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**A CASE OF HURLER SCHEIE SYNDROME, ATTENUATED FORM OF MUCOPOLYSACCHARIDOSIS TYPE I**Manali Sinharay<sup>1</sup>, Mousumi Mukhopadhyay<sup>2</sup><sup>1</sup>Department of Biochemistry, Medical College and Hospital, Kolkata, West Bengal, India<sup>2</sup>Department of Biochemistry, Institute of Postgraduate Medical Education and Research and SSKM Hospital, Kolkata, West Bengal, India

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**ABSTRACT**

Mucopolysaccharidosis type I or MPS I is an autosomal recessive inborn error of metabolism due to deficiency of  $\alpha$ -L-iduronidase enzyme activity and is characterized by accumulation of incompletely degraded Glycosaminoglycans that generally lead to impairment of organ and body functions. In this report a three year old child with history of normal birth, delayed growth, noisy breathing specially during sleep and bulging abdomen noticed recently was examined and investigated thoroughly to reveal corneal clouding, coarse facial features, hepatosplenomegaly, multiple radiographic evidence of dysostosis multiplex, manifestations of mild valvular heart disease as per echocardiography, and abnormally increased excretion of Glycosaminoglycans in urine without any neurological abnormalities. The history, clinical examination and laboratory investigations confirmed the child to be suffering from attenuated form of Mucopolysaccharidosis type I (Hurler Scheie syndrome).

**Keywords:**  $\alpha$ -L-iduronidase, Glycosaminoglycans, Hurler Scheie syndrome.

**INTRODUCTION**

Mucopolysaccharidoses are autosomal recessive disorder of Glycosaminoglycans (GAGs) metabolism, caused by deficiency or absence of the lysosomal hydrolase activity. As a result, intralysosomal accumulation of GAGs occurs in various organs with significant excessive elimination of GAGs in urine. Inability to degrade these ubiquitous molecules results in progressive multisystem disorder with ocular, auditory, cardiac, respiratory, skeletal and sometimes neurological manifestations. Several types of Mucopolysaccharidoses are recognized depending on the type of lysosomal hydrolases that is deficient. Mucopolysaccharidosis type I or MPS I (Hurler's syndrome) arise due to deficiency of  $\alpha$ -L-iduronidase <sup>(1)</sup>. Historically, MPS I has been classified into 3 syndromes (Hurler, Hurler-Scheie and Scheie). The clinical spectrum of the disease ranges from severe

(Hurler syndrome, presenting in infancy and characterized by relentless cognitive decline) to attenuated forms (Hurler-Scheie and Scheie syndromes, presenting in childhood with slower progression and moderate to absent CNS involvement) <sup>(2)</sup>. The estimated incidence of MPS I is 1 per 100,000 live births, and 20% of the total MPS I population is represented by the attenuated type <sup>(3)</sup>. Hurler's syndrome is considered the prototype of the mucopolysaccharidoses. The term "gargoylism" has been applied to this syndrome because of gross disfiguration resembling the gargoyles of Gothic architecture. Although this syndrome was first observed by Thompson in 1900, Hurler gave a more complete description in 1919. The term mucopolysaccharidosis was first used in 1952 by Brante <sup>(4)</sup>.

## CASE HISTORY

A 3 year old male child was admitted with complains of bulging abdomen (figure 1), noisy breathing especially during sleep and short stature. No history of consanguinity or delayed milestones was obtained and neither of his two siblings was affected until symptoms started recently. Any incidence of umbilical or inguinal hernia at birth was not reported by his parents. There was no history suggestive of any bowel alterations, bleeding, jaundice, seizure, or chronic diseases like Tuberculosis. His bladder habit was normal.

Physical examination revealed coarse facial features, frontal bossing (figure 2), open fontanelles, depressed nasal bridge, nasal flaring, corneal clouding and short neck. On oral examination a low arched palate and peg shaped teeth seen. His fingers were short, stubby and a gibbus (figure 3) was found in lower thoracic spine. Anthropometric examination showed him to be severely stunted with wasting (height 64 cm, weight 11kg). His head circumference was normal of his age. His abdomen was soft and slightly distended. His liver was 4 cm below the right costal margin in the mid-clavicular line, with a firm, sharp margin and a smooth surface. His spleen was 2 cm below the left costal margin in the mid-clavicular line. Cardiovascular examination revealed no audible murmur but there was tachycardia and the child was mild hypertensive. No abnormal breath sounds heard on auscultation, but there were evidence of obstruction in upper airways as suggested by noisy breathing. No hearing impairment was detected and Neurological examination was within normal limits.

Suspecting MPS, various investigations were done. As per routine tests Hb was 11.2, TC WBC-11,400, DC (WBC) Lymphocytes-40%, rest was normal. Liver function test, Serum Calcium, Phosphorus, Thyroid profile were normal. Radiological investigations suggested–enlargement of the skull, a thick calvarium, a J-

shaped sella turcica (figure 4), Chest X ray showed the ribs to be widened with the classic "oar shape" and the heart was seen to be markedly enlarged in transverse diameter. There was no evidence of pulmonary infiltration in either lung field. On the lateral film the anterior surface of the vertebral bodies exhibited the typical "hook-shaped" deformity and a thoracolumbar kyphosis or the gibbus deformity was seen. X ray of hands showed short, thin metacarpals with proximal tapering resulting in a bullet shape (figure 5). An electrocardiogram demonstrated right ventricular hypertrophy. A subsequent echocardiogram confirmed this finding, as well as a developing aortic stenosis. No hydrocephalus was detected on CT scan of brain. Routine urine examination was normal.

The fresh urine sample was centrifuged and analyzed for inborn errors of metabolism as follows: dinitrophenylhydrazine test for alpha keto acids; cyanide nitroprusside test for homocystine and cystine; ferric chloride test for phenyl pyruvic acid; Millon's test for tyrosine; Molisch test for carbohydrates; and Benedict's test for reducing sugar. Urine sample was also tested for bilirubin and proteins to rule out liver or kidney dysfunction. Molisch test was positive. To confirm the presence of Mucopolysaccharides in urine of the patient, assay of Urinary GAGs (figure 6,7) of the child was done against a normal urine sample by Cetyltrimethyl ammonium bromide(CTAB)-which being a quaternary ammonium compound reacted with the negatively charged GAGs to produce heavy white precipitates-confirming the diagnosis of MPS<sup>(5)</sup>. Five ml of fresh urine was added to 1 ml of cetyltrimethyl ammonium bromide (cetavilon) solution (50 g/l in citrate buffer (1 M) of pH 6. The amount of precipitate depends on the concentration of mucopolysaccharides. Depending upon their concentration, samples are classified as mild, moderate, and severe or negative for Mucopolysaccharides. Esbach's test

yielded negative result which suggested that the precipitate was not due to urinary protein.

The particular subtype of MPS needed to be confirmed by enzyme assay which the patient was unable to afford, but the typical age of onset and progress of the clinical manifestations and radiological findings and investigations specially the urinary assay of GAGs clinches the diagnosis of attenuated MPS I (Hurler Scheie syndrome).

## DISCUSSION

MPS I is caused by defective IDUA ( $\alpha$ -L-Iduronidase) gene, located on chromosome 4 at 4p16.3 site. Fifty two different mutations in the gene, IDUA have been shown to cause lysosomal enzyme,  $\alpha$ -L-iduronidase deficiency leading to MPS I<sup>(6)</sup>. MPS I has traditionally been classified into three categories: 1) Hurler disease for severe deficiency with neurodegeneration, cardio respiratory failure and severe skeletal disability causing early death, 2) Scheie disease for later onset without neurological involvement and less severe somatic manifestations, 3) Hurler Scheie disease for patients intermediate between the two. MPS I often presents in infancy and early childhood with chronic rhinitis, clouding of corneas and hepatosplenomegaly<sup>(7)</sup>. As the disease progresses, nearly every organ system can be affected. Most patients with attenuated MPS I survive into adulthood, albeit with moderate to severe disability. However, cases of attenuated MPS I show wide variation with respect to age of presentation, symptoms and disease course<sup>(7,8)</sup>.

Children with MPS I may be normal at birth but may have inguinal or umbilical hernias. Growth begins to slow before the child's first year ending and often ends at age three for severe variety. Many children may develop a short trunk leading to stature of less than four feet. Among the somatic manifestations, the child commonly presents with hepatosplenomegaly. A constellation of bony changes occurs such as severe and progressive joint deformities, dysostosis multiplex, kyphosis and joint

contractures constellation, secondary to GAG deposition and fibrosis. Dysostosis multiplex radiographically consists of multiple abnormalities as enlargement of skull, a thick calvarium, and a J shaped sella turcica; hook shaped vertebrae and spatulate ribs, hypoplastic epiphyses and thickened diaphyses. The metacarpals are short and thin with proximal tapering resulting in bullet shape. The gibbus deformity or thoracolumbar kyphosis serves often as a key diagnostic clue. The severity and onset of these manifestations depend on the subtype of MPS I<sup>(9)</sup>. Distinct facial features including bulging forehead, depressed nasal bridge and flat face become evident. The early ocular features that present in many children with MPS I include retinal degeneration, optic atrophy, optic disc swelling, ocular hypertension or glaucoma and corneal clouding<sup>(10)</sup>.

Cardiac abnormalities are common in children with MPS I which worsen with age. Angina type symptoms secondary to arteriosclerosis and ischaemia may occur in the child. They can present with valvular dysfunctions, hypertension, arteriosclerosis and ischaemia, hypertrophy of cardiac chambers, congestive heart failure, sudden cardiovascular collapse and death<sup>(3)</sup>. Obstructive airways diseases resulting in frequent respiratory tract infections and noisy breathing are commonly seen in patients with MPS I causing sleep apnea, cor pulmonale and severe respiratory compromise. Deafness is reported in some cases of MPS I which has combined neurosensory and conductive origin. Hurler Scheie disease is characterized by severe somatic disease without neurological deterioration<sup>(7)</sup>.

Currently there are two definitive treatments for MPS I<sup>(7)</sup>. Stem cell transplantation is the standard treatment for patients with severe MPS I (Hurler disease). The second currently available therapy, enzyme infusion therapy with laronidase (human recombinant  $\alpha$ -L-iduronidase) is effective for attenuated MPS I (Hurler Scheie and Scheie disease) as the enzyme cannot penetrate the CNS

but successfully addresses the hepatosplenomegaly, cardiac and respiratory disease. In the present instance where definitive treatment cannot be done, monitoring of patients with MPS I (Hurler Schei type) must include regular assessments, supportive care and treatment of a variety of systemic complications which is being done for this child. It has been recommended to undergo cardiac evaluation every 1 or 2 years after an initial diagnosis<sup>(11)</sup>. With the advent of hematopoietic stem cell transplantation and, more recently, enzyme replacement therapy, there exists a need for early diagnosis, better disease recognition and management<sup>(12)</sup>. Early detection of the disease and appropriate management through a multidisciplinary approach is recommended to improve the quality of life.

## CONCLUSION

The rarity of such a case of Hurler-Scheie syndrome has lured us to report it. Although most patients cannot afford definitive treatment, but early diagnosis, appropriate treatment and monitoring of the systemic complications will positively increase the life expectancy of these patients.

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**PHOTOGRAPHS**



**Figure 1-Bulging abdomen and short stature**



**Figure 3: Gibbus**



**Figure 2: Coarse facial features with frontal bossing**



**Figure 4: J-shaped sella turcica with open fontanelle**



**Figure 5: Proximal tapering of metacarpals (bullet shaped metacarpals)**



**Figure 7: White precipitate in urine (right) due to GAG (following addition of reagent) compared with the original sample (left)**



**Figure 6: Urinary glycosaminoglycan demonstration**