Maple Syrup Urine Disease

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Menkes, Hurst and Craig in 1954 described maple syrup urine disease (MSUD) as a syndrome which has as its basic defect a reduction of branched-chain keto acid decarboxylase activity. This results in an elevation in acids (leucine, isoleucine, and valine) (Table I). The characteristic maple-syrup odor to the urine gives the disease its name.

This rare syndrome has an autosomal recessive inheritance which involves phenotypic and genetic heterogeneity. The three typical phenotypic variants are classified as infantile, intermittent, and intermediate. Valine, leucine, and isoleucine are essential amino acids and cannot be completely eliminated from the diet. However, successful treatment of MSUD has been employed by supplying these three branched-chain amino acids in limited amounts. Other variants have been found, such as the one described by dietary restriction. The frequency of maple syrup urine disease is 1/250,000 live births with the carrier frequency being 1/250 persons.

In the classical common type of infantile MSUD, the onset of symptoms is from two days to four months. These symptoms include poor sucking, feeding difficulty, lethargy, seizures, areflexia, intermittent hypertonicity, and flaccidity and respiratory problems.

Mental retardation rapidly becomes evident and if the disease is undetected early death may occur. Previously reported ocular manifestations include apparent blindness, marked ptosis of eyelids (unilateral and/or bilateral), sluggish ocular reaction to light, mild hypertelorism, lack of vertical or lateral eye movements on doll's head movement, intermittent monocular short-arch horizontal nystagmus, and alternating convergent strabismus.

Case Report

J. S. (UAMC No. 25 25 38) was born April 6, 1971, with a birth weight of 6 lbs 6 oz, the product of an uneventful pregnancy. At 24 hours of age, he was noted to have cyanosis. The physical examination revealed a head circumference of 13 3/4 inches with overriding sutures and normal transillumination. At this time he was hypotonic and had edema of the hands and feet. Since he had a total bilirubin of 23.4 mg per cent, was hypotonic and feeding poorly, he was transferred to the University of Arkansas Medical Center on his eighth day of life.

Soon after admission, he was given an exchange transfusion, intravenous fluids, and...
TABLE I

AMINO ACIDS IN MAPLE SYRUP URINE DISEASE

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Keto Acid</th>
<th>Simple Sugar</th>
</tr>
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<tbody>
<tr>
<td>Leucine</td>
<td>α-Keto isocaproic acid</td>
<td>Isovaleryl-CoA</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>α-Keto β-methylvaleric acid</td>
<td>α-Methyl butyryl-CoA</td>
</tr>
<tr>
<td>Valine</td>
<td>α-Keto isovaleric acid</td>
<td>Isobutyryl-CoA</td>
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Metabolic Block in MSUD

albumin to help build up his general condition. The laboratory data revealed a persistent glycosuria, proteinuria, and an increase in the total reducing substance in the urine. A quantitative measurement on April 13, 1971, demonstrated 500 mg of reducing substance per 100 ml of urine of which apparently one-third was glucose and the other two-thirds was a separate reducing substance.

On the serum and urine electrophoresis, the child had valine, isoleucine, and leucine spots. He had a normal 46 chromosome count. The Pediatric Metabolic Unit felt that this was a mild case of maple syrup urine disease.

This child was seen by the Ophthalmology Department at five months of age because he had difficulty following light and had very sluggish pupillary reactions to light. On ocular examination he demonstrated a horizontal pendular nystagmus with underaction of the right and left lateral rectus muscles. He had a relative enophthalmos with prominent supraorbital ridges and a broad nasal base with fairly prominent epicanthal folds (Fig. 1). The conjunctiva and cornea were within normal limits. The anterior chamber was shallow but not unexpectedly so for a child this age. The pupil in moderately bright light was 0.5 mm and in low illumination 2.5 mm. With pupillary dilatation, there was maximum pupillary dilation of 3 mm. There appeared to be both nuclear and cortical cataracts and the fundus was not seen (Fig. 2). The cataracts within the next nine months slowly became more opaque. At 15 months of age bilateral cataract surgery was successfully performed.

The child has been demonstrated to have renal tubular acidosis and is on Shols' solution at the present time.

Discussion

In the most common variant of MSUD, the infantile type, the onset is from two days to four months. Feeding difficulty, refusal to suck, and lethargy dominate the clinical picture. Limiting the intake of the branched-chain amino acids leucine, valine, and isoleucine is effective in reducing these symptoms.

The intermittent form of MSUD has intermittent, recurrent episodes of ataxia, lethargy, nystagmus, and seizures with an onset from 10 1/2 months to eight years.

The intermediate type of MSUD has milder symptoms and these patients frequently do not need dietary management. The patient presented in this case report has the intermediate type of MSUD. No dietary restrictions have been placed on this child.

Diagnosis is only made with a high degree of suspicion. The characteristic

Fig. 1: Note the prominent supraorbital ridges, brow and lid elevation, and relative enophthalmos in this infant with maple syrup urine disease.
TABLE II
NORMAL HUMAN LENS EXPRESSED IN RESIDUES PER 1000 RESIDUES

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>0–10 yr</th>
<th>40–49 yr</th>
<th>70–79 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine</td>
<td>340.8</td>
<td>303.8</td>
<td>281.8</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>153.2</td>
<td>189.4</td>
<td>168.0</td>
</tr>
<tr>
<td>Valine</td>
<td>185.3</td>
<td>204.3</td>
<td>178.7</td>
</tr>
</tbody>
</table>

reaction to light, horizontal pendular nystagmus, underaction of the lateral rectus muscles, and enophthalmos with prominent supraorbital ridges. In addition, epicanthal folds and nuclear and cortical cataracts were observed. Ptosis and strabismus have been reported previously.

The ophthalmologist might suspect this syndrome with the ocular findings and retarded neurological development with seizures.

Acknowledgment

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References