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A Rare Case of Mucopolysaccharidosis Type - VI in an Indian Teenage Male

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Abstract

Mucopolysaccharidosis (MPS) is a group of inherited metabolic storage disorders caused by the absence or malfunction of lysosomal enzymes resulting in progressive accumulation of glycosaminoglycans (GAGs) in multiple tissues giving rise to a variety of clinical manifestations including skeletal, facial, ocular, cardiac, respiratory, neurological, lymphoreticular, dental abnormalities. Characteristic clinical findings, radiological and biochemical assay, specific enzymatic testing and finally genetic studies confirms the diagnosis of specific subtypes of MPS. Enzyme replacement therapy (ERT) remains the only key therapeutic option with different prognosis and outcome. We are here reporting a rare case of MPS type - VI with classical multisystem involvements from sub-Himalayan rural India.

Keywords: Mucopolysaccharidosis; Storage Disorders; Glycosaminoglycans; Lysosomal Enzymes; Genetic Study; Enzyme Replacement Therapy

Introduction

Mucopolysaccharidosis (MPS) is a set of diseases resulting from genetic mutation causing lysosomal enzymatic defect which in turn leads to gradual accumulation of Glycosaminoglycans (GAGs) in different tissues producing a series of diverse symptoms and signs notably skeletal deformities (dysostosis multiplex) like short stature, short neck, broad clavicle, joint abnormalities like joint stiffness and hip deformities, coarse facial changes like frontal bossing, depressed nasal bridge, large tongue, and ocular abnormalities predominantly corneal opacity, recurrent respiratory infections, cardiovascular abnormalities particularly mitral valve diseases (thickening / regurgitation), neurological manifestations including intellectual abnormality, seizure disorder, ventriculomegaly, cognitive and behavioral impairment, dental deformities like malocclusion and poor oral hygiene [1,2]. Diagnosis of MPS is fundamentally based on clinical features, enzymatic testing and genetic testing along with biochemical, laboratory and radiological investigations as a supporting tool.

MPS has seven subtypes classified based on deficiency of lysosomal enzyme variations. MPS - I (Hurler syndrome) is due to abnormalities of alpha- iduronidase enzyme resulting in excretion of dermatan sulphate and heparan sulphate in urine and the most predominant symptoms and signs include corneal opacity, upper airway obstruction and cardiomyopathy. In MPS - II (Hunter syndrome) there is lack of iduronate-2 sulphate sulphatase enzyme and important clinical findings includes mental retardation, loss of hearing, hepatosplenomegaly, and it is having male predominance and X-linked association. In type - III MPS (Sanfilippo syndrome) is of four subtypes (A, B, C, D) having seizure and mental alterations. MPS - IV (Morquio syndrome) there are predominant joint deformities (laxity / stiffness) due to deficiency of galactosamine - 6 - sulfatase and Beta - galactosidase enzymes. MPS - VII (Sly syndrome) is basically for Beta - glucuronidase enzyme deficiency resulting in mental retardation and cognitive behavioral changes in MPS - IX, the rarest type, is due to hyaluronidase enzyme deficiency. MPS- VI (Maroteux – Lamy syndrome), a rare autosomal recessive disorder, results from lysosomal enzyme malfunction because of genetic mutation in aryl sulphatase B (ARSB) leading to inappropriate and incomplete catabolism of CAGs (Chondroitin sulphate and Dermatan sulphate) [3]. The common clinical manifestations in this subtype includes corneal opacity, skeletal dysplasia (dysostosis multiplex), pulmonary malfunctions, organomegaly notably hepatosplenomegaly, otitis, hearing loss, sleep apnea, facial dysmorphism, hydrocephalus, Mongolian spots, hernia etc but with preserved mental- cognitive- behavioral function and optimal intellectual functions and uneventful growth and developmental milestones in most of the cases.

Clinical manifestations of MPS - VI are typically found in 2nd to 3rd decades of life due to slow progression unlike other subtypes. Overall incidence of MPS - VI reported worldwide is 1 per 320000 live births with highest incidence found in eastern Saudi Arabia and North- East Brazil whereas lowest is in Poland and South Korea. The incidence is higher in patients born of consanguinity [4].

Case Description

A 14 year Muslim boy from Purnia, Bihar, born from a nonconsanguineous marriage, having one healthy sibling, with no significant birth and family history, with normal developmental milestones and school performance developed insidious onset, gradually progressive bowing of his both legs and bending of both hands leading to difficulty in walking and facial dysmorphism at the age of 6 years and failure to gain height in next 8 years and whitish discoloration of both eyes for last 4 years, which progressed to more advanced stage .There was no history of headache, seizure, vomiting, visual and hearing disturbances, palpitation, shortness of breath, recurrent cough and cold, skin rash or pigmentation, bony pain or fracture, weight loss or unusual weight gain, mood swings, etc. On clinical examination there was facial dysmorphism with frontal bossing, depressed nasal bridge, hypertelorism, macrocephaly, coarse thick hair, low set ears, widened thick lips, bilateral corneal clouding, macroglossia, dysostosis multiplex notably genu valgum deformities, broad hands and claw like fingers with flexion deformities of bilateral elbow and wrist , kyphosis , short stature (Upper and lower segment ratio 0.9) hepatosplenomegaly, small umbilical hernia, soft S1, with no respiratory, neurological, lymphoreticular and thyroid abnormalities

and normal secondary sexual characters and sexual maturity rating by Tanner staging G4P2 [Fig: 1]. His height was 105.5 cm (< 3rd percentile), height standard deviation score was -6.4, BMI - 19.3 Kg/m2, Chronological age = Bone age = 14 years, Weight for age = Height for age = 5.5 year. His laboratory investigations showed mild anemia, low serum Vitamin-D3, borderline low IGF-I [Fig: 2]. Radiological imaging showed features of Rickets, genu valgum deformity, frontal bossing, J- shaped sella, ventriculomegaly [Fig: 3]. 2-D echocardiography revealed thickened both mitral leaflets, aortic and tricuspid valves and mild mitral stenosis. His urinary was positive for glycoseaminoglycans. Genetic study (next generation sequencing) revealed homozygous missense mutation in ARSB gene (c.1350G>C;p.Trp450Cys) [Fig: 4] and thus confirmed the diagnosis of Mucopolysaccharidosis Type VI (Maroteux - Lamy syndrome). Supportive treatment was initiated including physiotherapeutic rehabilitation, vitamin D3 supplementation, with Ophthalmology and Orthopedic consultation. Enzyme replacement therapy (ERT) with Galsulphase (Naglazyme) is planned for next level of definitive treatment.

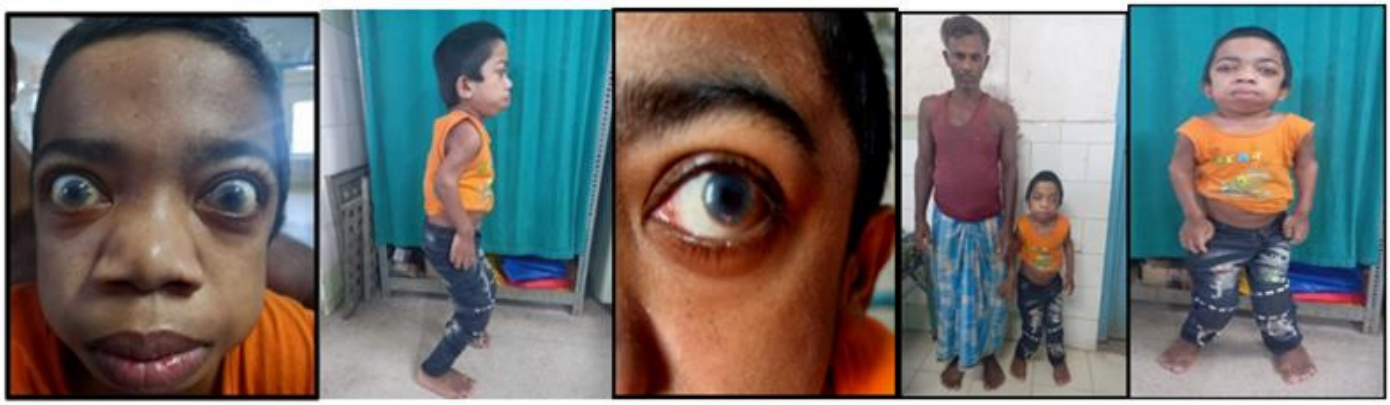

Figure 1: Clinical images of the patient

Lab results			
Hb	10.1 g/dL	Sr TSH	3.14 mIU/L
TLC	8220 cells/uL	fT4	2.6 ng/dL
Platelet	411000 cells/uL	Sr Vit D3	21.8 ng/mL
LFT	WNL	IGF-1	154 ng/mL (N=177-507 ng/mL)
Urea	25 mg/dL		
Creatinine	0.3 mg/dL	LH	5.04mIU/mL
Na	141 mmol/L	FSH	3.14 mIU/mL
K	4.8 mmol/L	Prolactin	7.45 ng/mL
Calcium	9.0 mg/dL	Testosterone	246.4 ng/mL
Phosphate	4.0 mg/dL	Cortisol	6.59 ug/dL
Uric acid	4.0 mg/dL	ACTH	10.30 pg/mL

Figure 2: Laboratory investigations

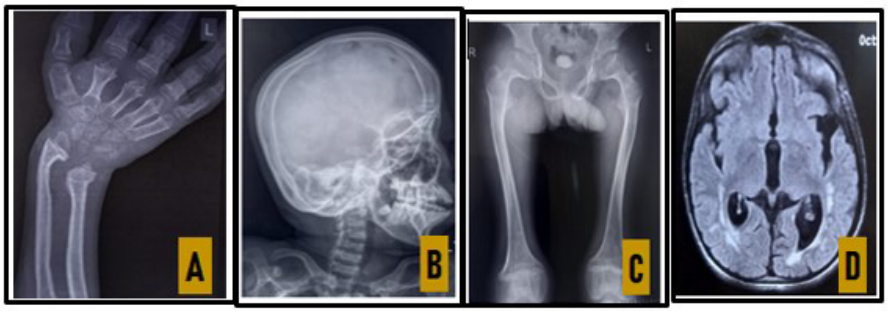

Figure 3: Radiology images

- A: X-ray B/L wrist joint: Bone Age = 12-13 yr, suggesting Rickets
- B: X-ray Skull (Lat view): Frontal bossing & J shaped sella
- C: X-ray of pelvis: Hip dysplasia and femoral epiphyseal widening
- D: MRI: Dilated ventricles, Hyperintensities in periventricular, fronto-parietal & temporal white matter.

Clinical History

Clinical indication: Short stature, corneal clouding, rickets
Investigations: Urinary glycosaminoglycan positive; Borderline low insulin like growth factor; ACTH borderline low
Clinical suspicion: Mucopolysaccharidosis (Hurler variety)

Test Results and Interpretation

HOMOZYGOUS PATHOGENIC VARIANT CONSISTENT WITH PHENOTYPE DETECTED. MOLECULAR DIAGNOSIS IS CONFIRMED.

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
ARSB (NM_000046.5)	Exon 8	c.1350G>C p.Trp450Cys [110x/110x]	Homozygous	Pathogenic	Mucopolysaccharidosis type VI (Maroteaux-Lamy)	Autosomal recessive

Figure 4: Genetic study

Discussion

MPS are extremely rare, genetically triggered metabolic disorders with diverse clinical features, biochemical alterations from enzymatic malfunctions [Fig: 5].5 Type VI MPS is an autosomal recessive disorder with distinct clinical manifestations involving skeletal, ocular, neurological, respiratory, oro-dental, cardio- vascular system but preserved normal mentation and intelligence with typical delayed clinical manifestations usually in 2nd or early 3rd decade. Type- VI also involves the most extensive multisystem clinical cascade with osteoarticular manifestations like short stature, dysostosis multiplex, joint stiffness or contracture, kyphoscoliosis, genu valgum deformity, hip dysplasia, ocular abnormalities like corneal clouding, refractive error problems, optic atrophy, optic disc swelling, retinopathy, glaucoma, neurological manifestations notably ventriculomegaly, hydrocephalus, myelopathy, carpal tunnel syndrome, spinal cord or nerve root compression, seizures, white matter and perivascular space related abnormalities, and cardiac problems like heart valve insufficiency or stenosis due to cardiac valve thickening, pulmonary hypertension, cardiomyopathy,

cardiac conduction system disorders, heart failure, fibroelastosis and respiratory abnormalities most commonly recurrent airway infections, sleep disorders, upper and lower airway obstruction are more predominant. Again, orodental findings like hypoplastic mandible, malposition of unerupted teeth, dentigerous cysts, macroglossia, gingival hyperplasia, high arched palate remains part and parcel of this disease spectrum. Other significant clinical manifestations include hearing loss, otitis media, chronic rhinosinusitis, adenoid hypertrophy, coarse facial features, hepatosplenomegaly, umbilical or inguinal hernia, delayed puberty, hirsutism etc. In MPS spectrum, type VI is extremely rare next only to type IX variety. Mortality in type - VI MPS is mainly due to respiratory or cardiac complications like fatal respiratory infections and or cardiac valvular abnormalities leading to respiratory or cardiac failure or fatal arrhythmias. The distribution of variant types in the ARSB gene are referred to in Figure 6. The incidence also varies among different populations in different geographical areas. Multisystem clinical involvement like skeletal abnormalities (dysostosis multiplex), corneal clouding and cardiac valve thickening remain the most common clinical features. Interesting fact is that in MPS type - VI neurological manifestations like mental retardation, intellectual disability and seizures are absent.

MPS Type	Nomenclature		Cognition	Incidence	Therapy
MPS I	Hurler: IH, severe	AR	Impaired	1: 100,000	SCT, ERT
	IH/S: less severe		Normal		ERT
	IS: least severe		Normal		ERT
MPS II	Hunter: IIA: severe	XR	Impaired	1:140,000 – 1:160,000	ERT
	Hunter IIB, less severe		Normal		ERT
MPS III	Sanfilippo A, IIIA	AR	Impaired	1:70,000 – 1:90,000 Most Common	ERT
	Sanfilippo B, IIIB		Impaired		Symptomatic
	Sanfilippo C, IIIC		Impaired		ERT
	Sanfilippo D, IIID		Impaired		Symptomatic
MPS IV	Morquio A, IVA	AR	Normal	1:200,000	ERT
	Morquio B, IVB		Normal		Symptomatic
MPS VI	Maroteaux – Lamy. VI	AR	Normal	1:240,000 – 300,000	ERT, SCT
MPS VII	Sly, VII	AR	Impaired	<1:250,000	SCT
MPS IX	Hyaluronidase def, IX	AR	??	Extremely rare	Symptomatic

Figure 5

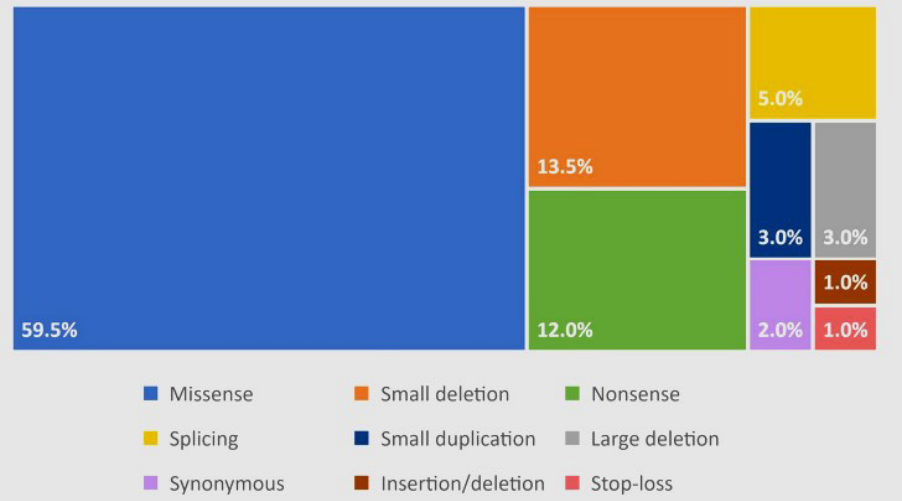

Figure 6: Distribution of Variant Types in the ARSB Gene.

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