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Sudden death in medium chain acyl-coenzyme a dehydrogenase deficiency (MCADD) despite newborn screening

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ABSTRACT

Introduction: Medium chain acyl-CoA dehydrogenase deficiency (MCADD) is the most frequent of the fatty acid oxidation disorders (FAOD), a group caused by defects in the mitochondrial B-oxidation of fatty acids. Fatty acid oxidation is critical in supplying energy during periods when glucose is limited or when energy needs are increased beyond the availability of glucose. In MCADD, this energy shortage can result in acute metabolic episodes or sudden death. The prevention of sudden death from MCADD served as the primary impetus to expand newborn screening. However, we have experienced sudden death in four children with MCADD despite their detection by newborn screening. The purpose of this report is to alert others to the danger of sudden death in MCADD even when it is detected by newborn screening, to identify the clinical symptoms that precede sudden death, and to examine the relationship between the newborn screening result and the risk for sudden death.

Methods: We describe these children and their metabolic findings with emphasis on their newborn screening octanoylcarnitine (C8) level, the primary marker for newborn detection of MCADD. We also performed a literature search of cases of sudden death in MCADD in which the clinical status preceding death is described.

Results: The newborn screening C8 levels in our four cases were markedly elevated, ranging from 8.4 to 24.8 μmol/L (cut off < 0.8 μmol/L). Only two of the children were homozygous for the common c.985A>G MCAD mutation; the other two were heterozygous for this mutation. Similarly, among the eight reported cases which included MCAD genotypes, five were homozygous for the c.985A>G mutation, while two were heterozygous and one was homozygous for a splice site mutation. Vomiting 12–24 h before sudden death was present in all four of our cases, and the review of reported cases of sudden death in MCADD disclosed vomiting as a frequent symptom.

Conclusion: We suggest that in MCADD (1) a newborn screening C8 level of 6 μmol/L or greater represents particular risk of sudden death; (2) that MCAD genotypes other than homozygosity for the c.985A>G mutation are also associated with sudden death; (3) that vomiting is a frequent symptom preceding sudden death; and (4) social support and medical follow-up of these families are crucial in reducing the occurrence of sudden death.

Introduction

Medium chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common fatty acid oxidation disorder (FAOD), and one of the most frequently detected disorders in newborn screening (NBS), with an incidence ranging from 1:8000 [1] to approximately 1:15,000 [2,3]. The enzymatic defect results in a decrease of ketone production as well as an increased concentration of medium chain fatty acids. The decrease in ketone production compromises the availability of ketones required for energy at a time of prolonged fasting or acute illness (Fig. 1). This energy shortage, manifested as hypoketotic hypoglycemia, primarily affects function of the

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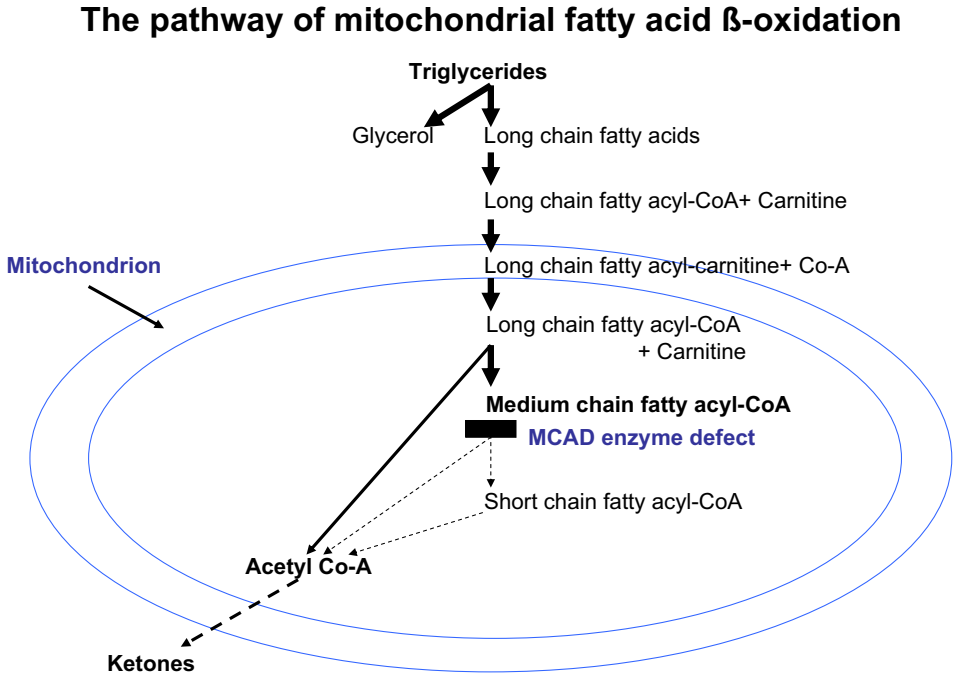

Fig. 1. The pathway of mitochondrial fatty acid β-oxidation.

ketone dependent skeletal and cardiac muscle as well as the brain, and can lead to death [3].

MCADD is usually a "silent" disorder in that affected individuals are clinically normal until a metabolic episode ensues, in infants and children almost always initiated by acute but often seemingly mild illness. The illness accompanied by gastrointestinal symptoms such as loss of appetite with vomiting and diarrhea begins the acute metabolic process with at least three clinical pictures. The most mild is lethargy. If not treated aggressively with intravenous glucose and careful observation, the lethargy can progress accompanied by hypoketotic hypoglycemia, metabolic acidosis, hyperammonemia, and fatty liver. However, the most dramatic outcome is sudden "unexplained" death, typically when the child is found dead in bed in the morning. Autopsy findings characteristically show marked fatty liver and cerebral edema [4]. This outcome is all the more shocking since the illness was considered mild and not concerning. It has been estimated that before expanded newborn screening 15–20% of children with MCADD died suddenly during a first episode [3–5].

The danger of sudden death in MCADD was a primary stimulant for the expansion of NBS by the novel methodology of tandem mass spectrometry (ms/ms) [6]. In Massachusetts, for instance, MCADD is the only disorder made mandatory when NBS was initially expanded in 1999 [7], based on the belief that presymptomatic diagnosis prevents sudden death by leading to the avoidance of prolonged fasting and to the prompt treatment of affected infants and children during acute illness [8,9].

Unfortunately, while the frequency of sudden death in MCADD has probably been reduced by NBS, it has not been eliminated. In this paper we describe four children, two from Massachusetts and two from Pennsylvania, who died suddenly despite having been known from NBS to have MCADD. We analyze the NBS characteristics of these children, we discuss the circumstances that led to their deaths, which were primarily the lack of appreciation of the potential severity of MCADD, and we describe the challenge of alerting parents and health care providers to the risk of sudden death without making the child "vulnerable" [10]. Finally, we examined the major clinical symptoms that preceded the fatal outcome in reported cases of sudden death in MCADD and that might alert parents and health care providers to this danger.

This experience indicates that NBS detection must be accompanied not only by explicit information to the family about this danger but also by education of the health care providers, including those in emergency rooms, as to the risks during acute illness and the appropriate immediate therapy. This experience also indicates that a psychosocial evaluation of the family and support when needed may be essential to the prevention of this tragic outcome.

Case reports

Patient 1

Thirteen-month-old boy, one of twins, born at 35 gestational weeks to a 26 year-old G1P2 mother via cesarean section required for failure to progress. Birth measurements included weight 2700 g (75%), length 45 cm (40%), and head circumference 31 cm (25%). Apgars were eight at 1 min and nine at 5 min. Physical exam was normal and he was discharged after a normal clinical course. Newborn screening suggested MCADD with an elevated octanoylcarnitine (C8) level of 24.8 μmol/L (cut off value for NBS C8 is 0.7 μmol/L).

Initial metabolic evaluation confirmed the diagnosis of MCADD with plasma levels of hexanoylcarnitine (C6) 1.8 μmol/L (normal range < 0.23 μmol/L), C8 13.4 μmol/L, decanoylcarnitine (C10) 1.0 μmol/L (normal range < 0.91 μmol/L), and decenoylcarnitine (C10:1) 1.1 μmol/L (normal range < 0.91 μmol/L). On MCAD gene analysis he was heterozygous for the 985A>G mutation[1] (985A>G/1178A>G). He was treated with carnitine at a dose of 100 mg/kg/day. His parents were given explicit instructions to feed him every 3 h, avoid fasting, and get medical attention for acute ill-

[1] The protein designation for this mutation is p. K304E.