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Case Report

Rare cases of classical Hurler-Scheie syndrome

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ABSTRACT

Mucopolysaccharidosis (MPS) are the rare inherited metabolic disorders typified by deficiency of lysosomal enzymes necessary for glycosaminoglycan (GAG) metabolism. The inadequate metabolism of GAGs results in its accumulation causing multi-organ dysfunction. Of the different MPSs, MPS-I is caused by deficiency of lysosomal enzyme α-L-iduronidase, and inherited in an autosomal recessive manner. The severity of the disease presentation varies widely and classically three phenotypes, Hurler syndrome (MPS IH), Hurler-Scheie syndrome (MPS-IH/S) and Scheie syndrome (MPS-IS) are described. This case report depicts MPS-IH/S in two consecutive male siblings with typical clinical and radiological features that helped in establishing the diagnosis.

Keywords: Mucopolysaccharidosis, Glycosaminoglycan, Autosomal recessive, Syndrome

INTRODUCTION

Mucopolysaccharidosis (MPS) are a group of inherited metabolic disorders caused by inborn errors of glycosaminoglycan (GAG) metabolism. MPS constitutes part of lysosomal storage disease family, characterised by deficiency of lysosomal enzymes required for GAG degradation resulting in their widespread accumulation and increased excretion in urine.[1] There are seven types of MPS (I, II, III, IV, VI, VII and IX). Amongst these types only MPS-II (Hunter syndrome) follows X-linked recessive inheritance pattern, while all others are inherited in an autosomal recessive pattern. A wide range of variability is observed in their phenotype.

MPS-I has an incidence rate of 1 in 100,000 to 1 in 500,000 births. It occurs due to mutation in IDUA gene mapped to short arm of chromosome 4 (4p16.3) which encodes *α*-L-iduronidase (IDUA; EC 3.2.1.76) enzyme.

Depending on the severity of the condition it has been traditionally sub classified into three phenotypes: Hurler syndrome (MPS-IH), Hurler-Scheie syndrome (MPS-IH/S) and Scheie syndrome (MPS-IS). MPS-IH is the most severe type while MPS-IS is at the mild end of the clinical spectrum. However due to significant overlap between their clinical presentation and minimal biochemical differences, a panel of international experts (2008) classified MPS-I into attenuated and severe type. MPS-I has been reported in different animals and this has helped not only in studying human MPS-I, but also to assess the effects of enzyme replacement therapy for its treatment.[2-4]

MPS is characterised by the spectrum of clinical manifestations including skeletal defects, respiratory and gastrointestinal complications, intellectual and ocular impairment and cardiovascular dysfunction.[5]

The purpose of this article is to highlight the distinctive presentation of rare case of MPS-IH/S in two consecutive male siblings.

CASE REPORT

Two male siblings, 10 (case A) and 12 (case B) year old (Figure 1A, B) with a known diagnosis of mucopolysaccharidosis were referred to the hospital for dental evaluation. Past history revealed diminished growth, limited body movements, and frequent gastrointestinal and respiratory tract infections since preschool age. Family history was non-contributory. General physical examination revealed stiff gait, short stature, facial asymmetry (case B>A), mildly coarse facies, depressed nasal bridge, wide nostrils, hypertelorism, corneal clouding, macrocephaly, protruded abdomen, umbilical hernia and heptoslenomegaly in both the cases. Cognitive function was normal. Examination of joints and extremities showed joint stiffness and stubby claw like hands (bent, bowed, curved fingers) with skin inelasticity. On audiometry, mild-moderate conductive hearing loss was evident in both the cases.

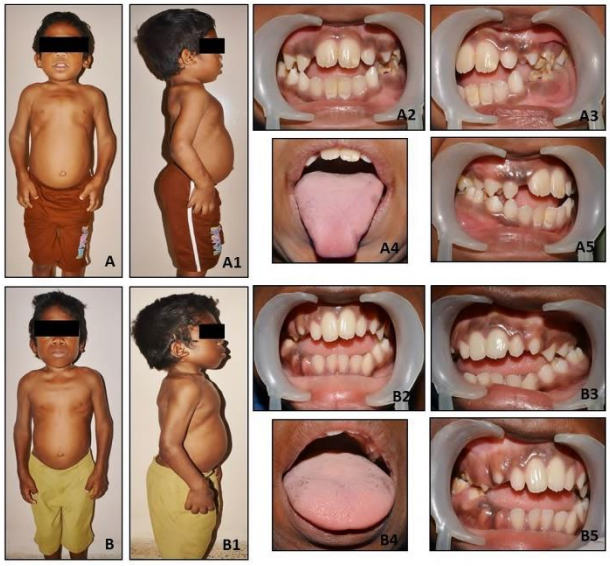

Figure 1: Patient A and B showing coarse facial features, depressed nasal bridge, abnormal chest, protruded abdomen and claw like hand (A, A1, B, B1); Intraoral photograph showing anterior open bite (A2, B2) in both patients and macroglossia (B4) in patient B.

Intraoral examination revealed incompetent lips, high arched palate and anterior open bite in both the cases, while decayed #55, #65, #75, #85 in case A and macroglossia was evident in case B (Figure 1). Oral hygiene status was good and periodontal status was not compromised. Roentgenological investigations included dental tomography, hand-wrist radiograph, PA and lateral skull and MRI. The panoramic dental tomography showed hypoplastic and flattened mandibular condyles and delayed tooth eruption (Figure 2a, 3a). PA skull revealed mild thickening of skull vault and bilateral protuberance over temporal region in case B (Figure 2b, 3b). Lateral cephalogram showed deepened J-shaped sella turcica (Figure 2c, 3c). Hand-wrist radiograph was evident for bullet shaped metacarpals (proximal pointing) (Figure 2e, 3e). Other radiographic abnormalities included abnormal shaped ribs (oar shape) and vertebrae, platyspondyly, flared iliac wings, inferior tapering of ilea and long and narrow femoral neck (Figure 2d, f, 3d, f).

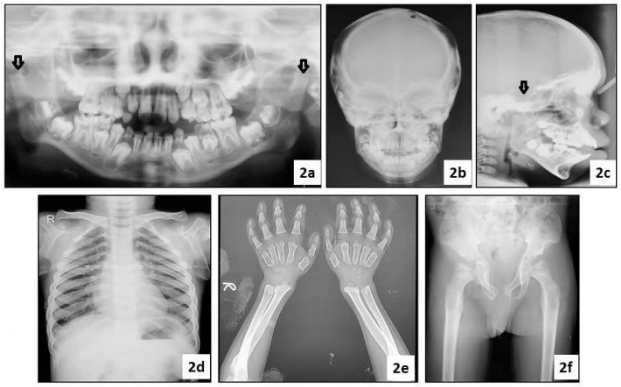

Figure 2: OPG shows hypoplastic mandibular condyles (arrow) and delayed tooth eruption (2a), PA skull did not show thickening of the skull vault (2b), lateral ceph shows J-shaped sella turcica (arrow) (2c), chest radiograph shows abnormal shaped ribs (oar shape) (2d), hand-wrist radiograph shows bullet shaped metacarpals (2e), and pelvic radiograph shows flared iliac wings and long and narrow femoral neck (2f).

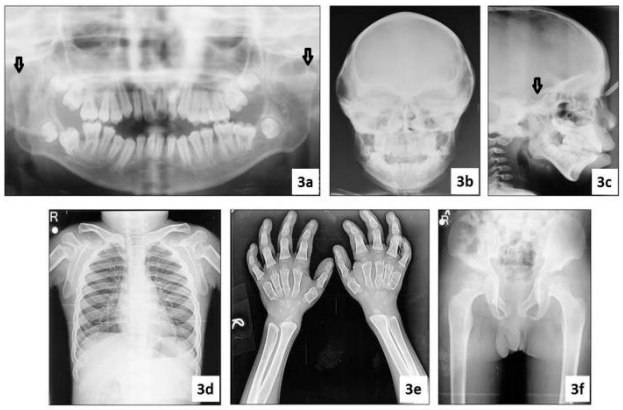

Figure 3: OPG shows hypoplastic mandibular condyles (arrow) (3a), PA skull shows mild thickening of the skull vault and bilateral protuberance over temporal region (3b), lateral ceph shows J-shaped sella turcica (arrow) (3c), chest radiograph shows abnormal shaped ribs (3d), hand-wrist radiograph shows bullet shaped metacarpals (3e) and pelvic radiograph shows flared iliac wings, inferior tapering of ilea and long and narrow femoral neck (3f).

Haematological findings, thyroid, renal and liver function tests were with in normal limits. Urine analysis was positive for the presence of glycosaminoglycan (GAG). Dental management included conventional periodontal treatment, restoration of decayed teeth, and extraction of

over retained deciduous dentition. Importance of regular medical and dental visits was emphasised to the parents.

DISCUSSION

The interstitial type of extracellular matrix (ECM) makes up the bulk of ECM and is mainly composed of collagen and proteoglycans with a protein core covalently attached to GAGs. These proteoglycans are cleaved by the action of proteolytic enzymes to GAGs, and depending on their molecular structure it undergoes intracellular digestion in lysosomes via one of the four degrading pathways. Their degradation occurs in series of distinct stages catalysed by different enzymes such as glycosidase, sulfatase, transferase; and their deficiency results in different types of MPS. The chronic and progressive nature of MPS is due to uninterrupted presentation of GAGs for degradation to cells with defective lysosome function. This leads to excess storage of undegraded GAGs in lysosomes causing them to swell and thereby affecting the functioning of other cell organelles. The accumulation of partially processed or unprocessed GAGs in the lysosomes gradually leads to multiple organ dysfunctions.[2]

Clinically, MPS-I is featured by coarse facial appearance, clouding of cornea, intellectual impairment, dysostosis complex and heptoslenomegaly. The affected child is apparently normal at birth but gradually develops characteristic appearance over a period of first few years. Cardiac, respiratory, ocular and neural complications are commonly seen, though quite variable in the extent of their involvement. The earliest clinical manifestation of MPS is generally the otolaryngological problems such as recurrent otitis media, hearing loss (conductive>sensorineural), recurrent upper respiratory tract infections, obstructive sleep apnoea syndrome and adenotonsillar hypertrophy.[6,7] Ocular complications such as visual acuity loss, glaucoma, retinopathy, swelling and atrophy of optic nerve and ocular hypertension may be present.[8] The characteristic corneal opacification is due to irregular organisation of corneal collagen and storage of GAGs in corneal cells causing reflection and refraction of light.[2] Similarly, cardiomyopathy is secondary to GAG accumulation in myointima of coronary arteries, myocardium and spongiosa of cardiac valves, causing change in the shape of cells of cardiac valves from fusiform to round. This results in thickened valve leaflets and cordae tendinae impeding normal cardiac function leading to valvular stenosis with or without regurgitation.[2,9]

Typical skeletal deformities reported in MPS-I include facial dysmorphia, short stature, thoracolumbar gibbus, hip dysplasia, joint contractures, genu valgum and ribs, vertebrae and long bone deformities. Roentgenological examination usually shows ‘J’ shaped sella turcica, thickened cranial vault, hypoplastic epiphysis, distally curved and shortened diaphysis, notched proximal part of humerus, long and narrow femoral neck, round iliac wings often with inferior tapering, paddle or oar shaped ribs and flattened vertebrae.[10] Dental abnormalities may be present in MPS-I including caries, delayed eruption, high arched palate and open bite are sometimes observed, as depicted in this report.

To conclude, diagnosis of MPS-I in a proband is usually established on the basis of clinical, radiological and laboratory findings supplemented with or without molecular testing.[11,12] Currently, MPS therapeutics includes enzyme replacement therapy and hematopoietic stem cell transplantation. The time of initiating the treatment determines the course of this metabolic disorder.[3,13]

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