Medium-Chain Acyl Coenzyme A Dehydrogenase Deficiency

Occurrence in an Infant and His Father

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Background: Autosomal recessive inborn errors of metabolism often present as life-threatening disease in infancy and have adverse effects on the nervous system. Parents are usually heterozygotes. This is true of most disorders of fatty acid oxidation, which are rare and present with hypoketotic hypoglycemia. However, the gene for medium-chain acyl coenzyme A dehydrogenase (MCAD) deficiency is common in white people, raising the possibility that a parent may be homozygous.

Objective: To document the occurrence of MCAD deficiency in a 12-month-old boy and his father, both of whom were homozygous for the A985G mutation.

Design: Clinical observations and definitive biochemical testing.

Setting: Children’s hospital and university laboratory.

Participants: One child and one adult.

Interventions: Diagnosis and treatment.

Main Outcome Measures: Clinical outcome; analysis results of plasma and urine for carnitine and organic acids.

Results: An infant admitted with an acute illness requiring intensive care was found to have carnitine deficiency and dicarboxylic aciduria; MCAD deficiency was diagnosed by assay of his DNA for the common mutation. Test results of the father revealed him also to be homozygous.

Conclusion: In MCAD deficiency, as opposed to the usual rare autosomal recessive metabolic disease, a parent may also be an affected homozygote.

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REPORT OF CASES

CASE 1

A 12-month-old infant was admitted to the pediatric intensive care unit at Children’s Hospital and Health Center in San Diego, Calif, because of diarrhea, an upper respiratory tract infection, and lethargy. Parents were not consanguineous. For the first 9 months of his life, his mother had awakened him at 2 AM for a feeding, but at age nine months he began to sleep through the night. At about this time the mother began to incorporate meals of solid food and to develop more of a 3-meals-a-day program. Nine days prior to admission he had been treated with an antibiotic because of a diagnosis of otitis media, but this treatment was discontinued after 3 days. Vomiting and diarrhea began 2 days prior to admission. He was brought to the emergency department where a barium enema was admin-

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METHODS

Organic acid analysis was performed using gas chromatography–mass spectrometry. Urine and plasma levels of carnitine were determined with a radioisotopic enzyme assay. Analysis of DNA for the A985G mutation was carried out by polymerase chain reaction to amplify a 63-base pair (bp) fragment with mismatched oligonucleotide primers. The product was digested with the restriction endonuclease NcoI and analyzed by electrophoresis on 12% polyacrylamide gel. With the mismatched primer, the mutant DNA yielded a 43-bp fragment that could be distinguished from the normal 63-bp fragment.

RESULTS

When patient 2 (the 29-year-old father of the patient in case 1) and his wife were told of the diagnosis of their son’s illness and its nature and treatment, the history emerged that patient 2 at age 11 months had developed what was called hypoglycemic shock after a period of extended fasting. This resolved, but he experienced a second episode soon after that. Thereafter he had studiously avoided fasting. He would eat at other than normal mealtimes and would often wake up from sleep to eat. In addition, throughout his childhood, family members were encouraged to give him carbohydrates to prevent a recurrence. Blood was sent for molecular studies, and he was found to be homozygous for the A985G mutation. Carnitine therapy was initiated.

CASE 2

The findings of analysis of concentrations of amino acids in the plasma of case 1 were notable for a concentration of alanine of 642 µmol/L. Analysis of organic acids of the urine was carried out the day prior to discharge when he was clinically well, and the results revealed that the suberylglycine level was 12 mmol per mole of creatinine.

Carnitine Concentrations in Plasma and Urine

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<thead>
<tr>
<th></th>
<th>Plasma*</th>
<th>Urine†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 1</td>
<td>Case 2</td>
</tr>
<tr>
<td>Total carnitine</td>
<td>2.8</td>
<td>22.0</td>
</tr>
<tr>
<td>Free carnitine</td>
<td>0.3</td>
<td>14.4</td>
</tr>
<tr>
<td>Carnitine esters</td>
<td>2.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Esterified carnitine–free carnitine ratio</td>
<td>8.3</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are micromoles per liter.  †Unless otherwise indicated, data are millimoles per mole of creatinine.


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In dealing with families of patients with inherited metabolic disease, it is generally expected that the parents are heterozygotes and asymptomatic. This is because most disorders are the result of rare autosomal recessive genes. However, MCAD deficiency is different in that the gene is relatively common in white populations. Results of a literature search showed that this situation has occurred previously. Hepptinstall et al described in 1995 a family in which the father and his proband daughter were both homozygous for the A985G mutation. In this family the proband presented at age 6 months with a life-threatening hypoglycemic episode, while the father was asymptomatic. He had always had a predilection for sweet food. A brother of the proband was found to be homozygous by analysis of cord blood. Nevertheless, the possibility that a parent and child are both homozygous is not generally considered.

In our kindred, direct transmission of the mutant allels from each parent to case 1 is the logical explanation. The alternative uniparental disomy is unlikely. The importance of these experiences is the utility of investigation for homozygosity in a parent of a child with a prevalent mutation. This is particularly relevant to MCAD deficiency, a disorder in which sudden death can be an initial presentation at any age.

An MCAD deficiency usually presents first in infants between ages 6 months and 2 years. In the usual situation, acute intercurrent infection is followed by decreased oral intake and vomiting. Fatty acid oxidation is required when glycogen stores are depleted, and this usually occurs after 12 hours or more of fasting. At the same time, it is clear that some individuals can live many years before experiencing a long fast as a teenager or adult.

The findings of the organic acid analysis in the urine of patient 2 were unremarkable. His plasma free carnitine level was low (Table). In the urine, the esterified carnitine-free carnitine ratio was high.

Analysis of genomic DNA extracted from blood and amplified prior to restriction enzyme digestion revealed the 43-bp fragmentation in each patient and the expected 63-bp fragment in controls, indicating that both patients were homozygous for the A985G mutation (Figure). In the brother and the mother of patient 1, the presence of both the 63-bp and 43-bp fragments indicated heterozygosity.

**COMMENT**

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Our proband was admitted to the hospital at age 12 months with dehydration and lethargy, and 2 different viral infections were found: a rotavirus and respiratory syncytial virus. Thus, he seemed to have adequate cause for serious infantile illness. He was not considered clinically hypoglycemic, but the initial concentration of glucose was 1.83 mmol/L (33 mg/dL). It was only the actions of an alert infectious disease consultant that led to the submission of the urine sample for organic acid analysis, which led to the diagnosis. Classic MCAD deficiency presents with hypoketotic hypoglycemia. Initial urinalysis indicated a trace amount of ketones, and even a small amount can be misleading. The elevated creatine kinase level could have served as an alerting marker. Increased levels of creatine kinase and uric acid characterize acute episodes of metabolic imbalance in disorders of fatty acid oxidation. Findings of uric acid status were not available immediately; most clinical chemical analysis panels in children’s hospitals do not include uric acid. The significance of the elevated creatine kinase level is highlighted by the occurrence of the cardiac arrhythmia. This is another way in which disorders of fatty acid oxidation may become life-threatening. In the index patient, all of the clinical manifestations of acute disease resolved promptly, and he was sent home.

The dicarboxylic aciduria of MCAD-deficient individuals is characteristically evident only at times of acute illness. The father’s urine was unrevealing. The pattern includes elevated amounts of adipic (C6), suberic (C8), and sebacic (C10) acids and the glycine conjugates hexanoylglycine and suberylglycine. Phenylpropionylglycine excretion is helpful when present, but in most acutely ill patients in the intensive care unit, this compound is absent because of antibiotic therapy. Both patients were found to be deficient in plasma free carnitine and to have increased amounts of esterified carnitine in the urine. The accumulation of coenzyme A esters of carboxylic acids results in esterification with carnitine and preferential excretion in the urine. The consequent depletion of body stores of free carnitine may further exacerbate the disordered fatty acid oxidation in this disease.

The relative frequency of MCAD deficiency makes the assembly of rigorous epidemiological data possible. In a study from the Netherlands,8 the incidence of the common A985G mutation in 6195 newborn screening cards gave a carrier frequency of 1 in 55 persons. Calculations based on Hardy-Weinberg equilibrium predict a homozygote frequency of 1 in 12000. The odds that a parent might be a homozygote would doubtless be lower because there are no data on the proportion of homozygotes surviving to a childbearing age. In a prospective surveillance report from England, Pollit and Leonard found a disease frequency of 1 in 22,222. There are few data on other ethnic groups. Among gypsies in...
Spain, a carrier frequency for the common mutant allele was 1 in 17, which led to an estimated frequency of homozygosity of 1 in 1156.

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REFERENCES