

I-cell disease—mucopolipidosis II

NEIL GORDON
M.D., F.R.C.P.

Royal Manchester Children's Hospital, Pendlebury, Nr Manchester

Summary

I-cell disease is an example of the mucopolipidoses, a group of diseases which show features of both the mucopolysaccharidoses and the sphingolipidoses. A clinical description is given of a child suffering from this condition. The diagnostic criteria are discussed, as well as some of the necropsy findings.

THE genetic mucopolipidoses are a group of diseases which show the symptoms and signs of both the mucopolysaccharidoses and the sphingolipidoses (Table 1). Some of them such as Gm₂ gangliosidosis and infantile sulphatidosis are related to known enzyme defects, but in others the cause is unknown. Among the latter some of the affected children have been described as Hurler's variants as they show many of the features of Hurler's syndrome, but excrete normal amounts of urinary mucopolysaccharides.

Case report

M.W. born 29 May 1967.

The child was referred to Booth Hall Children's Hospital, Manchester, at the age of 2½ years. She had been born at home and was the second child in the family, the older sibling having developed normally. The pregnancy and birth were normal. Multiple deformities had been recognized from birth and she had been treated for a dislocation of the right hip. At the time of her referral she could not sit up herself and made no effort to stand. In general development was around 8-9 months. Three times

in the past year the child had lost consciousness and become cyanotic. There was no other past history or family history of note.

On examination the unusual appearance of the child was highly suggestive of gargoylism (Figs. 1 and 2). The bridge of the nose was broad and flattened, the nostrils anteverted, and the tongue was large. The eyelids were puffy, the eyebrows prominent, and the cheeks were highly coloured. The skin was coarsened. The abdomen was protuberant and chest expansion was limited. There was flattening of the left side of the skull and a fairly prominent lumbo-dorsal kyphosis. There was fair movement in the legs and feet, but the gluteal muscles appeared to be weak. The right thumb was flexed in the palm and could not be extended or abducted. Both hips were held in about 45° of abduction by contractures, probably in the abductor muscles. There was no clouding of the cornea and the optic fundi appeared normal. Muscle tone was slightly reduced, but the tendon reflexes were present and equal. The liver was enlarged one and a half finger's breadth, but the spleen was not palpable, and there was no evidence of cardiac involvement.

Over the next 2 years the child was greatly troubled by chest infections, sometimes severe enough to be classified as broncho-pneumonia. She showed some evidence of development, and began to stand in splints and seemed to benefit from wearing a spinal jacket. She started to say a few words.

At the age of 2 years 7 months the patient weighed 7.05 kg (third percentile at this age 10.4 kg), and her

TABLE 1. The distinguishing features of the mucopolipidoses, mucopolysaccharidoses and sphingolipidoses

	Mucopolipidoses (e.g. Gm ₁ gangliosidosis, juvenile sulfatidosis, I-cell disease)	Mucopolysaccharidosis (e.g. Hurler's, Hunter's and Sanfillipo's syndromes)	Sphingolipidoses (e.g. Gm ₂ gangliosidosis (Tay-Sachs' disease, Gaucher's disease, infantile metachromatic leucodystrophy)
Appearance	Gargoyle-like features	Gargoyle-like features	Normal
Skeletal abnormalities	Present	Present	None
Liver	Slightly enlarged	Grossly enlarged	Normal
Corneal and retinal changes	None	Corneal clouding	Cherry-red spot at macula
Urinary mucopolysaccharides	Normal	Increased	Normal
Major storage substance	Mucopolysaccharides and glycolipids	Mucopolysaccharides	Glycolipids

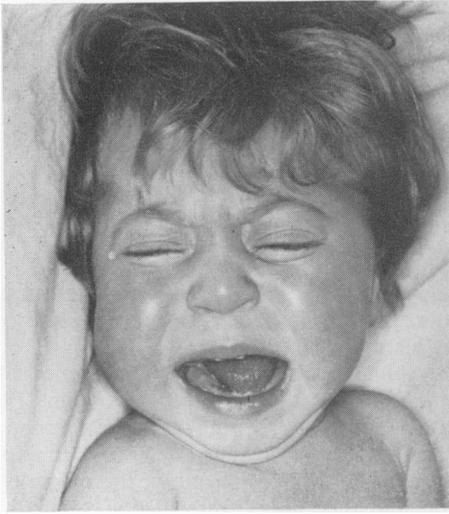


FIG. 1. Patient aged 2½ years.

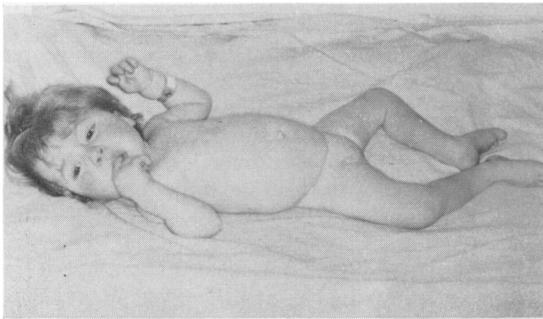


FIG. 2. Patient aged 2½ years.

height was 70.1 cm (third percentile at this age 83 cm). The GQ on the Griffiths Mental Development Scale was 27.2. X-ray of the skull showed very marked asymmetry. On X-ray of the spine and pelvis there was scoliosis convex to the left, and widening of the interpedicular spaces in the lumbar spine (Fig. 3). The posterior borders of the vertebral bodies in the lumbar spine were concave. The proximal ends of both the femora were constricted (Fig. 4). The X-rays of the hands showed that the metacarpal and the phalangeal medullary cavities were widened. The cortices were very narrow and thin. The lower ends of both the ulna and radius were tapered. The EEG was characterized by a generalized increase of slow wave activity. There were no epileptic discharges.

There was no excess excretion of mucopolysaccharides in the urine. Abnormal vacuoles were found in approximately 30% of mononuclear cells. No evidence of metachromasia was found. Some granules in the monocytes were Sudan black positive.

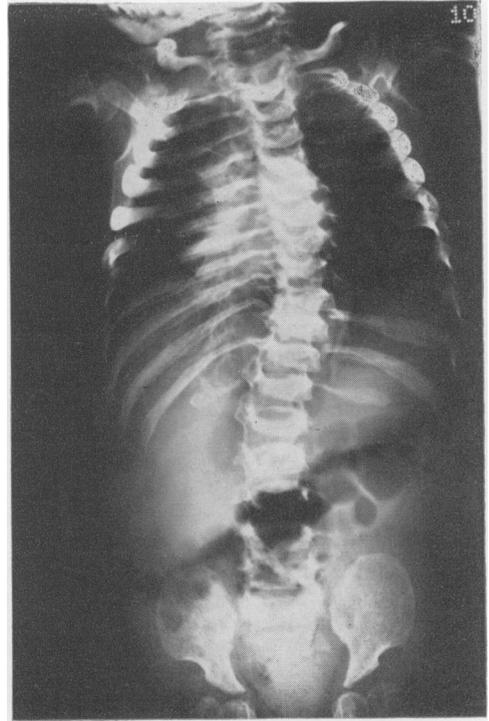


FIG. 3. X-ray of the spine.



FIG. 4. X-ray of proximal ends of the femora to show constriction.

Bone marrow aspirations yielded dry taps. The urine amino acid chromatogram was normal, as were the liver function tests. On one occasion the plasma true glucose was 20 mg/100 ml, but the presence of hypoglycaemia was not confirmed on a number of other occasions. Fibroblast cultures were attempted but were unfortunately unsuccessful. Plans had been made to repeat these cultures when the child was admitted to hospital with broncho-pneumonia and

died soon afterwards. Permission for necropsy was refused.

Discussion

The name 'I-cell disease' was derived from the striking granular inclusions seen in the cultured fibroblasts from children suffering from this syndrome. From the few reported cases it seems likely that the condition is inherited as an autosomal recessive. Slow development is recognized early in life, as well as the hypotonia. Congenital dislocation of the hips, herniae, and hyperplasia of the gums are also a feature. Recurrent upper respiratory tract infection seems to be a characteristic feature, and often a cause of death when complicated by congestive heart failure. Development does not seem to proceed further than sitting and standing without support, and a few social responses such as smiling and early vocalization. Unaided walking is not accomplished, nor is toilet-training or self-feeding. The affected children do not seem to survive more than a few years (Leroy *et al.*, 1971).

The appearance of the child becomes strikingly similar to children with Hurler's syndrome. The tongue is large, the earlobes fleshy, the forehead high, the epicanthic folds prominent, the bridge of the nose flat, the nostrils anteverted, and the upper lip elongated (Sprangler & Wiedemann, 1970a). In fact this is the diagnosis likely to be made. Apart from the facies, dwarfed stature and severe retardation, there is kyphoscoliosis, limited joint mobility with claw hands, and sometimes enlargement of the liver and spleen; but no clouding of the corneae. The X-ray findings are somewhat similar as well. There is marked periosteal new bone formation. The tubular bones of the arms are short and plump. The metacarpals are irregular and expanded and the phalanges are bullet-shaped. The distal ends of the radius and ulna are tilted. The vertebral bodies are short and rounded and there may be beaking of the last dorsal and first lumbar vertebrae. The ribs are broad and the cranial vault is thickened. However, the mucopolysaccharide excretion in the urine is normal.

The peripheral lymphocytes and monocytes are vacuolated and finely vacuolated cells are present in

the bone marrow. Cultured fibroblasts contain coarse, regular, refringent inclusions staining blue with toluidine blue, which are PAS and Sudan black positive (Sprangler & Wiedemann, 1970b). Special staining may also reveal metachromasia, indicating that they contain mucopolysaccharides as well as lipids (Matalon *et al.*, 1968).

At necropsy foam cells are found in the endocardium, lungs, spleen, liver, kidneys, adrenals and aorta. Electron microscopy does not reveal the lipid inclusions (zebra bodies) typical of Hurler's syndrome. The lipid content of the tissues is generally normal, except for some increase in total values (Leroy *et al.*, 1971). Liver acid β -galactosidase activity has been found to be decreased, with hyperactivity of a number of other enzymes (Tondeur *et al.*, 1971). Although the findings so far suggest a storage disease involving both lipids and mucopolysaccharides no definite cause can yet be suggested.

The differentiation from Hurler's syndrome is made by the normal urinary excretion of mucopolysaccharides. A somewhat similar clinical picture occurs in mucopolipidosis I or lipomucopolysaccharidosis, but the features of gargoylism are not so marked and the course of the disease is much more protracted. Gm₁-gangliosidosis, type I, has also been referred to as pseudo-Hurler's syndrome because of the appearance of the affected child, but the diagnosis of this disease is confirmed by the abnormal ganglioside pattern on thin layer chromatography of brain extracts.

References

- LEROY, J.G., SPRANGLER, J.W., FEINGOLD, M., OPITZ, J.M. & CROCKER, A.C. (1971) I-cell disease: a clinical picture. *Pediatrics*, **79**, 360.
- MATALON, R., CIFONELLI, J.A., ZELLWEGER, H. & DORFMAN, A. (1968) Lipid abnormalities in a variant of the Hurler's syndrome. *Proceedings of the National Academy of Science*, **59**, 1097.
- SPRANGLER, J.W. & WIEDEMANN, H-R. (1970a) The genetic mucopolipidoses. *Neuropädiatrie*, **2**, 3.
- SPRANGLER, J.W. & WIEDEMANN, H-R. (1970b) The genetic mucopolipidoses. *Humangenetik*, **9**, 113.
- TONDEUR, M., VAMAS-HURWITZ, E., MOCKEL-POHL, S., DERENNE, J.P., CREMER, N. & LOEB, H. (1971) Clinical, biochemical, and ultrastructural studies in a case of chondrodystrophy presenting the I-cell phenotype in tissue culture. *Pediatrics*, **79**, 366.