

## Case Report

## Mucopolysaccharidosis type II (Hunter syndrome) – A case report

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## ABSTRACT

Hunter syndrome or mucopolysaccharidosis (MPS) type II is an X-linked recessive disorder caused by a defect in the metabolism of glycosaminoglycans (GAGs). We present a rare case of MPS with a typical presentation of coarse facies, short stature, mild mental retardation and absence of corneal clouding. His radiographic findings were suggestive of MPS and diagnosis was confirmed by demonstrating deficient Iduronate-2-sulphatase enzyme in plasma. We present this case to highlight the distinctive manifestations as well as radiological and definitive diagnostic findings of the Hunter syndrome.

**Key words:** *Facial Dysmorphism, Hunter Syndrome, Mucopolysaccharidosis, Short Stature*

**M**ucopolysaccharidosis (MPS) is a group of hereditary metabolic disorders caused by absence, or malfunctioning of the lysosomal enzymes essential for breakdown of glycosaminoglycans (GAGs) [1]. This leads to collection of GAGs in the cells, blood, and connective tissues resulting in progressive permanent cellular damage which manifest as facial dysmorphism, organomegaly, joint stiffness, contractions, pulmonary dysfunction, myocardial enlargement, and neurological impairment [1-4]. Hunter syndrome or MPS type II is an X-linked recessive disorder caused by deficiency of iduronate-2-sulfatase (I2S) enzyme resulting in accumulation of dermatan and heparin sulfates in various tissues [5]. Treatment is mainly palliative as no effective therapy is readily available; however, bone marrow transplant and enzyme replacement therapy with recombinant human iduronate-2-sulfatase has been successfully tried [6].

**CASE REPORT:**

A 7 yr old male child brought to pediatric outpatient department with complaints of was not gaining height and

joint stiffness with decreased movements of hands and legs for past 3 years. Restriction of movements started from hands and gradually progressed to involve knee, ankle and small joints of toes. Parents felt child was apparently well till 3 yr of age, when mother noticed gradual distention of abdomen which was not associated with pain in abdomen, any urinary complaints or change in bowel habits. Abdominal distension was associated with breathing difficulty on and off which used to increase in lying down posture with no diurnal variation. He also had recurrent cough cold and decreased hearing for past 2 yr; however, there was no history of hospitalization.

There was no history of trauma, history of contact with tuberculosis, and any deformity in back/spine. There was no history of any neurological deterioration, abnormal movements or behavior, vision problems or regression of milestones. He was the first of two siblings, born out of non-consanguineous marriage. His younger brother was normal and developing appropriately. His antenatal, natal and post-natal history was uneventful. He was completely immunized for age and his development was appropriate for age except mildly delayed speech. Child can speak in short sentences but cannot tell a story.



**Figure 1-3. Figure 1 – Child with short stature, protuberant abdomen, large head, coarse facies, and stiff joints. Figure 2 – X-ray hands and pelvis show generalized osteopenia, delayed appearance of carpal centres with short and wide metacarpals and phalanges and tapering of metacarpal bones of hands. Figure 3 – X-ray spine (AP and lateral views) shows relative decrease of antero-superior height of lumbar vertebrae with central beaking of L1 & L2 and normal intervertebral spaces.**

On examination, child was afebrile, conscious, well oriented with stable vitals. He underweight (weight - 14 kg, <3 SD for age) and short statured (height - 91 cm, <3 SD for age) with upper and lower segment ratio of 1/1 and head circumference of 52.5 cm (50<sup>th</sup> percentile). He had coarse facies, prominent frontal bulge, narrow nostrils, short, broad and stubby fingers and lumbar lordosis (figure 1). He had knock knees, flat foot with inversion, and joint stiffness with limitation of extension at knee, ankle, elbow and wrist joints. There was no corneal haziness. On respiratory system examination, thorax was symmetrical but short and narrow with normal breath sounds. Cardiovascular system examination was normal except an ejection systolic murmur in aortic area. Per abdomen examination revealed hepatosplenomegaly.

His routine laboratory investigations including complete hemogram, serum calcium, phosphorus, liver and renal function tests were within normal limits. His thyroid and lipid profile was also normal. On skeletal survey, dysostosis multiplex was present (figure 2 and 3). Echocardiography revealed mild aortic regurgitation with thickening of valves and moderate mitral regurgitation. CT Head findings were also suggestive of inherited metabolic disorder. On the basis of clinical and radiological examination, probable diagnosis of MPS was made and

sample was sent for enzyme studies which showed deficient activity of I2S enzyme (5.2 nmol/4 hr/ml, normal – 167-475). Thus, confirmatory diagnosis of Hunter syndrome was made.

Decongestive treatment was started and cardiology opinion was taken for further management. Tympanometry of both ears were performed in view of decreased hearing which were suggestive of tympanic membrane perforation. Further, genetic analysis by peripheral blood culture revealed polymorphism with aneuploidy, and other abnormalities suggestive of Hunter syndrome such as rosette formation, Acrocentric Association, and Robertsonian translocation. Counseling of the parents was done and management options were explained including bone marrow transplant; however, HLA of the sibling could not be matched. Other supportive management such as physiotherapy to mobilize the joint and hearing aid was advised.

## DISCUSSION

MPS are hereditary progressive disease of degradation of GAGs caused by decreased or absent lysosomal enzyme activity leading to intercellular deposition of GAG fragments. Distended lysosomes get deposited in cells and

interfere with cellular functions giving characteristic radiological and clinical pictures. Overall incidence of MPS is 3.5-4.5/100,000 live births, of which most common subtype is type III followed by type I and type II. All MPS are autosomal recessive disorders except type II MPS (Hunter syndrome) which is X-linked recessive disorder caused by deficiency of enzyme I2S [1-3].

In 80% patients with Hunter syndrome, mutation has been identified. It occurs exclusively in males with an incidence of approximately 1 in 170,000 live male births [2-3]. It has wide clinical spectrum and common clinical presentations are coarse facies, short stature, dysostosis multiplex, joint stiffness, hepatosplenomegaly, and normal to moderate intelligence. Airway involvements, hearing impairment, carpal tunnel syndrome and valvular dysfunction are other features seen in Hunter syndrome. Sparing of cornea and absence of inguinal hernia differentiate them from Hurler syndrome. Two forms of Hunter syndrome have been described on the basis of the length of survival and presence or absence of central nervous system (CNS) involvement [3-4].

Type A is the severe form with an early onset between 18 months and 4 years of age and life expectancy of 10-15 years while type B is the milder form where clinical features appear in second decade of life with a life expectancy of 30-50 years [1-3]. Patients with type A Hunter syndrome have severe mental retardation with loss of skills and while those of milder form although may have mild mental retardation but their intelligence usually is normal. Death in both the forms usually occurs due to cardiac failure or obstructive airway diseases.

Cardiovascular manifestations include incompetence of the valves, mitral valve prolapse, ischemic heart disease, and cardiomegaly resulting in heart failure. Sensorineural deafness is a common feature seen in almost all the cases of Hunter's disease. Though corneal clouding is absent in patients with Hunter's disease, retinitis pigmentosa, papilledema, and optic atrophy has been noted in some cases. Our patient did not have any ophthalmic problem on fundoscopy but he had hearing problems [1-3].

Clinical diagnosis of MPS can be made on the basis of clinical presentation and skeletal survey [4]. Excess urinary heparan and dermatan sulfates are suggestive of MPS type I, type II, or type VII. However, confirmatory diagnosis can only be made by enzyme assay in

leukocytes, fibroblasts or dried blood spots, and plasma samples. Absent or low I2S activity in males is diagnostic of Hunter syndrome, if other sulfatase deficiency has been ruled out. In our patient also, plasma I2S enzyme activity was remarkably reduced confirming the diagnosis of Hunter syndrome [5-6].

Bone marrow transplantation (BMT) and umbilical cord blood transplantation are the potentially curative treatment for MPS. However, these are not routinely advocated in clinical practice due to high risk profile and lack of evidence for efficacy [7]. Secondly, problem of HLA matched donor is always there as happened with our patient. Enzyme replacement therapy (ERT) has emerged as a new treatment and recently the United States and European Unions have approved the use of idursulfatase (Elaprase), a recombinant human I2S, for the management of MPS type II given as weekly intravenous infusion over 3h at a dose of 0.5 mg/kg [7-9]. However, more studies are needed to confirm its long term efficacy and safety [10]. In recent years, substrate reduction therapy and gene therapy have been rapidly gaining greater recognition as potential therapeutic avenues as they may prevent the neurodegeneration not affected by ERT [7].

However, these definitive treatments are not readily available in most of the developing countries and supportive management is mainstay of therapy to improve the quality of life of these patients such as physiotherapy to mobilise the joints, nutritional management, prevention and treatment of infections, blood transfusion, and management of cardiac and respiratory complications. Prenatal diagnosis using amniocentesis and chorionic villus sampling should be offered in next pregnancy to detect the possibility of a fetus either carrying a copy of defective gene or being affected with the disorder. Genetic counselling can help parents with a family history of MPS to determine if they are carrying the mutated gene [2,3,5].

#### CONCLUSION:

Hunter syndrome (MPS type II) is a multisystem disorder which may present with wide spectrum of clinical features. With the advent of hematopoietic stem cell transplantation and enzyme replacement therapy, there exists a need for early diagnosis, better disease recognition, and management. Even if definitive treatment is not available, appropriate management through a multidisciplinary approach can improve the quality of life of these patients.

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