Case reports

Acute myelogenous leukaemia in Hurler's syndrome

SUMMARY The occurrence of the Hurler syndrome and acute myelogenous leukaemia in a 2½-year-old girl is described. This represents the first published report of the concurrence of these two diseases.

In this report we describe a patient with mucopolysaccharidosis type I (Hurler's syndrome) (Bach et al., 1972; Stevenson et al., 1976), in whom acute myelogenous leukaemia developed. The occurrence of these two rare diseases in the same person has not been previously documented.

Case report

A 6-month-old white girl was referred to the University of Minnesota Health Sciences Center in September 1974 because of a heart murmur. Past medical history showed that the mother's pregnancy and delivery and the patient's newborn period were uncomplicated. At 1 month of age the child was treated for otitis media and at 3 months of age had an episode of severe diarrhoea which required admission to hospital. At 5 months, she developed persistent oral thrush and a urinary tract infection which was successfully treated with antibiotics. The patient's heart murmur was thought to be caused by a small ventricular septal defect which did not require immediate intervention.

At the age of 11 months, the patient was admitted to the University of Minnesota Hospitals in acute renal failure caused by persistent diarrhoea and dehydration. Physical examination showed facial dysmorphism resembling that of the Hurler syndrome, an umbilical hernia, and hepatomegaly. Radiological examination disclosed the bony changes characteristic of dysostosis multiplex. Blood counts, including a leucocyte differential count, were normal. Examination of blood smears showed cytoplasmic inclusions in approximately 20% of the lymphocytes. These inclusions were usually coarse, sharply delineated, and surrounded by small clear haloes. They stained darkly with Wright's-Giemsa stain and were metachromatic when stained with toluidine blue. Urinary total acid mucopolysaccharide was 10·6 mg/24 hr (normal: 0–6 mg/24 hr). Urinary excretion of dermatan sulphate was 6·6 mg/24 hr (normal: 0 to 1·0 mg/24 hr) and excretion of heparan sulphate was 1·5 mg/24 hr (normal: 0 to 1·5 mg/24 hr). The diagnosis of mucopolysaccharidosis type I-H was made by the demonstration of defective \( \alpha-L \)-iduronidase activity; the levels of enzymatic activity in leucocytes and cultured skin fibroblasts from the patient and her parents are shown in the Table. The patient's \( \alpha-L \)-iduronidase activities in both sources were much decreased. Both parents had intermediate levels of enzymatic activity consistent with heterozygosity for the Hurler gene.

During the ensuing 18 months, the patient had recurrent episodes of bilateral otitis media and required myringotomies with placement of P-E tubes; she had no other serious medical problems. At 2½ years of age, the patient was once again admitted to hospital, this time after a 6-week history of easy bruising. In addition to the previously described phenotypic manifestations, generalised ecchymoses and splenomegaly were observed on physical examination. Blood studies revealed anaemia, thrombocytopenia, and a leucocytosis of 29 600/mm\(^3\) with 41% myeloblasts. Approximately 20% of the blasts stained positive for peroxidase and occasional blasts contained Auer rods (Fig. 1a). Approximately 15% of the blood lymphocytes had cytoplasmic inclusions as described above, characteristic of Hurler's syndrome (Fig. 1a). Ultrastructural examination of the lymphocytes showed multiple single membrane bound vacuoles which were nearly empty (Fig. 1b); presumably these vacuoles were secondary lysosomes which were engorged with undegraded mucopolysaccharide before processing for ultrastructural studies. The bone marrow showed hypercellularity, with 26% myeloblasts. A diagnosis of acute myelogenous leukaemia was made. Histiocytes filled with cytoplasmic inclusions similar to those in the lymphocytes were found in the marrow (Fig. 2).

The patient died one week after admission. Necropsy showed massive retroperitoneal haemorrhage and haemorrhagic staphylococcal pneumonia. Extensive leukaemic infiltration was present in the bone marrow, liver, spleen, and lymph nodes. Hurler's cells

| Table \( \alpha-L \)-iduronidase activity* |
|-----------------|-----------------|
| **Source**      | **Leucocytes**  | **Cultured skin fibroblasts** |
|                 | (nmol/18 hr per mg protein) |                  |
| Patient         | 10·6†‡          | 0·92              |
|                 | 7·1†‡           |                  |
| Mother          | 25·9§           |                  |
| Father          | 57·††           |                  |
| Normal range    | 111–272         | 1450–3242         |
| (m = 180·0)     | (m = 2213)      |                  |

* Assayed with phenyl-\( \alpha-L \)-iduronide as substrate (Hall and Neufeld, 1973).
† Activity in mixed leucocytes isolated by dextran sedimentation (Desnick et al., 1973).
§ Activity in peripheral blood granulocytes (Boyum, 1968) post-leukaemia.
" Activity in peripheral blood lymphocytes and monocytes (Boyum, 1968) post-leukaemia.
Figure 1a (top) Blood smear showing a myeloblast with an Auer rod (arrow). A lymphocyte (upper right) has multiple coarse darkly staining inclusions surrounded by clear haloes characteristic of Hurler's syndrome. (Wright's-Giemsa. × 1000.)

Figure 1b (bottom) Electron micrograph of a lymphocyte with several single membrane bound vacuoles which appear nearly empty after processing for ultrastructural studies. (Uranyl acetate, lead citrate. × 13 000.)

were found in multiple organs including the liver, spleen, lymph nodes, brain, and mitral valve.

Discussion

Several genetic disorders have been associated with an increased incidence of leukaemia. The most striking example is Down's syndrome with a twentyfold increase in the development of acute leukaemia (Krivit and Good, 1957; Conen and Erkman, 1966). A remarkably frequent occurrence of acute leukaemia has also been reported in patients with Fanconi's anaemia (Bloom et al., 1966; Swift and Hirschhorn, 1966) and Bloom's syndrome (Sawitsky et al., 1966).
In all of these conditions, however, either an abnormal chromosomal constitution (Conen and Erkman, 1966) or an increased susceptibility to in vitro chromosome breakage (Sawitsky et al., 1966; Swift and Hirchhorn, 1966) has been shown. No chromosome abnormalities or increased susceptibility to chromosomal breakage in vitro have been identified in Hurler’s syndrome.

Both Hurler’s syndrome and acute myelogenous leukaemia were well documented in the present patient; both are rare diseases. The estimated frequency of Hurler’s syndrome is approximately one case per 40 000 (McKusick, 1972) to 100 000 births (Lowry and Renwick, 1971). The death rate for myelogenous leukaemia in persons less than 20 years of age is approximately 0.28 to 0.62 deaths per year per 100 000 population (Stark and Oleinick, 1966). The chance association of these two disorders in the same child would be extremely rare, presumably accounting for the fact that no previous descriptions of such an occurrence have been reported in the medical literature.

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**Meckel’s syndrome (dysencephalia splanchno-cystica) in two Pakistani sibs**

**SUMMARY** A Pakistani couple, who were first cousins once removed through their fathers, and whose mothers were also related, had two live-born children, a boy and a girl. Both children died within 2 hours of birth with occipital encephalocele, microcephaly, polycystic kidneys, and cystic distension of intrahepatic bile ducts. Both children had normal karyotypes. These abnormalities constitute Meckel’s syndrome (dysencephalia splanchno-cystica); this is the fifth report of parental consanguinity, adding further support to the evidence for autosomal recessive inheritance of the disorder.

Sibs with microcephaly, occipital encephalocele, and polycystic kidneys were first reported by Meckel in 1822. Both patients had, in addition, polydactyly and cleft palate. Numerous case reports in both this and the last centuries have appeared, including a review by Gruber (1934), who added one case of his own observation and proposed the name dysencephalia splanchno-cystica. Opitz and Howe (1969) described a further case and called the disorder Meckel’s syndrome; they suggested that it was inherited in an autosomal recessive manner. Hsia et al. (1971) reported 7 patients including 2 pairs of concordant monozygotic twins in 1 family and 3 sibs in another. Fried (1973) has drawn attention to the relatively high prevalence among oriental Jews. Sibs, born to consanguineous Pakistani parents, are presented here; they provide additional supporting evidence for autosomal recessive inheritance.

![Fig. 1](a) First case (IV.14). (b) Second case (IV.15).
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