specimen showed a characteristic profile with markedly elevated C6, C8, and C10:1 species. A free fatty acid profile showed elevated octanoic acid (174 μmol/L; controls 1–8), cis-4-decenoic acid (35 μmol/L; <0.4), and decanoic acid (13 μmol/L; 4–9). These results were strongly suggestive of a diagnosis of MCAD deficiency, which was confirmed by molecular analysis showing homozygosity for the A985G (K304E) mutation. The patient had two children, born in 1981 and 1985 both after uneventful pregnancy and delivery, and a full sibling reportedly in good health who has declined repeated requests to be evaluated.

This case raises two important issues. First, it confirms that in MCAD deficiency there is a tangible risk for sudden and unexpected death at any age as a consequence of prolonged fasting. This outcome is possible well beyond childhood, and sudden and unexpected death triggered by fasting intolerance could occur even with a completely negative past medical history. Pathologists and medical examiners should consider a biochemical work-up of all adult cases with otherwise unexplained postmortem finding of hepatic steatosis, regardless of their age. Second, the life-time risk of potentially fatal episodes of metabolic decompensation lends additional support to the call for implementation of newborn screening programs for MCAD deficiency.[5]

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