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Hunter syndrome presenting as macrocephaly and hydrocephalus

SUMMARY A 2-year-old boy with macrocephaly, communicating hydrocephalus, and mild hepatosplenomegaly was found to have mild Hunter syndrome (MPS II). Establishment of the latter diagnosis was complicated by the paucity of obvious physical findings because of the patient's young age and his ethnic origin.

Hydrocephalus is a rare finding in children with genetic metabolic disorders. Among the mucopolysaccharidoses, communicating hydrocephalus has been described in the Hurler (MPS I), Hunter (MPS II), and Sanfilippo (MPS III) syndromes (Fowler et al., 1975), sometimes accompanied by papilloedema (McKusick, 1972). In this report we describe a 2-year-old black boy with communicating hydrocephalus, macrostomia, and hepatosplenomegaly who represented a diagnostic dilemma until the presence of the Hunter syndrome was finally established.

CASE REPORT

The patient, a 2-year-old black boy, was a product of an uncomplicated pregnancy and delivery. Delivery was by vertex presentation, and the birthweight was 3370 g. From the time of birth he grew rapidly and gained weight so that at the age of 7 months his weight was about 12.5 kg. His psychomotor development seemed to be normal until the age of 13 months, at which time he could stand and walk with support or in his walker. Thereafter, motor regression was noticed: he stopped walking and was unable to sit for longer than several minutes.

At 14 months of age, the patient was admitted to hospital for evaluation of motor retardation. On physical examination, he presented as a large obese child. His head circumference was 57 cm (97th centile for his age), and the anterior fontanelle was large, flat, and slightly tense. Funduscopic examination was normal, and there was no evidence of any facial or bulbar weakness. There was a moderate spastic diplegia with tightness in the legs and slight hypertonia of the arms; the deep tendon reflexes were normal in the arms, but very hypoactive in the legs. X-ray films of the lateral thoracic and lumbar spine revealed hypoplasia of the second lumbar vertebral body and a kyphosis at this level. There was no anterior beaking, and the pedicles were within normal limits.

Computerised axial tomography revealed large ventricles, and a study with 125I-serum albumin (RISA) disclosed poor outflow from the ventricular cavities. The diagnosis of communicating hydrocephalus was made and a ventriculoperitoneal shunt performed. After shunting, his motor development improved and he again was able to walk with support.

At the age of 24 months, he was referred to the Genetic Clinic of the University of California, San Francisco, because of the referring physician's suspicion that a mucopolysaccharide disorder might be present. He was a large and very heavy boy, with mildly coarse facial features (Fig.) His height was 93 cm (90th centile) and weight 19.9 kg (44 lb) (50th centile for age 6 years). His mental development seemed to be within the normal range for his age. The head circumference was 57 cm (adult male size) and there was frontal bossing. The inner canthal distance was 3.5 cm (>97th centile) and outer orbital distance 11 cm (>97th centile). A lower thoracic kyphosis was present, and the abdomen was protuberant with diastasis recti and bilateral inguinal hernias. The liver and spleen were palpated 3 cm below the costal margin. His hands were short and stubby, and neurological examination showed generalised spasticity. Corneal clouding (by slit lamp examination) and heart murmurs were not found. The radiological findings were typical for mucopolysaccharidosis: J-shaped sella turcica, broad and spatulate ribs, mild anterior beaking of the first and second lumbar vertebrae, and kyphosis at the second lumbar level.

Cardiac evaluation at 33 months of age showed evidence of minimal thickening of the mitral valve (by echocardiography) and minor electrocardiographic abnormalities.

The family history did not disclose the presence of any other individuals with similar problems, and the parents were unrelated. The father was observed to be very tall and stout and to have a large head.

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LABORATORY STUDIES
Urinary mucopolysaccharide determinations (Švejcar and Robertson, 1967) by Dr W. Van B. Robertson of Stanford University showed a total MPS excretion of 57 mg uronic acid/g creatinine (normal 6-5-21-5), a heparan sulphate (as sulphaminohexose) excretion of 31% of total MPS (normal <14%), a dermatan sulphate (as napthoresorcinol reactive material) of 60% of total MPS (normal 10-31%), and a keratan sulphate (as galactose) excretion of 1.9 mg galactose/g creatinine (normal <2-6).

In correction experiments performed by Dr E. F. Neufeld of the National Institutes of Health, addition of iduronate sulphatase (Neufeld et al., 1975) in the form of the Hunter corrective factor (Neufeld and Cantz, 1971) produced an 81% reduction in accumulation of $^{35}$SO₄-MPS in cultured fibroblasts. This response is diagnostic of the Hunter syndrome.

Discussion
There were several factors that made the early diagnosis of Hunter syndrome difficult in this patient. He was relatively young (13 months) at the time he first presented with motor retardation and macrocephaly. The only positive signs for MPS II at that time were a mild gibbus, explainable by hypoplasia of a vertebra, and slight hepatosplenomegaly. Second, because the child's head circumference was proportional to other measures of growth and because of his father's large head, macrocephaly was not initially considered to be the result of hydrocephalus and/or storage disease. However, the onset of regression of motor performance associated with positive neurological findings and a relatively higher incremental rate of growth in head size eventually pointed towards the diagnosis of communicating hydrocephalus of 'unknown origin'. Third, the relatively mild coarse facial features passed unnoticed because of the ethnic origin of the boy. It was, therefore, the combination of young age, 'mild' nature of primary disease, large overall size (probably on a familial basis), and ethnic origin that prevented the immediate diagnosis of MPS II.

There is no direct evidence that the communicating hydrocephalus found in our patient is the result of the
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mucopolysaccharidosis. However, since this combination has been described in the literature and since no other primary cause has been found to explain the hydrocephalus, a causal relation between the two is plausible. It is also important to recognize that communicating hydrocephalus may be a contributing factor in mental retardation (Tew and Laurence, 1975). This may be particularly relevant in MPS II which is known to manifest itself with and without mental retardation (McKusick, 1972; Yatziv et al., 1977). As a result, when hydrocephalus is present it may be difficult to determine in a given case whether the mental deterioration is primarily the result of storage in the central nervous system or of the accompanying hydrocephalus or of both. In our case, the insertion of a ventriculoperitoneal shunt apparently resulted in improvement of motor performance, but it is still too early to assess the patient's mental status adequately.

The authors wish to thank Dr Stephen L. Kaufman for referring this case to us. His alertness to the possibility of a storage disorder, despite the paucity of objective physical findings, made possible the diagnosis of MPS II and the proper counselling for this disorder.

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**Supernumerary small ring chromosome**

**Summary** A supernumerary small ring chromosome was found in 30% of cultured peripheral leucocytes and 50% of skin fibroblasts in a 6-year-old boy with mild mental retardation and midline cleft palate. The extra chromosome appeared to carry a densely staining region on Giemsa banding. The banding patterns of the remaining 46 chromosomes were normal. C banding indicated that the ring chromosome contained mainly centromeric constitutive heterochromatin.

Chromosome analysis of both parents showed normal karyotypes by both conventional and banding techniques; thus the origin of the ring chromosome could not be determined.

Supernumerary small chromosomes have occasionally been reported, appearing mainly as metacentric (Borgaonkar et al., 1971; Abbo and Zellweger, 1970; Froland et al., 1963; Gamstorp et al., 1966), or acrocentric chromosomes (Latta and Hoo, 1974). Some of the cases were associated with congenital malformations and others with normal phenotypes (Ellis et al., 1962; Nielsen and Rasmussen, 1975).

Mosaicism for an extra small ring chromosome (46,XY/47,XY,+r), was reported in a 10-year-old boy with cheilo-palato-gnathoschisis and mental retardation (Hoo et al., 1974). We report another patient with mild retardation, midline cleft palate, and mosaicism of 46,XY/47,XY,+r). The similarity of the clinical findings to the previously reported patient is of interest.

**Case report**

This patient (100468) was born at term after a normal pregnancy to a 24-year-old mother and a 31-year-old father. The mother had been treated with iodine for a 'goitre' until about 2 years before this conception. She was on no treatment before and during the pregnancy. The baby weighed 3400 g at birth and was considered as a normal newborn except for the midline cleft palate. The mother first became concerned about the child's development at 9 months of age when she noted that he had a big head and generalized hypotonia. He could not distinguish her from other people. He began sitting at 1½ years,
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