Medium-Chain acyl-CoA Dehydrogenase

Medium-chain acyl-CoA dehydrogenase (MCAD; OMIM database No. 201450)[133] deficiency is a disorder of fatty acid oxidation (FAO) first described in 1982–1983.[134] All together, 10 disorders affecting mitochondrial FAO and ketogenesis have been identified. Among these, MCAD deficiency seems to be the most important because it is the most common and it has been implicated in some cases of sudden infant death syndrome (SIDS) and Reye syndrome.[135]

Incidence

MCAD deficiency has been diagnosed almost exclusively among individuals of northwestern European origin, with frequencies ranging from 1 in 46000 to 1 in 6400.[136,137] The heterozygote frequency is 1% to 2%. A few cases have been identified in other populations, including one Pakistani patient, one black patient, and isolated cases in individuals of Southern European and Northern African origin.[138,139] Newborn screening in Japan did not identify any carriers.[138]

Clinical Manifestations

The classic presentation is an episode of vomiting and lethargy after a period of fasting in a child between 3 and 15 months of age. The child may have had a previous viral infection (gastrointestinal or upper respiratory) resulting in decreased oral intake that would have little consequence in an unaffected child.[139] The episode may result in coma, and the child may remain obtunded even after hours of treatment with intravenous glucose. Undiagnosed disease has a mortality rate of 20% to 25%, many times with death occurring during the initial episode.[140] In a clinical review of 94 families with MCAD deficiency, 19 families (20%) had one or more unexplained child deaths. The diagnosis of MCAD deficiency was made postmortem in all cases.[141]

There are few reports of first symptoms after 4 years of age and fewer recurrent episodes after 4 years of age. Symptoms that require hospitalization during the second decade are unusual. The earliest onset of symptoms and sudden death is in the neonatal period, although this is rare, and the latest documented onset of the first episode was at 14 years of age. Most deaths would be preventable if dietary therapy and measures to prevent fasting were begun before the onset of symptoms. Cases in which children have died have, in some instances, resembled cases of SIDS or Reye syndrome. There is marked clinical variability even within the same family. There are families reported with several affected children with one child in the family dying on the first episode before 2 years of age and other children as old as 10 years never having had an episode.[139]

Although death is certainly the most important potential outcome of not screening for MCAD deficiency, there are findings in survivors that are very concerning regarding morbidity. A follow-up survey of 78 MCAD-deficiency survivors (all

older than 2 years) revealed a number of unexpected problems, including developmental disabilities, speech and language delay, behavioral problems, attention-deficit/hyperactivity disorder (ADHD), proximal muscle weakness, chronic seizure disorder, cerebral palsy, and failure to thrive. The finding of ADHD was seen in 9 patients (12%), 8 of whom were female, in contrast to the usual male preponderance of ADHD in the general population. The development of muscle weakness was strongly correlated with length of time between symptomatic presentation and the institution of appropriate measures to prevent additional episodes of illness.[141,142]

Pathophysiology

MCAD deficiency is one defect in the pathway of mitochondrial ß-oxidation. It is primarily a disease of hepatic FAO, with the most frequent presentation being episodic hypoketotic hypoglycemia provoked by fasting. FAO disorders do not present under nonfasting conditions and, therefore, have escaped attention for many years. The plasma and urinary metabolites of MCAD deficiency are of 2 types: general indicators of impaired function of the ß-oxidation pathway (eg, dicarboxylic acids) and specific metabolites (eg, octanoylcarnitine). The inability to break down fats to ketone bodies for an energy source while fasting eventually leads to hypoglycemia. In addition, medium-chain (C8–C12) acyl-CoA intermediates accumulate in mitochondria, with the end result being inhibition of mitochondrial ß-oxidation. Fatty acid is incorporated into triglycerides, resulting in accumulation of fat in the liver during acute episodes. The clinical presentation and many of the routine laboratory observations in MCAD deficiency are indistinguishable from those in Reye syndrome.[143] Encephalopathy and cerebral edema are secondary to accumulation of fatty acids within the central nervous system. Coma results from a combination of hypoglycemia and toxic effects of fatty acids or their metabolites.[134]

Inheritance

MCAD deficiency is inherited as an autosomal recessive trait. The causative gene is known, and multiple mutations have been identified. In studies of clinically affected patients with MCAD deficiency, 90% of mutant alleles identified have a single missense mutation (A985G); other mutations identified seem to individually account for less than 1% of the mutant alleles.[144] Virtually all of the A985G alleles arose on a background with the same haplotype, which suggests a founder effect, with the mutation beginning in northwestern Europe and then spreading throughout the rest of the world.[145] Recent molecular studies performed as follow-up to newborn screening by MS/MS technology have found a lower percentage of individuals with the common A985G mutation.[136,146] A second common mutation (T199C) has been observed in US populations identified initially by MS/MS screening. The T199C mutation is a mild mutation that produces a biochemical phenotype but has never been observed in clinically affected patients.[146]

Benefits of Newborn Screening

The benefits of and rationale for using newborn screening for diagnosis of MCAD deficiency are obvious. As noted above, many individuals affected with MCAD deficiency will die during the presenting episode, sometimes having been misdiagnosed with SIDS or Reye syndrome. Not only is this a tragic outcome for the loss of the child, but the family also has a 25% recurrence risk for the condition or may already have affected children who have not yet had clinical symptoms. The condition is relatively common, with a frequency of 1 in 15001 in prospective newborn screening of 930078 blood spots from different areas of the United States.[146]

Screening

The most efficient and sensitive method of screening for MCAD deficiency is MS/MS, measuring octanoylcarnitine (a compound normally not present) on the filter-paper blood spot. The optimal time for testing is the newborn period, because levels of octanoylcarnitine are significantly higher in the first 3 days of life than later (8 days to 7 years).[147] Individuals who are homozygous for the common mutation (A985G) who are most likely to present clinically will have octanoylcarnitine concentrations higher than 2.3 µmol/L, and individuals with one copy of 985 and one copy of a milder mutation (eg, T199C) will have octanoylcarnitine present but most likely at a lower concentration (≥1.0 µmol/L). The latter group is more challenging to determine the best course of follow-up.

Follow-up and Diagnostic Testing

Any child with an octanoylcarnitine concentration of 1.0 µmol/L or greater will require definitive diagnostic testing. Follow-up testing will consist of plasma acylcarnitine analysis, urinary organic acid analysis, and molecular testing. The plasma acylcarnitine analysis and urinary organic acid analysis will confirm the diagnosis. The molecular analysis should provide guidance regarding prognosis.

Brief Overview of Disease Management

Treatment for MCAD deficiency consists of avoidance of fasting and mildly decreased intake of dietary fat coupled with L-carnitine supplementation. MCAD deficiency results in a secondary deficiency of carnitine, because carnitine couples with toxic intermediates, resulting in their excretion while depleting carnitine stores. Although it remains questionable how helpful supplemental carnitine is during periods when the patient with MCAD deficiency is healthy, there is no doubt that exogenous carnitine is recommended during times of illness.[139] Another important point is that patients should be treated aggressively even during minor illnesses (eg, otitis media) to avoid a severe episode. There should be no hesitation to institute therapy with intravenous glucose and carnitine.

Current Controversies

Genotype/phenotype correlation is not straightforward, and the treatment of individuals with milder mutations remains controversial.[148,149] There are questions yet to be answered, such as whether some (or all) individuals with the less deleterious mutations (either in combination with the common 985 mutation or in combinations with one another) who have a biochemical phenotype would ever have medical problems. In addition, would some such individuals have serious episodes and others would not because of unknown modifying factors? Until we know the answer to these and other questions, we would be remiss in not treating everyone identified, perhaps overtreating some individuals. Newborn screening for MCAD deficiency will be key in answering some of these questions.

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