Medium-Chain Acyl-CoA Dehydrogenase Deficiency: a Useful Diagnosis Five Years after Death

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We report a family in whom a fatal case of medium-chain acyl-CoA dehydrogenase (MCAD; EC 1.3.99.3) deficiency was diagnosed by enzymatic analysis of heart tissue that had been stored for five years. Three healthy siblings underwent subsequent investigation with the 3-phenylpropionic acid loading test. All siblings had been asymptomatic; however, one (age 2.5 years) excreted large amounts of 3-phenylpropionylglycine in response to the load and exhibited an organic aciduria consistent with the diagnosis of MCAD deficiency. The other two siblings did not demonstrate 3-phenylpropionylglycinuria after the loading test. This case underlines the importance of considering family history and using appropriate diagnostic tests in the recognition of hereditary metabolic disorders.

Additional Keyphrases: heritable disorders • metabolism • organic aciduria

Deficiency of medium-chain acyl-CoA dehydrogenase [acyl-CoA:(acceptor) 2,3-oxidoreductase, MCAD; EC 1.3.99.3] is being recognized with increasing frequency in children having a broad spectrum of clinical presentation, ranging from symptomatic hypoglycemia through a syndrome resembling Reye's syndrome to sudden and unexpected death including sudden infant death syndrome (1–4).

The diagnosis of MCAD deficiency may be suggested by an abnormal organic aciduria during an acute attack. Gas chromatography–mass spectrometry of urine for organic acids will reveal the presence of a hypoketonuric medium-chain-length dicarboxylic aciduria, with greatly increased amounts of hexanedioic (adipic), octanedioic (suberic), and decanedioic (sebacic) acids resulting from the microsomal omega-oxidation of nonmetabolized medium-chain fatty acids (2–4). The excretion of adipic acid in healthy subjects is of the order of 10 mmol/mol creatinine; suberic and sebacic are not normally detected. During an acute attack in a patient with MCAD deficiency, the excretion of dicarboxylic acids is of the order of 1–10 mol/mol creatinine. Between attacks, therefore, the pattern of urinary organic acids may appear quite normal because mobilization of triglyceride stores and utilization of the fatty acid beta-oxidation pathway as a source of direct energy (muscle) or ketogenesis (liver) to prevent hypoglycemia form an intermittent pathway that is switched on only during periods of fasting or infection-related catabolism (3, 4).

MCAD can be assayed in cultured fibroblasts, leukocytes, or biopsy tissues (5) or in tissues collected postmortem (6). These assays are highly specialized and not routinely available; thus, the recognition of the MCAD deficiency in children who are not acutely ill may present difficulties. Provocative tests such as prolonged fasting or lipid loading may be used but are liable to precipitate an acute attack and are considered by many workers to be rather dangerous. Recently, Rumsey et al. (7) proposed that loading with 3-phenylpropionic acid (PPA), a nontoxic substance metabolized by MCAD, and measuring the unusual metabolite 3-phenylpropionylglycine in urine by HPLC may be useful for detecting asymptomatic cases of MCAD deficiency. The detection of urinary 3-phenylpropionylglycine by stable-isotope-dilution gas chromatography–mass spectrometry without a PPA load has also been proposed as a screening test for MCAD deficiency (8, 9).

We report here a fatal case of MCAD deficiency, diagnosed by enzymatic assay of postmortem heart tissue that had been stored for five years, and the subsequent investigation of three asymptomatic siblings by using the PPA loading test and analyzing for urinary 3-phenylpropionylglycine.

Case Report

L.S., a 16-month-old girl, presented in June 1982 with a three-day history of diarrhea without blood or mucus. On the third day she was noticed by her parents to be unresponsive and floppy and was admitted to the hospital. The only prior medical history of note was an admission at five days of age after an apneic attack thought to be associated with neonatal polycythemia (hemoglobin 210 g/L).

On admission she was unconscious, with generalized tonic convulsions and circulatory peripheral shutdown. Plasma concentrations of glucose were 0.9 mmol/L, urea 14.6 mmol/L, bicarbonate 16 mmol/L, and ammonia 52 μmol/L. Aspartate aminotransferase activity was 188 U/L, alanine aminotransferase, 32 U/L. Initially her liver was just palpable. Septicemia was diagnosed and treatment was begun with penicillin and chloramphenicol.

Convulsions continued and coma deepened. An apneic attack required intubation and ventilation. Metabolic acidois persisted (bicarbonate 15 mmol/L). The diagnosis of Reye's syndrome was considered and a computed tomographic scan revealed severe cerebral edema. Within 24 h of admission, her liver size had increased to 4 cm. Treatment for cerebral edema included thiopentone by intravenous drip. Despite all efforts, she developed signs of cerebral coning on the second day. On the third day sedation was stopped, and 24 h later an electroencephalogram recorded no cerebral function. Brain stem tests indicated death and, on the fourth day after admission, supportive management was withdrawn.

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Postmortem examination confirmed the presence of severe cerebral edema. There was no gross evidence of fatty infiltration of liver or other organs. Microscopic examination revealed panlobular micro- and macrovacuolar fatty change in the liver with periportal accentuation. No microvesicular fatty change was demonstrated in the heart or skeletal muscle, although such changes have been demonstrated in other patients subsequently shown to have MCAD deficiency (10). Histochemically there was a patchy decrease of succinic dehydrogenase in the liver, but cytochrome oxidase activity was normal, suggesting that other mitochondrial enzyme systems were intact. There was no significant ultrastructural change in the hepatic mitochondria, as is seen in the general mitochondrial dysfunction found in Reye’s syndrome. Therefore, the pathological findings were not considered to be characteristic of Reye’s syndrome, although the clinical history had many similarities.

Materials and Methods

This patient was reviewed in a retrospective survey of 200 consecutive cases of sudden infant death (6). The possibility of a fatty acid oxidation defect was recognized but no liver tissue was available for further study. Recently, with the development of improved assay methods (5), it became possible to determine acyl-CoA dehydrogenase activities in long-stored tissue samples. We therefore analyzed a sample of heart muscle that had been stored at −80°C for five years. Activity of long-chain acyl-CoA dehydrogenase was normal, but there was no detectable activity of MCAD (11).

After this diagnosis, we reviewed the status of the deceased patient’s three siblings, their ages at that time being 2.5, 4.5, and eight years. All had been in good health, and their growth and development were normal. None had had a major encephalopathic illness. None were being given antibiotics. Each was given an oral load of purified PPA, according to the protocol of Rumsby et al. (7). Urinary organic acids were examined by gas chromatography–mass spectrometry as described previously (12), but with marmaric acid as the internal standard instead of stearic acid.

The two older siblings did not excrete 3-phenylpropionylglycine in response to the PPA load, and their excretion of urinary organic acids was unremarkable. The youngest excreted large amounts of 3-phenylpropionylglycine after the loading test, indicating an impaired ability to beta-oxidize PPA to benzoic acid (Figure 1). The preload urine from this child contained small but clearly abnormal amounts of 3-phenylpropionylglycine, which did not require the added sensitivity of selective-ion detection to determine, as well as moderate amounts of suberylglycine and n-hexanoylglycine and small quantities of suberic and adipic acids, these findings being fully supportive of a diagnosis of MCAD deficiency (8, 9).

Discussion

In most cases of MCAD deficiency, some triggering factor—usually prolonged fasting or intercurrent infection—is needed before the disease is expressed. Possibly the nature and severity of the triggering insult determines the mode of presentation. In the absence of such a stress, individuals with MCAD deficiency may remain completely asymptomatic (13, 14), but the risk of a sudden and potentially fatal attack remains high well into childhood and possibly into later adult life. Probably the majority of such attacks can be prevented by maintaining an adequate energy supply as carbohydrate when caloric intake is reduced during illness and by close attention to prodromal symptoms. Thus the diagnosis of MCAD deficiency in the younger sibling of our index patient may well have been life-saving despite the delay in being made. Our experience emphasizes the need for thorough biochemical investigation of children presenting with Reye-like illness and for family studies when an inherited metabolic disorder is found. Similarly, adequate histological and, where appropriate, biochemical investigation of cases of unexpected infant death are called for, if unnecessary recurrences within affected families are to be avoided.

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References


