



Hunter Disease: A Report of Two Siblings

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ABSTRACT

Hunter disease (MPS-2), an X-linked recessive disorder is caused by deficiency of iduronate-2-sulfatase (I2S) enzyme. Coarse facial features, short stature, dysostosis multiplex, joint stiffness, mental retardation manifest between 2 - 4 years of age. Skin manifestations, male affection, absence of corneal clouding are strong pointers to the diagnosis. We report an interesting case of two male siblings-6 years and 10 months of age with history and examination indicative of a storage disorder. Investigations revealed mucopolysacchariduria in both cases, dysostosis multiplex on skeletal survey of elder sibling; a strong clincher to the diagnosis. Our diagnosis was ascertained by the unique affection of male siblings, unaffected female sibling, clinical characteristics, urinary GAG levels and skeletal survey. Purpose of this case report is to highlight the distinctive presentation of Hunter disease, to enable earlier detection, to discuss the treatment options and the role of genetic counselling.

Keywords-Hunter disease, iduronate-2-sulfatase, dysostosis multiplex, mucopolysaccharides, corneal clouding.

INTRODUCTION

Mucopolysaccharidoses (MPS) are a family of inherited defects in the catabolism of sulphated components of connective tissue known as *glycosaminoglycans* (GAGs). In affected patients, one or more of three specific polymers-dermatan

sulphate, heparan sulphate, keratan sulphate, accumulates within the cells causing dysfunction and are excreted in excess in the urine[1].

Enzymes for GAG catabolism are lysosomal hydrolases and MPS patients have < 1%

residual enzyme activity. The MPS disorders tend to present in one of three ways-

- Dysmorphic syndrome(MPS-IH,MPS-2,MPS-6)
- Learning difficulties, behavioural disturbances , dementia(MPS-3)
- Severe bone dysplasia(MPS-4)

Diagnosis is based on clinical and radiological examinations followed by urinary examination for GAG excretion and finally by specific enzyme assay.

MPS disorders are multisystem diseases and effective management depends on a multidisciplinary approach involving different specialities; the paediatrician having a major role in orchestrating the various members of the therapeutic team.

Mucopolysaccharidosis type II or Hunter disease is caused by a deficiency of iduronate-2-sulfatase as described by Neufeld [13] with a prevalence of one in 170,000 male live births.

We report this case of MPS-2 to emphasize its unique X-linked recessive pattern of inheritance in comparison to the autosomal recessive mode seen in others. The report also intends to be an eye-opener not only because of the distinctive features but also because of the rarity of the entire entity of MPS, with an overall frequency of 3.5-4.5 per 1 lakh population.

CASE REPORT

Six year old boy (CASE 1), the first child of a consanguineous marriage, presented with history of progressive abdominal distension since 7 months of age and enlargement of the head since 2 years of age. There is past history of recurrent respiratory tract infections for which he was hospitalised twice.

He had 2 younger siblings- 4 year old female, 10 month old male. The female had normal

physical appearance with no developmental delay. Mother revealed that she had noticed similar complaints in the 10 month old male which prompted us to evaluate the child (CASE 2).



Fig.1 The affected siblings; CASE 1, CASE 2.

There was history of progressive enlargement of the head and the abdomen since 2 months in CASE 2. Both siblings had a home delivery with an uneventful postnatal period, fully immunised for age and were developmentally normal except that the vocabulary was confined to bi-syllables and incoherent speech in CASE 1.

Examination of CASE 1 revealed coarse facial features, large sized head with frontal bossing, broadened nasal bridge, large tongue, short neck, short trunk, clawed and stubby fingers (brachydactyly), protuberant abdomen, swollen wrist joints, clumsy gait and a clear cornea. Height-90cm (short stature), head circumference - 51cm(macrocephaly), upper : lower segment ratio - 1.2(expected for age-1.7). Abdominal examination revealed moderate hepatosplenomegaly. Other systems-normal. Intelligence quotient determined by 'draw a man' test was in the mild mental retardation range.

Examination of CASE 2: Length - 74cm, weight -7 kg, head circumference -47cm (macrocephaly), extensive mongloid spots on the buttocks and back, protuberant abdomen with moderate hepatosplenomegaly, clear cornea and no skeletal deformities.

Fundoscopy examination revealed bilateral macular oedema in CASE 1 and was normal in CASE 2. Audiometry revealed

sensorineural hearing loss in CASE 1. Radiographic evaluation was done for elder sibling, younger sibling exempted due to low age.

Skull x-rays (Anteroposterior, lateral) showed enlarged, J-shaped sella turcica. Skull bones and sutures appeared normal for age. X-rays of the dorso-lumbar spine showed anterior beaking and ovoid vertebral bodies.



Fig.2 Enlarged J shaped sella turcica

X-rays of hands revealed widening of metacarpals and phalanges with proximal tapering of the metacarpals. Chest x-ray showed widened ribs, with tapered posterior ends (spatulated appearance); lung fields - normal.



Fig.3 Widened metacarpals and phalanges with proximal tapering of metacarpals.



Fig 4. Spatulated appearance of ribs

Urinalysis in both cases revealed a marked increase in dermatan sulphate and heparan sulphate. Enzyme assay for Iduronate-L-sulphatase

could not be done due to non availability. Our diagnosis of MPS-2 was confirmed from the history of 2 affected male siblings, unaffected female suggesting X-linked recessive inheritance, clinical examination, urinary gag levels and skeletal survey.

DISCUSSION

Mucopolysaccharidosis, first described by Charles Hunter a Canadian physician in 1917, described it as a rare disease in two brothers [2]. The accumulation of GAG within the lysosomes is responsible for the clinical manifestations, a characteristic appearance called "gargoyles"[3]. MPS affected infants are normal at birth and MPS-like phenotype present birth suggests mucopolysaccharidosis type 2(I cell disease) or GM1 gangliosidosis

MPS type II is classified into mild (type II, HB) and severe (type II, HA) based on the length of survival and the presence of central nervous system (CNS) disease [4]. In our CASE 1 there was mild mental retardation. Young *et al* [5] established that patients with Hunter disease fall into two groups according to intellectual deterioration

The clinical features are limited to short stature, large head, short neck, coarse facial features, skin eruptions, and mild mental retardation.

Cutaneous features (as in CASE 2) may be the initial manifestation in mild disease, although patients in both groups may have skin involvement. These findings were ascertained by Demitsu and colleagues [6] and by Ogubuyi [3]

Young *et al* [7] noted sensorineural deafness in majority of cases (as in CASE 1).

Hunter's disease subjects can have airway obstruction, respiratory failure, obstructive sleep apnoea, explained by the deposition of GAGs in soft tissues which explains the recurrent respiratory infections in CASE 1.

Ophthalmological findings like retinitis pigmentosa, papilledema (as in CASE 1) and optic atrophy are common in Hunter disease, though corneal clouding is absent.

Radiological involvement in MPS is termed *dysostosis multiplex*. *Urinalysis* for GAGs (heparan and dermatan sulfate) is the screening test; however, is not diagnostic. Confirmatory diagnosis is by enzyme assay in leukocytes, fibroblasts, or dried blood spots [15], which shows absent or low I2S activity. Enzyme assay was not done in our patient due to lack of facility, but careful history and prudent physical examination backed with a good radiological investigation helped in making a diagnosis.

Prenatal diagnosis using amniocentesis and chorionic villus sampling can identify an affected fetus. Genetic counselling can help parents with a family history of mucopolysaccharidoses [5]

Only palliative treatment is available.

Enzyme replacement therapy (ERT) is intuitively attractive as a treatment. Idursulfase (Elaprase), a recombinant human I2S, has been recently approved in the United States and the European Union. [4] Weekly intravenous infusion is given over 3 hours at a dose of 0.5 mg/kg diluted in saline. Its limitations include inability to cross the blood brain barrier and mild immune mediated reactions.

Since 1980, bone marrow transplantation have been in use as a crude form of 'gene therapy' in MPS. Reports showed marked reversal except for the irreversible skeletal changes. However both treatments are very expensive and our patients neither received ERT nor BMT owing to poor resources in a country like India having numerous other health care needs.

Supportive management in the form of physiotherapy (to improve joint mobility), nutrition and infection management carries an important role.

CONCLUSION

Mucopolysaccharidosis is a rare multisystem disorder with a constellation of clinical findings. Clinical presentation, urinary gag levels and skeletal survey helps to diagnose MPS. A careful and systemic approach is needed to accurately diagnose the exact type as enzymatic studies are not available in most centres. Early detection of the disease and appropriate management through a multidisciplinary approach is recommended to improve the quality of life.

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