

Case report

An unusual case of short stature – Morquio’s syndrome

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Abstract:

Mucopolysaccharidosis (MPS) are rare genetic conditions in the group of lysosomal storage disorders, characterised by constellation of symptoms and signs due to accumulation of lysosomes by undegraded glycosaminoglycans (GAGs) resulting in cellular and organ dysfunction. Morquio’s syndrome or MPS type IV is characterised by skeletal manifestation, short stature and normal intellectual. There is paucity of clinical reports on mucopolysaccharidosis across the world and there are very few case reports of Morquio’s syndrome in Indian literature and hence this case is reported for its varied presentation and its rarity. Early clinical suspicion by a comprehensive examination of the patient for starting enzyme replacement therapy (ERT) before the onset of irreversible organ damage and a multidisciplinary approach of the patient are the mainstay of treatment for this progressive condition.

Keywords: Mucopolysaccharidosis, Morquio’s syndrome, short stature

Introduction:

Mucopolysaccharidosis (MPS) are lysosomal storage disorders characterized by accumulation of glycosaminoglycans (GAGs) in various tissues, due to deficiency of one of the lysosomal hydrolases which are normally involved in the stepwise degradation of glycosaminoglycans. This results in accumulation of partially degraded products inside the lysosomes resulting in multiple organ involvement predominantly skeletal tissues and most of the affected individuals suffer from mental retardation. The clinical manifestations and severity of the disease in the affected individual depends on the tissue or organ predilection for the accumulated undegraded GAGs substrates. These group of hereditary disorders are relatively rare with a frequency ranging from 1:20000 to 1:2,50,000 live

births. Our patient presented to us with constellation of symptoms consisting of short stature, cardiovascular symptoms, inguinal hernia and a diagnosis of Morquio’s syndrome was made based on clinical and biochemical parameters. This case is reported for its multi system involvement and for the rarity of this condition as very few case reports of Morquio’s are available in Indian literature. Early suspicion of this syndrome enables the clinician to diagnose this condition at the earliest so that patient can be benefited from enzyme replacement therapy which are recently approved for this condition.

Case History:

A 22 year old stunted male presented to the department of internal medicine, outpatient service, Sri Manakula Vinayagar medical college and

hospital (SMVMCH), Pondicherry, with complaints of short stature which started at the age of 7 years and progressed thereafter. The growth retardation was associated with history of shortening of limbs, bending of knees, waddling gait. Patient gave history of swelling in the right groin since birth which is increasing in size for few months. There is history of difficulty in hearing since childhood and hoarseness of voice for few months. History of progressive worsening of dyspnoea on exertion for 3 months duration was present. Patient was born out of non-consanguineous parents. His elder brother also was short statured and suffered from similar illness clinically and died in second decade of life. On examination patient was poorly built with a height of 120 cms and weight 28 kgs. His upper segment: lower segment ratio (US/LS) was 1.18. Patient had facial dysmorphism in the form of macrocephaly, frontal bossing, depressed wide nasal bridge, hypertelorism, dental caries, large mouth, small narrow widely placed teeth, dental caries, enamel hypoplasia, corneal clouding resulting in corneal opacity, bilateral sensorineural hearing loss. Other systemic examination revealed low pitched mid diastolic murmur (MDM) in mitral area, with loud P2 in pulmonary area, right sided inguinal hernia. Skeletal examination showed short neck with short extremities, kyphoscoliosis, knock knees, ulnar deviation of hand, with waddling gait. On investigation echocardiography showed moderate mitral regurgitation with moderate mitral stenosis, with mitral valve orifice of 1.3 cm² and mild pulmonary hypertension with features of myxomatous mitral valve disease was found. Ultrasonography of the abdomen showed right sided inguinal hernia, audiometry of bilateral ear showed bilateral moderate to severe sensory neural hearing loss and on laryngoscopy bilateral false cord edema was present. Skeletal survey

showed hypoplastic carpal bones, proximal radioulnar joint synostosis and disruption of distal radio ulnar joint with excessive bowing of both radius and ulna. Anterior bowing of tibia with severe osteoporosis of tibia and femur, and osteoarthritic changes of both knee joint and wrist joint. Patient's urine sample was analysed for GAG and there was elevated levels of keratansulfate. Based on the clinical and biochemical parameters our patient was diagnosed as Morquio- Brailsford syndrome. Patient was given supportive and rehabilitation therapy for his symptoms.

Discussion:

Mucopolysaccharidosis (MPSs) are group of lysosomal storage disorders which results due to deficiency of enzymes involved in the degradation of glycosaminoglycans (GAGs). GAGs or mucopoly-saccharides includes heparansulfate (HS), dermatansulfate (DS), chondroitin 6sulfate (C6S), chondroitin 4 sulfate and keratansulfate (KS) and they play a vital role in the formation of extracellular matrix, bone, cartilage, ligaments, cornea, skin. They are made up of a protein core to which are attached sulphated amino and acidic sugar disaccharide units. Either single or multiple gene mutation may result in deficiency of the enzyme involved in mucopolysaccharide catabolism leading to progressive accumulation of undegraded mucopolysaccharides resulting in specific syndromes. MPS is classified into various types, MPS I-IX¹ namely MPS type I (Hurler, Hurler-Scheie, Scheie syndromes), MPS type II (Hunter syndrome) MPS type III (Sanfilippo syndrome), MPS type IV (Morquio syndrome), MPS type VI (Maroteaux-Lamy syndrome), MPS type VII (Sly syndrome), MPS type IX (hyaluronidase deficiency) depending on the deficient enzyme. All the MPSs are inherited as autosomal recessive except Hunter syndrome (MPS type II), which is X-linked.

Mucopolysaccharidosis type IV is otherwise known as Morquio-Brailsford syndrome is divided into two subgroups A and B based on the enzyme deficient. It is a rare autosomal recessive disorder. MPS IV A is due to gene mutation mapped to chromosome 16q24.3 characterised by deficiency of the enzyme N-acetyl galactosamine-6-sulfatase (GALNS) which participates in the degradation of Keratansulfate (KS) and chondroitin 6 sulfate (C6S). Over 220 mutations in the GALNS gene have been identified². MPS IVB is due to deficiency of β -galactosidase. Both these subgroups share a similar clinical feature except for few minor variations. Morquio's syndrome was initially described in the year 1929 by Morquio and Brailsford independently and hence this syndrome is described by their name and the frequency of Morquio's syndrome varies from 1: in 76,000³ to 1 per 625,000 live births⁴. Keratansulfate is predominantly present in cartilage, bone, ligaments and hence accumulation of the undegraded products of KS and C6S as in Morquio's syndrome has predominant skeletal and connective tissue abnormalities. The severity of the clinical manifestation varies depending on the percentage of enzyme deficient due to allelic heterogeneity. Morquio's syndrome is characterised by its skeletal habitus such as short stature with short trunk⁵, pectus carinatum, kyphosis, gibbus, scoliosis, genu valgus, flaring of the lower ribs, joint laxity, platyspondylyolysis, odontoid hypoplasia, spondyloepiphyseal dysplasia⁵, hyperlordosis, widening of metacarpals with proximal pointing, and other organ involvement like hepatomegaly and mixed valvular heart disease⁶. Dental involvement in the form of enamel hypoplasia⁷ small, narrow and widely placed teeth are highly specific for MPS IVA⁸ which differentiates it from other MPS types and from Morquio's type IV B.

Our patient presented to us in his 3rd decade of life with proportionate short stature associated with facial dysmorphism, corneal clouding, bilateral sensory neural hearing loss, oedema of false vocal cord, myxomatous mitral valve, hernia, dental and skeletal abnormalities, with normal cognition which is consistent with Morquio's type A. Lee et al⁹ study described bony deformities, short stature, and gait disturbance as initial presentations of Morquio's syndrome as in our patient who is also short statured and had specific skeletal manifestations. R M John et al D Hunter in their case reports on echocardiography in MPS type IV concluded that Morquio's patients have predominant left sided valve involvement with high prevalence of silent cardiac abnormalities as in our case who had moderate mitral stenosis due to myxomatous mitral valve. Rekka et al, and Kinirons et al described dental manifestations in MPS, and mentioned it as specific for MPS IVA. Our patient had enamel hypoplasia with small widely spaced teeth, a feature of Morquio's type A. Our patient did not have any respiratory disease¹⁰ except for the upper airway involvement in the form of edema of false cord or hepatomegaly and few other skeletal manifestations as described in literature.

Screening for Morquio's is done by urinary analysis of GAGs, especially levels of keratin sulfate and chondroitin sulfate in blood and urine. Serum levels of keratansulfate can be measured using highly specific tandem mass spectrometry. In Morquio's patients less than 20 years of age both blood and urine levels of Keratansulfate correlate with the severity, thereafter only urinary levels of Keratansulfate remain high, but urinary levels of KS may not accurately reflect the cartilage involvement. Demonstration of reduced enzyme activity of GALNS in dried blood spot, fibroblasts, and leucocytes is used as definitive tests for

Morquio's syndrome. Confirmative test includes demonstration of genetic mutation by molecular analysis.

Management of mucopolysaccharidosis includes symptomatic therapy, rehabilitation therapy and more definitively a multidisciplinary approach involving coordination of a physician, orthopaedic surgeon, cardiologist, dental surgeon, otolaryngologists, ophthalmologists. Symptomatic and supportive therapy includes anti inflammatory drugs, physiotherapy which may decrease the progression of osteoarthritic changes in bone. Enzyme replacement therapy (ERT) are found to be useful especially in MPS IV and MPS VI phenotypes, when the disease is identified at the earliest before the development of irreversible organ damage. Hence early confirmation of the specific type of MPS by molecular analysis is needed to start the ERT at the earliest. Elosulfase-alfa which is the recombinant human GALNS is a boon to Morquio's patients, if administered at the earliest, and is approved for Morquio's MPS IVA, with a less adverse reaction. Elosulfase-alfa is administered at the dose of 1.0-2mg/kg/week¹¹ and it showed decrease in the KS substrate. A comprehensive assessment of the patient at the time of diagnosis helps to plan for a multispecialty intervention and prevent irreversible clinical damage. Gene therapy using Adeno Associated Virus (AAV) derived vectors are still in experimental stage for Morquio A disease¹². Substrate reduction therapy are not found to be useful in Morquio's syndrome. Hematopoietic stem cell transplantation (HSCT) with bone marrow or umbilical cord blood stem cells are known to be

beneficial in certain MPS like MPS I, VI and VII but it failed to prevent progression of Morquio's disease. Serious life threatening complications which the Morquio's patients suffer includes atlanto-axial instability leading to cervical myelopathy, restrictive pulmonary disease and cardiac disease. Various chest deformities predisposes these patients to recurrent respiratory infections. Life expectancy is usually less than 30 years among Morquio's patients¹³ Prognosis of this condition varies as the GAGs accumulate leading to premature death with a life expectancy ranging from 10 to 20 years of age to almost normal in some patients⁴

Conclusion:

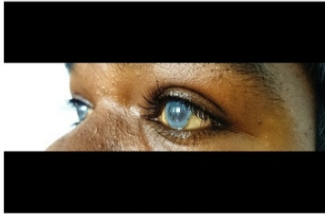
Multidisciplinary treatment, supportive therapy, rehabilitation therapy and recently enzyme replacement therapy are the mainstay of treatment in Morquio's syndrome. Short statured individuals should be screened clinically, biochemically for mucopolysaccharidosis. Hence knowledge of the clinical features of the various types of MPS is essential among the physicians, as well as for other specialities as Morquio's syndrome has multisystem involvement and patients can present with varied manifestations. Early suspicion and confirmation are the initial steps in the management of this rare condition.

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A Morquio Syndrome patient with Facial Dysmorphism and dental abnormality.



Corneal Opacity.



A Morquio Syndrome patient with short stature.



X-ray bilateral forearm with wrist AP view: a) Bilateral proximal radio-ulnar synostosis, b) Bowing of both radius and ulna, c) Hypoplastic distal radio-ulnar joint along with disruption, d) Hypoplastic carpal bones.



X-ray cervical spine lateral view: Hypoplasia of all the vertebral bodies.



X-ray bilateral knee lateral view: a) Anterior bowing of tibia,
b) Radiolucency present in both tibia and femur.

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