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Mucopolysaccharidosis Type 4 (Morquio Syndrome): A Case Report from Kashmir Valley

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Abstract

Mucopolysaccharidosis type IVA (MPS IVA), also known as Morquio syndrome, is a rare lysosomal storage disorder caused by a deficiency in the enzyme N-acetylgalactosamine-6-sulfatase (GALNS). It is an autosomal recessive condition characterized by progressive skeletal abnormalities and other systemic complications. This case report discusses a 3-year and 8-month-old boy from the Kashmir Valley diagnosed with Mucopolysaccharidosis type IVA (Morquio syndrome), a rare lysosomal storage disorder due to a deficiency in the enzyme N-acetylgalactosamine-6-sulfatase (GALNS). The patient, presenting with short stature and skeletal deformities, was confirmed to have a homozygous mutation in the GALNS gene. Radiographic findings were consistent with MPS IVA, and the patient was planned for enzyme replacement therapy with Elosulfase Alfa. This case underscores the importance of early diagnosis and genetic testing in managing Morquio syndrome, highlighting the potential benefits of targeted enzyme replacement therapy in improving patient outcomes.

Keywords: Mucopolysaccharidosis Iva; Morquio Syndrome; Enzyme Replacement Therapy; Genetic Mutation

Introduction

Mucopolysaccharidosis type IVA (MPS IVA), also known as Morquio syndrome, is an exceptionally rare lysosomal storage disorder, that is caused by deficiency in the enzyme N-acetylgalactosamine-6-sulfatase (GALNS) due to an autosomal recessive mutation in the GALNS gene [1]. Morquio A is the third most common MPS in India, the United States, and most of Europe; and the second most common MPS behind MPS II in Southern and Eastern Europe [2]. In 1929, Luis Morquio first reported 4 Swedish patients with MPS IV (now classified as MPS IVA) [3]. In the same year, Brailsford also reported a patient with MPS IV [4]. Regrettably, Morquio syndrome is characterised by progressive deterioration, exacerbating as affected children advance through their developmental stages. Herein, we present an MPS IV case presenting as short stature and bony deformities.

Case Presentation

A 3-year-old, 8-month-old boy, 2nd in birth order, product of non-consanguineous marriage, presented at the Endocrinology clinic with parental concern of short stature and skeletal deformities. There's no family history of a similar condition. He has a history of obstructed inguinal hernia operated last year. On Physical examination Pulse 70/min, Blood pressure 100/64 mmHg, SpO2 97%. Disproportionate short stature (height SDS -3.2), pectus carinatum, hypertelorism and bowing of the lower extremities at the knee joint. The patient was then assessed and found to be with normal intelligence, ophthalmology and hearing assessment. Radiographic findings (X-rays) (Figure 1) were genu valgum, flared iliac bones with a flattened acetabulum, bullet-shaped phalanges, short metacarpals with proximal pointing, and flattened vertebral bodies (platyspondyly) with anterior beaking and delayed bone age. Genetic study (homozygous mutation in GALNS gene located on Exon 8) confirmed mucopolysaccharidosis IV/Morquio syndrome. Approved drug for Morquio syndrome is recombinant human GALNS enzyme replacement therapy (Elosulfase Alfa) [5], 2 mg/kg/week, was planned for treatment (Table 1,2).

Discussion

Mucopolysaccharidosis type IVA (MPSIVA; Morquio A disease) (OMIM #253000) is an autosomal recessive Lysosomal Storage Disorder (LSD) caused by a deficiency of N-acetylgalactosamine-

6-sulfate sulfatase (GALNS, EC 3.1.6.4). The absence of this enzyme leads to the accumulation of glycosaminoglycans (GAGs) Keratan Sulfate (KS) and Chondroitin-6-Sulfate (C6S) [6-8]. In MPSIVA patients, the accumulation mainly occurs in chondrocytes and the extracellular matrix of cartilage. This alters cartilage and bone development, leading to abnormal chondrogenesis and endochondral ossification [9]. Initial symptoms, including skeletal dysplasia, can be detected at a mean age of 2.1 years in most patients [10]. Other non-skeletal manifestations include respiratory complications and valvular heart disease [11]. Clinical pathology varies significantly from patient to patient depending on the mutation in the GALNS gene. It ranges from a severe and rapidly progressive early-onset form to a slowly progressive later-onset form.

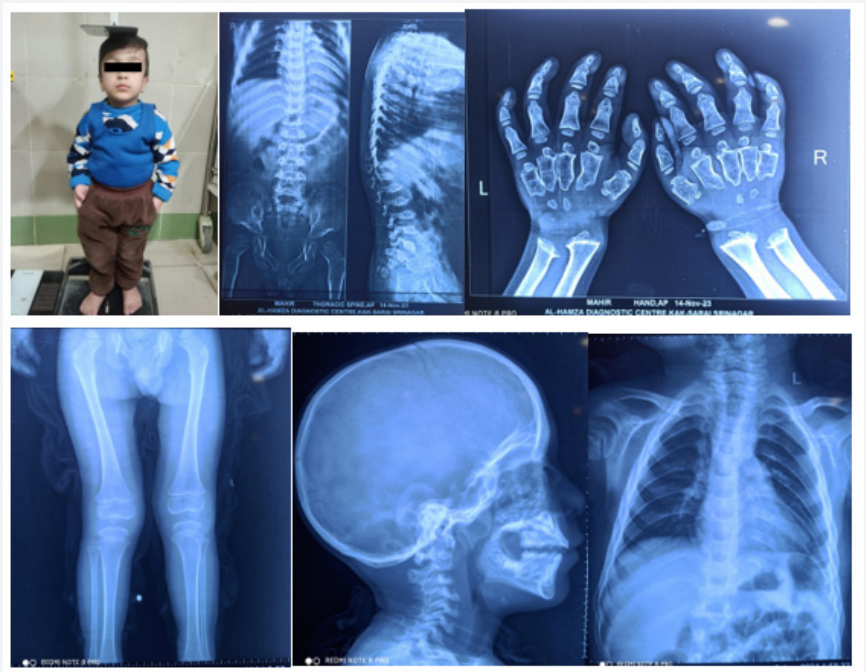

Figure 1: Bone survey of the patient.

Table 1: Baseline Investigations.

Baseline Investigations	
Hemoglobin	12.2 g/dl
Blood urea	28 mg/dl
Creatinine	0.4 mg/dl
ALT	20 U/L
AST	46 U/L
Total Protein	7.6 g/dL
Albumin	4.6 g/dL
Alkaline phosphatase	204 U/L
Calcium	8.4 mg/dl
Phosphate	4.1 md/dl
Vitamin D	46 ng/ml
Blood pH	7.36
Bicarbonate	24.2 mmol/L
Lactate	2.0 mmol/L
USG Abdomen and Pelvis	Unremarkable

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Table 2: Genetic study of the patient.

Gene # (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classifications
GALNS (-) (ENST00000268695.10)	Exon 8	c.871G>A (p. Ala291Thr)	Homozygous	Mucopolysaccharidosis IVA (OMIM#253000)	Autosomal recessive	Pathogenic (PS3, PM1, PM2, PP3, PP5)

More than 30 genetic alterations are associated with attenuated phenotypes, while over 100 mutations result in severe alterations. The most frequent and severe mutation is c.1156C>T, leading to p. Arg386Cys in the GALNS protein [12,13]. In the presented case, a 3-year and 8-month-old boy from a non-consanguineous marriage exhibited short stature and bony deformities, which are classic presentations of Morquio syndrome. Despite the absence of a family history of similar conditions, the patient had a history of obstructed inguinal hernia operated on last year. Physical examination revealed disproportionate short stature (height SDS -3.2), pectus carinatum, hypertelorism, and bowing of the lower extremities at the knee joint. Radiographic findings support the diagnosis with features such as genu valgum, flared iliac bones with a flattened acetabulum, bullet-shaped phalanges, short metacarpals with proximal pointing, and flattened vertebral bodies (platyspondyly) with anterior beaking and delayed bone age. Genetic study confirmed a homozygous mutation in the GALNS gene located on Exon 8 (c.871G>A, p. Ala291Thr), confirming mucopolysaccharidosis IV/Morquio syndrome.

In MPSIVA patients, death generally occurs among the second and third decade of life, although less severe forms present longer life expectancy [14]. Treatment is challenging due to the early onset of bone pathology and the difficulty of treating isolated target tissues such as avascular cartilage [15-17]. The control of the disease is symptomatic, aimed at improving quality of life. The first approved treatment is enzyme replacement therapy (ERT) with a modified recombinant human GALNS (VIMIZIM) [5]. For the presented case, Elosulfase Alfa, a recombinant human GALNS enzyme replacement therapy, was planned at a dosage of 2 mg/kg/week. The variability in the clinical course of the disease underscores the importance of early diagnosis and tailored therapeutic approaches to manage the disease effectively and improve patient outcomes.

Conclusion

This case highlights the critical aspects of diagnosing and managing MPSIVA, emphasizing the importance of early detection and genetic testing in providing targeted treatment and improving patient outcomes. Ongoing research and advancements in therapies are essential for better management and potentially extending the life expectancy of individuals with Morquio syndrome.

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