International Journal of Physical Medicine & Rehabilitation

Sharma and Sharma, Int J Phys Med Rehabil 2015, 3:4
DOI: 10.4172/2329-9096.1000291

Case Report open access

Spectrum of Skeletal and Non-Skeletal Manifestations of Morquio A Syndrome in an Adult: A Case Report

Sharma VP and Sharma K Arvind*

Department of Physical Medicine and Rehabilitation, King George's Medical University, Lucknow, India

***Corresponding author:** Sharma K Arvind, Junior Resident, Department of Physical Medicine and Rehabilitation, King George's Medical University, Lucknow, Uttar Pradesh, India, Tel: 917379967999; E-mail: drarv25@gmail.com

Received date: May 21, 2015; **Accepted date:** July 03, 2015; **Published date:** July 05, 2015

Abstract

Morquio syndrome is an autosomal recessive mucopolysaccharidosis which includes type IVA, a deficiency of the enzyme N-acetylgalactosamine-6-sulfatase and type IVB a deficiency of β-galactosidase. We report a 28-year-old Indian male patient affected by Morquio A syndrome demonstrating the characteristic musculoskeletal and nonskeletal manifestations of this disease on clinical and radiological examination. Digital x-ray of the spine, pelvis, chest and knees together with magnetic resonance imaging of the entire spinal column were done. The main abnormalities were atlantoaxial subluxation, anterior beaking of the vertebrae with thoracolumbar kyphosis, platyspondyly, hypoplasia of the odontoid process, short thorax with wide anterior posterior diameter, genu valga deformity and severe multiple degenerative changes of the hips, knees, and ankle joints.

Based on clinical findings and radiological features it is possible to diagnose a case of Morquio A syndrome. Non-skeletal abnormalities may also provide key insight into the clinical diagnosis of MPS IVA. Careful and systemic approach is needed to accurately diagnose the exact type as enzymatic studies are not available in most centers. Radiological examination is crucial for assessment of the skeletal and joints changes, and the rehabilitation strategies to be followed.

Introduction

Morquio syndrome is an autosomal recessive mucopolysaccharidosis, which was first described in 1929 by Luis Morquio [1] and James Brailsford [2]. The Morquio syndrome in its variants, are characterized by severe skeletal changes, including hypoplasia of the odontoid process, short neck, pectus carinatum, thoracic kyphoscoliosis, and dwarfism [3]. X-rays features include wide flaring of the ilium, shallow acetabula, flattening of femoral heads, coxa and genu valga, and dysostosis multiplex, while skeletal abnormalities of the spine are platyspondyly with central beaking and hypoplasia, or absence of the odontoid process [4].

MPS IV has been categorized as two types [5], IVA and IVB. Distinct from MPS IVA, patients with MPS IVB have relatively mild [5] symptoms, normal or near normal stature [6] with normal neck development.

The incidence of MPS IVA is 1:201,000 [7]. MPS IVA is caused by mutations in the gene encoding the enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS, EC 3.1.6.4) [8] resulting in impaired catabolism of 2 glycosaminoglycans (GAG), chondroitin-6- sulfate (C6S) and keratan sulfate (KS) [9].

KS and C6S accumulation typically results in short stature and skeletal dysplasia (Wraith 1995). Bone deformity is the most common initial manifestation [10,11] of skeletal dysplasia. Additional compromised systems include visual, auditory, cardiovascular, and respiratory system [12]. The central nervous system is not believed to have significant manifestations of GAG accumulation and normal intelligence appears to be preserved [13].

However, patients have a high risk of developing neurological complications caused by a combination of odontoid hypoplasia, incomplete ossification of the anterior and posterior rings of the atlas and deposition of GAGs in the anterior extradural space. This results in atlantoaxial subluxation and spinal cord compression, with cervical myelopathy, consequential quadriparesis or even death [12].

Clinical presentation varies from severe or classical to mild or attenuated phenotypes. As well, an intermediate subtype of MPS IVA has been proposed [14]. Onset of disease symptoms commonly occurs prior to 1 year of age in severely affected patients or as late as the second decade of life in less severely affected patients [10]. Diagnosis is typically based on clinical examination, skeletal radiographs, and the enzymatic activity of GALNS in blood cells or fibroblasts [10,11].

Except for a recent study [15] who reported scintigraphic features, no other studies have been recently published presenting typical clinical features and systematic imaging collection of this rare disease. The aim of our study is therefore to describe the unique clinical and radiological features in an adult case of type IV A MPS.

Case Presentation

Patient is a 28 years old male, only child of healthy parents, without known consanguinity. The clinical history begins at two years when after a normal postnatal development, parents noticed delay in growth and deformity in both knees but there was no mental retardation. Patient was initially seen by an orthopedic surgeon and was given POP cast followed by orthosis for both LL. At the age of 5 years, he had the second visit to the hospital for treatment, because he developed chest deformity and the growth retardation was also apparent, following which patient developed wasting in lower limbs with worsening of

deformities in knee and chest. Gradually he developed joints stiffness and pain all over body with difficulty in walking. Since the age of 20 years till now, the physical condition of the patient has worsened for a further deterioration of his joints, with difficulty in walking and recurrent pain. Patient also had history of diminution of vision and inward deviation of right eye. Clinical examination revealed normal intelligence, truncal dwarfism (height; 124 cm), pectus carinatum, stubby neck, kyphoscoliosis of dorso-lumbar spine, knock knee and right equinovarus deformity. (Figure 1) Bilateral wrist joint laxity with insufficient grip was also present. The patient did not follow any supportive measures or rehabilitation protocol to treat the skeletal manifestations of his disease. The neurological examination revealed decreased motor power in both upper and lower limbs, hypereflexia, positive babinski and paresthesias.

Ophthalmologic examination revealed right esotropia, with left glaucomatous optic disc. On dental examination spaced dentition and spade-shaped incisors were observed (Figure 1).

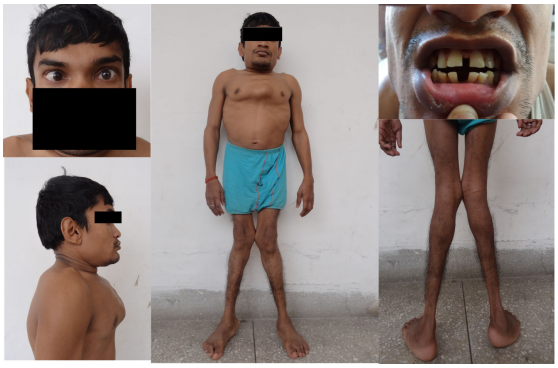

Figure 1: Clinical photographs; A) Right Esotropia, B) Pectus carinatum, C) Full length picture showing dwarfism, short neck, chest deformity, D) Spaced dentition, E) Knock knee with Right equinovarus.

Skeletal survey of multiple parts of the body was done, including skull, complete spine, chest, hips, and limbs. The Anteroposterior view of the spine showed a mild thoraco-lumbar right scoliosis; the lateral view demonstrated kyphotic curvature in dorsolumbar junction with irregular, flat and antero-posteriorly enlarged vertebral bodies. The cervical spine showed wedge shape of the vertebral bodies and hypoplasia of the odontoid process (Figure 2).

Roentgenographic findings of the chest included a relatively small size of his chest with paddle shaped ribs. The iliac wings of the pelvis were flared, with short femoral necks and marked degenerative changes of the hip joints. In the lower extremity, the lower ends of the femur and the upper ends of the tibia were large with an evident genu valgus deformity. Severe degenerative changes of the knee joints were present (Figure 2).

Multiplanar MRI of whole spine done on 1.5 Tesla machine using T1 weighted spin echo, T2 weighted fast spin echo and fast STIR sequences. MRI due to its multiplanar features confirmed radiographic findings adding further information on the degenerative alterations. Cervical spine showed atlantoaxial subluxation with focal cord edema/ischaemia at C1 level. Increase in the distance between the anterior arch of C1 and dens were noted. Spinal cord was found to be compressed between the dens and posterior arch of C1 vertebra. It showed hyperintense signal intensity on T2 weighted images. All the discs showed reduced signal intensity on T2 weighted images. In thoracic spine D11-12 and D12-L1 discs showed posterior bulge indenting the thecal sac. L1-2 and L2-3 discs showed diffuse posterior bulge compressing the thecal sac. On screening of whole spine platyspondyly, end plate irregularity, and anterior beaking of the vertebral bodies characteristics of dysostosis multiplex, were present.

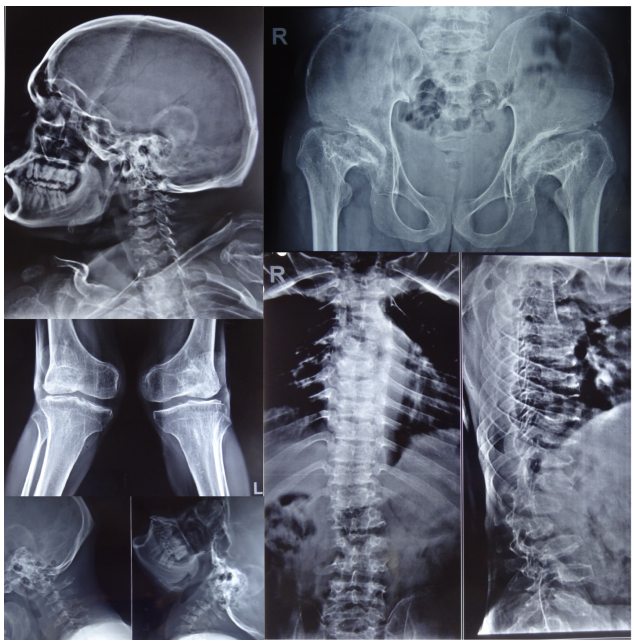

Figure 2: Radiographic features; A),C) Lateral view of cervical spine with wedge shaped vertebral bodies and hypoplasia of the odontoid process, B) Standing anteroposterior view of the knees showing genua valga with overgrowth of both medial femoral condyles and severe degenerative changes. D) Long pelvis with constricted iliac wings, short femoral necks with severe degenerative changes of hip joints E) AP view of the thoracolumbar spine depicting paddle-shaped ribs and decreased vertebral height, lateral view of the thoracolumbar spine depicting varying degrees of platyspondyly with anterior wedging of vertebral bodies, with irregularity of the end plates.

A follow up MRI of CV junction with cervical spine showed Os-Odontoideum (orthotopic type) higher up in position and hypoplastic dens. Severe primary canal stenosis (7 mm) was noted at C2-3 level with thinning and signal intensity alterations in cervico-medullary junction and upper cervical cord suggestive of compressive myelopathic changes. Clivus is seen mildly deformed in shape.

The PFT was within normal limit with FEV1/FEV6 ratio of 0.88. No evidence of organomegaly or other pathology was found on USG whole abdomen. On cardiac assessment ECG was within normal limit and there was no evidence of any valvular heart disease.

On 6 minute walk test, for assessing submaximal functional capacity endurance was found impaired.

On clinical and radiological examination diagnosis of MPS was made. Unfortunately we could not perform any measurement of GAG, keratan and heparan sulphates in his urine because of the lack of test

kits. Enzyme assay for iduronate sulfatase is not carried out in our laboratory therefore it was not performed either. Our diagnosis of MPS was confirmed from his history, clinical examination and skeletal survey (Figure 3).

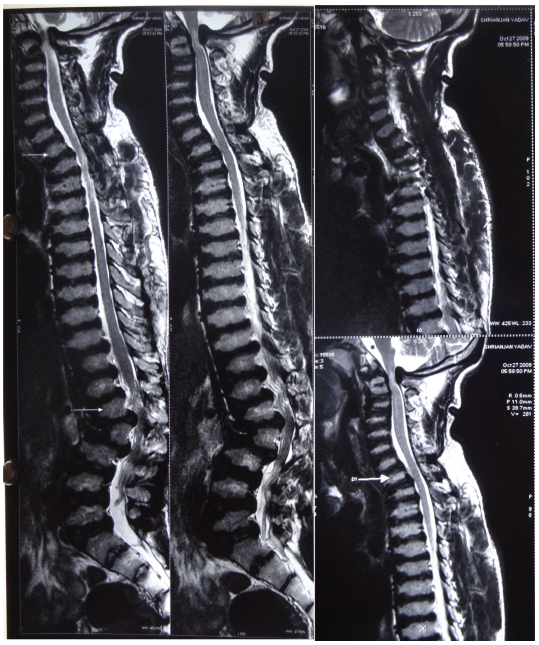

Figure 3: MR Imaging; Cervical spine showing atlantoaxial subluxation with focal cord edema/ischaemia at C1 level showing hypoplasia of the odontoid process with a mild cord compression at the level of C2-C3, Thoracic spine D11-12 and D12-L1 discs showing posterior bulge indenting the thecal sac, L1-2 and L2-3 discs showing diffuse posterior bulge compressing the thecal sac. On screening of whole spine platyspondyly, end plate irregularity, and anterior beaking of the vertebral bodies characteristics of dysostosis multiplex.

Rehabilitation: Submaximal intensity endurance exercises were taught. Mobilisation was encouraged with walker initially; then patient was able to walk with stick only. Endurance improved as found on various submaximal intensity tests. Significant improvement in ADL was also noted.

Discussion

This case describes a patient with MPS IV A, who presents with classic musculoskeletal and non-skeletal manifestations. Patients with Morquio syndrome usually can be clinically distinguished from patients with other MPSs because they do not have coarse facial features or mental retardation and they have additional skeletal manifestations derived from a unique spondyloepiphyseal dysplasia and ligamentous laxity [3]. These skeletal manifestations include odontoid hypoplasia, a striking short trunk dwarfism, and genu valgus.

These patients tend to have greater spine involvement with scoliosis, kyphosis, and severe gibbus, as well as platyspondyly, rib flaring, pectus carinatum, and ligamentous laxity [16]. Odontoid hypoplasia is the most critical skeletal feature to be recognized in any patient with Morquio syndrome.

Radiographically, skeletal changes in MPS IVA can appear very similar to those seen in the osteochondrodysplasias classified by the International Working Group on Constitutional Diseases of Bone [17] as spondyloepiphyseal dysplasias (SEDs). Congenital SEDs can usually be differentiated from MPS IVA because symptoms are present at birth. Two SEDs, Dyggve-Melchior-Clausen syndrome (DMC) and SED, Maroteaux type, were previously known as pseudo-Morquio syndrome types 1 and 2, respectively, due to their skeletal resemblance to MPS IVA [18]. DMC, originally reported as Morquio-Ullrich's disease, is caused by mutations in the DYM gene [19] and can be clinically differentiated from MPS IVA because patients are intellectually disabled. However, mutations in the same gene can also cause Smith-McCort syndrome (SMC), a condition radiographically identical to DMC in which intelligence and psychomotor development are normal. In radiographs, both DMC and SMC appear similar to MPS IVA, including the presence of atlantoaxial instability caused by odontoid hypoplasia, but can be differentiated by a characteristic lace-like appearance of the iliac crests [20] which is absent in MPS IVA.

Additional differential diagnoses include spondylometaphyseal dysplasia, Kozlowski type (SMDK) and brachyolmia. Individuals with SMDK have platyspondyly, overfaced vertebral pedicles, irregular proximal femoral growth plates, and carpal ossification delay [21]. Brachyolmias are a heterogeneous group of skeletal dysplasias characterized radiographically by generalized platyspondyly without significant long bone abnormalities [22].

Joint hypermobility (of the wrist in particular) may develop and can be especially helpful in establishing clinical suspicion as it is unique to MPS IVA and MPS IVB among the MPS disorders. The absence of intellectual disability is also helpful in differentiating MPS IVA from several other lysosomal storage diseases [23].

Non-skeletal abnormalities may also provide key insight into the clinical diagnosis of MPS IVA. Signs of respiratory compromise, such as limited endurance, frequent respiratory tract infections, sleep apnea, and snoring, are common in MPS IVA [24]. Other non-skeletal findings include mitral and/or aortic value regurgitation and thickening, conductive and sensorineural hearing loss, and muscle weakness [24]

Visual impairment in MPS IVA differs slightly from other MPS disorders. Corneal clouding, although common, is milder; astigmatism can occur, and reported cases of glaucoma have been open-angle as opposed to closed-angle as reported for other MPS disorders [24]. Dental abnormalities, including spaced dentition, pointed cusps, spade-shaped incisors, and enamel hypoplasia are also characteristic of MPS IVA [24].

The full diagnostic process involves clinical examination, skeletal radiographs, enzyme activity analysis in fibroblasts or leukocytes and confirmation by molecular analysis [23]. Radiographs and MR imaging provide useful information about the gravity of characteristic of skeletal and joint changes. Odontoid hypoplasia is the most critical feature to recognize and for this reason MRI of the neck must be used to determine if the upper vertebrae are underdeveloped, providing more accurate diagnosis on possible neurological risk conditions; moreover, it is helpful in confirming a possible cervical myelopathy and cord compression.

Once diagnosed, MPS IVA requires a multi-disciplinary approach to patient care. While management of skeletal manifestations and the associated neurological complications is critically important, management of other organ systems, including visual, auditory,

cardiovascular, and respiratory systems, are also important to assure quality of life of individuals with MPS IVA. The preservation of functionality is an increasing challenge in the treatment of patients with Morquio syndrome and maintenance of occupational performance should be defined as one of the main goals to be reached by the rehabilitation measures used.

In conclusion, we would like to stress the uniqueness of our imaging collection; we believe that for the study of chronic progressive course with multijoint involvement of the Morquio disease, subsequent MRI imaging assessments can provide useful information, giving the patients a substantial impact about the evolution of this pathologic condition. It moreover allows the physiatrist to play a major role ensuring control of the acute and chronic pain symptoms and to monitor bone and joint function, adopting the more appropriate rehabilitation strategies to be followed. Physical therapy and pain medication can be beneficial to manage musculoskeletal manifestations in some patients. A walking aid or wheelchair can help improve mobility and pain. However, efforts should be made to keep patients independently mobile as long as possible as the quality of life (QoL) drops dramatically when patients become wheelchair dependent.

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