Cystathionase deficiency in fibroblast cultures from a patient with primary cystathioninuria

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Familial cystathioninuria is a rare, hereditary amino-acid disorder with an autosomal, recessive pattern of inheritance (Harris, Penrose, and Thomas, 1959; Frimpter, 1972). There is no consistent clinical picture associated with the condition but rather a mixture of mental, neurological, and somatic disorders and indeed healthy and mentally normal children have also been described (Perry et al, 1968; Scott et al, 1970; Lyon, Procopis, and Turner, 1971). Diagnosis is made on the basis of elevated plasma cystathionine levels and excessive urinary cystathionine excretion. In the majority of cases it has proved possible to correct these biochemical abnormalities by oral pyridoxine administration. This enables the patients to handle a methionine load more efficiently and causes a decrease in the plasma and urinary cystathionine levels with a concomitant increase in urinary sulphate excretion (Frimpter, Haymovitz, and Horwith, 1963; Frimpter et al, 1967), however, variations in the degree of response to pyridoxine have been reported (Berlow, 1966; Scott et al, 1970).

The nature of the defect was established by Frimpter, and Laster et al in 1965 by demonstrating a specific deficiency of hepatic cystathioninase activity in patients with cystathioninuria, thus explaining the abnormal tissue levels of cystathionine found in such patients (Harris et al, 1959; Brenton, Cusworth, and Gaull, 1965).

Case History. S. C. was admitted to hospital at 2½ months of age with a history of recent recovery from a bout of gastroenteritis and with a respiratory infection associated with vomiting. Mild hepatosplenomegaly was present. His symptoms gradually cleared. He is now 3 years of age and apart from repeated chest infections has remained well with normal developmental milestones. On his first admission he was found to excrete large amounts of cystathionine in the urine which disappeared with oral administration of pyridoxine (20 mg daily) but reappeared when the therapy ceased.

Materials and Methods

Skin samples were obtained from non-cystathioninuric control subjects and from S.C. by pinch biopsy from the fore-arm. The cell lines were cultured in Minimal Essential Medium (Glasgow modification) supplemented with 10% fetal bovine serum (Flow Laboratories). Penicillin (100 u/ml.) and streptomycin (110u/ml.) were routinely incorporated into the medium.

Cystathionase assays were carried out according to the method of Gaul, Rassin, and Sturman (1969), cystathionine synthase activity was determined by the method of Mudd et al (1965) and methionine-activating enzyme activity measured using a modification of the method of Cantoni and Durrell (1957). The total protein concentration was estimated according to the technique of Lowry et al (1951).

Results and Discussion

The results are reproduced in the Table. The skin fibroblasts cultured from S.C. had cystathionine synthase and methionine-activating enzyme activity levels within the control range. Cystathionase activity measured in a reaction mix containing 0-125 micromol of pyridoxal-5-phosphate in 0-5 ml. was 15% of the mean control value. This is higher than the levels of hepatic cystathionase activity reported by Finkelstein et al (1966) with their patient but in agreement with the findings of Tada et al (1968). Values for cystathionase activity have not previously been reported in skin fibroblast cultures, although Eagle, Piez, and Oyama, (1961) confirmed the existence of the trans-sulphuration pathway in their

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cystathionase</th>
<th>Cystathionine Synthase</th>
<th>Methionine-activating Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.C.</td>
<td>1-0</td>
<td>14-1</td>
<td>16-3</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>8</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Range</td>
<td>3-2-16-1</td>
<td>7-2-37-5</td>
<td>7-0-32-6</td>
</tr>
<tr>
<td>Mean</td>
<td>6-6</td>
<td>21-3</td>
<td>24-8</td>
</tr>
<tr>
<td>Median</td>
<td>5-8</td>
<td>20-9</td>
<td>25-7</td>
</tr>
</tbody>
</table>

All activities are expressed in mg/nanomol protein/hr.
serially propagated human cell lines. The use of skin fibroblast cultures in the diagnosis and investigation of several of the inborn errors of metabolism has been documented. The above results indicate that this technique may be successfully employed in the study of familial cystathioninuria.

REFERENCES


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