I-Cell Disease

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A 6-month-old female infant presented with severe psychomotor retardation, coarse facies, gingival hyperplasia, thick skin, restricted joint movements and radiological features suggestive of the Hurler syndrome. Her urine showed no excess excretion of mucopolysaccharides. I-cell disease was suspected from the onset of clinical features in early infancy, the subsequent progress and the absence of mucopolysacchariduria. Marked elevation of the activity in serum of three lysosomal enzymes confirmed the diagnosis. This patient had repeated convulsions, a feature not previously reported in this condition. This is the first case report of I-cell disease from India.

I-cell disease (ICD), or mucolipidosis II (McKusick 25250), is a rare inborn error of lysosomal metabolism. Although mucopolysaccharidoses of all types have been reported from many parts of India there is no report of ICD. This may be due to lack of awareness, absence of facilities to carry out the special enzyme determinations and misdiagnosis due to the clinical resemblance to the Hurler syndrome.

We report here an infant who presented with features of Hurler syndrome but did not excrete mucopolysaccharide in the urine. Her elevated serum lysosomal enzymes confirmed our suspicion of ICD.

CASE REPORT
The proband was the product of 38-week gestation, normal delivery, born to a 26-year-old gravida 4, para 3 mother and a 33-year-old father. At birth she weighed 2 kg and appeared normal. She had repeated convulsions since 2 months of age. Her milestones were retarded and she had numerous respiratory tract infections over the next 4 months.

At 6 months of age, when she first presented to us, her length was 57.5 cm (50th centile), head circumference was 37 cm (below 3rd centile) and she weighed 3.4 kg. She had a coarse facies with frontal bossing, proptosis, synophrys, flat nasal bridge, anteverted nostrils and leathery ears. She had a striking gingival hyperplasia and marked pallor. The liver was palpable 2 cm below the costal margin and the spleen was just palpable. Skin was thickened over wrists and shoulders. Skeletal abnormalities included stiff joints (fingers, elbows, shoulders, hips), a narrow chest, thoracolumbar kyphosis and thickened epiphyseal ends of long bones (Figure 1a, b, c). Her development was retarded, with poor head control and inability to roll over or sit up. She did smile and follow light with her eyes. Both fundi were normal. There was no corneal clouding.

Figure 1 (a) X-ray of chest and abdomen showing cortical thickening of long bones and ribs. (b) X-ray of spine showing hypoplastic anterior vertebral bodies and long thin pedicles. (c) X-ray of hands showing short, broad first metacarpals
The eldest sibling of the patient was a healthy 7-year-old sister. Two other older siblings had generalized convulsions and a phenotype similar to the patient. They had died at 3 and 4 months of age respectively.

INVESTIGATIONS

The patient's investigations revealed haemoglobin concentration of 4.5 g/100 ml. The acid albumin turbidity test (Carter et al., 1968) and Toluidine Blue spot tests on her urine were negative. Skeletal X-rays showed hypoplastic vertebrae, anterior expansion of ribs, bullet-shaped metacarpals with coarse trabecular pattern (Figure 1). The activity in lyophilized serum of the lysosomal enzymes arylsulphatase A and N-acetyl-β-D-glucosaminidase were markedly elevated (Table 1). Iduronate sulphatase was elevated five-fold over the control mean. The arylsulphatase A and N-acetyl-β-D-glucosaminidase were measured by Dr G. Thomas (Baltimore) and iduronate sulphatase by Dr E. Neufeld and Dr Clara W. Hall (Bethesda, USA).

The patient was lost to follow-up, although the 25% risk of recurrence and the availability of prenatal diagnosis was explained.

Table 1  Activities (nmol/ml per h) of lysosomal enzymes in patient's serum

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Patient</th>
<th>Control</th>
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<tbody>
<tr>
<td>Arylsulphatase A</td>
<td>800</td>
<td>9.7</td>
</tr>
<tr>
<td>N-acetyl-β-D-glucosaminidase</td>
<td>7227</td>
<td>638</td>
</tr>
<tr>
<td>Isoenzyme A (% of total)</td>
<td>9</td>
<td>58</td>
</tr>
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DISCUSSION

ICD, or mucolipidosis-II, is a disorder of lysosomal metabolism, clinically, biochemically and genetically distinct from the mucopolysaccharidoses and lipidoses (Leroy and De Mars, 1967; Leroy et al., 1971; Lightbody et al., 1971). The precise biochemical abnormality is unknown. However, the finding of reduced activity of several lysosomal enzymes in cultured cells and a marked increase in their activity in the culture medium (Wiesmann et al., 1971a) and in the patient's serum (Kelly et al., 1973; Wiesmann et al., 1971b; Den Tandt et al., 1974) suggest that the lysosomal membrane may be defective in this disorder (Wiesmann et al., 1971b; Wiesmann and Herschkowitz, 1974). However, the defect may lie in an inability to pinocytose exogenous acid hydrolases and to incorporate them into lysosomes because of abnormal and altered 'recognition markers' on the hydrolase molecules. The recognition marker may be a carbohydrate chain or residue (Hickman and Neufeld, 1972).

The diagnosis of ICD is usually made between 6 and 12 months of age when classical Hurler phenotype becomes evident. The suspicion is raised when in such a patient acid albumin turbidity test, as well as spot tests on urine using Alcian Blue and Toluidine Blue, are negative. The Alcian Blue test can be quantitative and is also quite a good and simple test (Whiteman, 1973).

Markedly increased activity of several lysosomal enzymes in serum confirm the diagnosis. A screening test for serum arylsulphatase A is very useful before undertaking more detailed studies (Kelly et al., 1973). The low hydrolase activities in cultured fibroblasts are of corroborative value and are not essential for diagnosis (Spritz et al., 1978). Our patient had the clinical, radiological as well as serum enzyme findings consistent with the diagnosis of ICD. The proportion of isoenzyme A (9%) in the serum of our patient is lower than in that of the control (58%), similar to that reported by Lie et al. (1973). However, the increase above normal in this heat labile fraction (isoenzyme A) in our patient was only double compared to a five-fold increase in theirs. The increase in the heat stable (I, or P) isoenzyme (25 x here and 28 x in theirs) is comparable in the two studies. One feature not described in previous patients is the presence of repeated, generalized convulsions (Spritz et al., 1978).

In our patient's family, two siblings who had died during infancy also had generalized convulsions.

Spritz et al. (1978) have shown that the patients with ICD can be diagnosed at birth. During the neonatal period, the face is not coarse but is wizened, with bulbous nose and long philtrum, reminiscent of a little old man. The skin is thick and doughy, with redundant folds, and downy hair covers much of the body. Gingival hyperplasia, hepatosplenomegaly, arachnodactyly with broad thumbs, restricted joint movements and gross bony deformities may be evident.

Prenatal diagnosis of ICD has been achieved (Aula et al., 1975). Biochemical diagnosis was established on the basis of the finding of 5–20-fold increase of various lysosomal enzymes in the amniotic fluid and a marked decrease in their activities in cultured amniotic fluid cells. The diagnosis was confirmed by finding inclusions in the cells of all organs obtained at necropsy of the fetus.

References

Kelly, T. E., Thomas, G. H. and Taylor, H. A. Screening for mucolipidosis. Lancet 2 (1973) 1089