



Vertebral Pathology and Vertebrogenic Myelopathy in Patients with Mucopolysaccharoidosis Type IV A (Morquio Syndrome)

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Abstract

Background: Upper cervical spine instability in patients with Morquio's syndrome is of common occurrence. Dysplastic odontoid is one of the prominent aetiologies behind the development of atlanto-axial instability which eventually leads to morbid vertebrogenic myelopathy.

Material and Methods: We describe 10 children (7 boys and 3 girls) with the phenotype/genotype of Morquio's syndrome (MPS IVA). Lumbar kyphosis occurs at the age of six months, followed by apparent waddling gait at the age of 3 years. Clinical phenotype and genotype are the baseline tools to set up a crystal clear long term management. Firstly, we proceed via clinical assessment of C1-2 instability. The latter is carried out with full dynamic lateral cervical spine radiographs. Instability can be visualized through the precise interpretations of the anatomical structures around the atlanto-axial segments. 3D sagittal CT scan has been applied to further localize the exact pathology. In 7 cases, there was an initial myelopathy at the level of the cranio-vertebral junction.

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Results: The most threatening complication of MPS IVA is the vertebrogenic myelopathy. The latter emerged as a notorious complication in connection with atlanto-axial instability and progressive thickening of the spinal cord due to accumulation of Glycosaminoglycan (GAGs). Vertebrogenic myelopathy have been encountered in seven children. All underwent decompression and stabilization of the cervical spine

Conclusion: Patients with MPS IV, in their first year of life usually manifest growth deficiency and lumbar kyphosis, but unfortunately passed unnoticed by most of the paediatricians. Progressive dysplasia of the acetabulae is the reason behind the waddling gait. The misconception of generalized ligamentous hyper laxity accompanied with waddling gait were the main incentives of confusion among most of the paediatricians and physicians. Thereby, the false diagnosis of Duchenne Muscular dystrophy has been falsely considered by some colleagues. The purpose of this paper is threefold. First, overlooking the early mal-development of the backbone (lumbar kyphosis) is not a simple mistake. Second, marked ligamentous hyperlaxity warrants the attention toward cervical ligaments, and as ligaments are the main supporters of the craniocervical junction and spine stability, such abnormality demands prompt clinical attention. Third, is to assess the vertebral pathology and vertebrogenic myelopathy from the standpoint of syndromic assessment and the efficiency of decompression and stabilization operations.

Keywords

Neurological Deficits; Mucopolysaccharoidosis Type IV; Orthopedic Pathologies

Introduction

Morquio in Uruguay, and Brailsford in UK, simultaneously and independently described the entity now known to result from a lysosomal storage disorder, namely deficiency of galactosamine-6-sulfatase [1,2]. Notable features included osseous dystrophy, in addition to visual and heart disorders such as corneal clouding and aortic valve disease. Urinary excretion of keratosulfate has been noted. Onset may be in the first three years of life, started with waddling gait and changed into circumduction gait when knock knees (genu valgum) developed. The abnormal gait is part of sequence of pathological events in connection with loose joints (generalized ligamentous hyperlaxity). Clinical phenotype showed short trunk and short neck. By time facial features become coarse. Corneal problem is mild but hearing loss may be a problematic [3-5]. Atlanto-axial instability in connection with hypoplastic C2 is a major and life threatening abnormality [6]. Progressive skeletal deterioration may lead to disruption of the normal anatomy of the cranio-cervical junction, the axial and the articular components respectively. Neurological deficits are the most hazardous morbid/fatal outcome.

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It's of extreme rarity patients with the severe type of MPS IV survive past the second or third decade of life. In type A Morquio there is deficiency of the enzyme galactosamine-6-sulphatase causing faulty degradation of keratan sulphate with glycosaminoglycan deposits in the body tissues. Keratan sulphate is excreted in large amounts in urine [7]. In type B Morquio syndrome there is deficiency of the enzyme beta galactosidase. The phenotype however is milder than in type A [8]. The development of a series of orthopedic pathologies, including the vertebral pathology and vertebrogenic myelopathy. Therefore, comprehensive clinical examination of the upper and lower extremities is mandatory [9,10].

Vertebrogenic myelopathy is not of uncommon occurrence which resulted from stenosis at the level of the foramen magnum and upper cervical spine, resulting in compression [11]. Stenosis at the level of the foramen magnum in patients with MPS IV A with subsequent development of compressive myelopathy is a dreadful complication. And it may involve multiple levels, and can lead to compressive myelopathy or myelomalacia [12]. Numerous types of scoring tools have been used to validate the assessment the magnitude of cervical cord compression/stenosis. Frankel grade classification has been applied to evaluate any associated abnormalities in connection with vertebrogenic myelopathy [13]. Nurick scale system is to gauge the degree of spinal cord injury has been used as well. It consists of five-grade system (0-5) based on the difficulty in walking [14]. The severity of myelopathy was also evaluated using the modified scale of Japanese Orthopedic Association mJOA (JOAScore) and Nurick scale [15]. Atlantoaxial instability in association with generalized ligamentous hyperlaxity in MPS IV A and accumulation of glycosaminoglycan because of impaired degradation, are adverse factors in favor of spinal cord compression /stenosis.

Materials and Methods

The study protocol was approved by Ethics Committee of the (Ilizarov Scientific Research Institute, No.4 (50)/13.12.2016, Kurgan, Russia). Signed permissions were obtained from the patient's parents and guardians. Ten children (seven boys and three girls) have been enrolled in this study. Comprehensive clinical documentation has been enforced with detailed skeletal survey via conventional radiographs, MRI and CT scan. The average age of children referred to our orthopedic Institute was between 6 months to 5 years respectively. All exhibited circumduction gait, growth deficiency (50th percentile), dolichocephaly, anteverted nares, abnormally shaped and widely spaced teeth, and enamel dysplasia. Musculo-skeletal examination revealed generalized ligamentous hyperlaxity and thoracic kyphosis. The pathological course of MPS IV A can be illustrated in accordance with our clinical expertise. A-6-month-old-girl was brought to seek advice regarding her lumbar gibbosity. Loose joints were the first alarming sign and the child was unable to sit unsupported. Lateral spine radiograph confirmed the lumbar kyphosis and showed the beaked wedged vertebral body of L1 (Fig. 1). A-3-year-old-boy was referred because of thoracic kyphosis and a history of

delayed walking and a waddling gait. No specific craniofacial abnormalities at this age have been encountered. But, nevertheless, lateral spine radiograph revealed generalized platyspondyly of the lumbar vertebrae and the diagnostic feature of a hook-shaped vertebral bodies associated with exaggerated lumbar lordosis (Fig. 1).

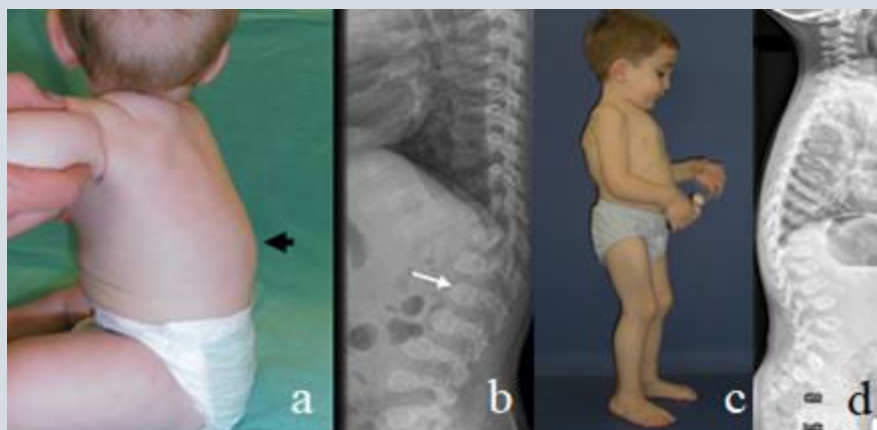


Figure 1: (a-d): A-6-month-old-girl was brought to seek advice regarding her lumbar gibbosity (1,a). Loose joints were the first alarming sign and the child was unable to sit unsupported. Lateral spine radiograph confirmed the lumbar kyphosis and showed the beaked wedged vertebral body of L1 (1,b). A-3-year-old-boy was referred because of lumbar kyphosis and a history of delayed walking and waddling gait was the paramount feature because of progressive acetabular dysplasia. He did not exhibit any specific craniofacial abnormalities at this age (1,c). But, nevertheless, lateral spine radiograph revealed generalized platyspondyly of the lumbar vertebrae and the diagnostic feature of a hook-shaped vertebral bodies have been identified (1,d).

A-9-year-old- girl presented with MPS IV a, she manifested growth deficiency, short neck/ trunk and thoracic kyphosis. Lately she manifested myelopathy and clinical phenotype of cervical cord compression. Sagittal MRI of craniovertebral transition and cervical segments, confirmed myelopathy and stenosis at the level of C1/2 (Fig. 2). Another 15-year-old patient with MPS IV A manifested early signs of myelopathy (Fig. 2). 3D reformatted CT scan showed, hypoplastic posterior arch of C1 associated with odontoid process hypoplasia (arrow) with subsequent development of C1/2 instability and cervical cord compression at the level of C1/2 - 4 mm (Fig. 3).



Figure 2: (a,b): A-9-year-old- girl presented with MPS IV A, clinically growth deficiency, short neck/ trunk and thoracic kyphosis. Lately she manifested myelopathy as expressed by her clinical phenotype and the neurological examination (a). Sagittal MRI of craniovertebral junction showed C1/2 instability and confirmed stenosis at the level of C1/2 (space of the spinal cord =4 mm) (b).

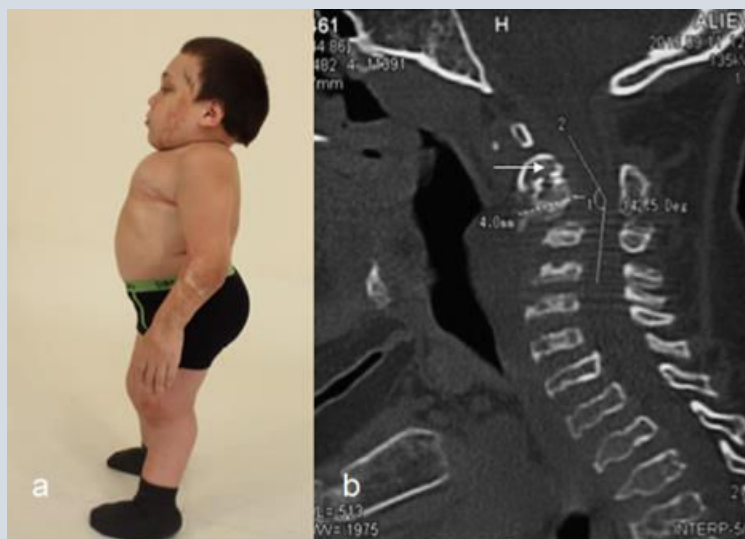


Figure 3: (a,b): A 15-year-old patient with MPS IV A manifested early signs of myelopathy (a). 3D reformatted CT scan showed, hypoplastic posterior arch of C1 associated with odontoid process hypoplasia (arrow) with subsequent development of C1/2 instability and cervical cord compression at the level of C1/2 – 4 mm (b).

The neurological status of these children has been evaluated via the application of Frankel scale with simultaneous assessment of the severity of myelopathy through the application of the modified scale of Japanese Orthopedic Association mJOA (JOAScore) and Nurick scale as well. The aforementioned scales showed that Frankel scale was at D level, a 6-minute walk test showed -240 m, and at -(2-3).

Surgical interventions and results

The necessities and indications for surgical intervention were based upon the following elements:

A. Deterioration of the neurological deficits

B. The full dynamic conventional lateral radiographs and dynamic MRI showed features of myelopathy in connection with C0/2 instability of stenosis

In order to avoid failure of intubation, we performed maximal care to choose patients with no massive respiratory and or cardiovascular abnormalities. Moreover, as our patients are manifesting C1/2 subluxation, we maximized our efforts to prevent any form of spinal cord injury during intubation. Patients with instability and subluxation of the atlanto-axial joint might have abnormal mobility during intubation or amid the craniocervical decompression in the prone position. Anesthesiological application included total intravenous anesthesia as a combination of the hypnotic propofol (2-10 mg/kg/h) with the narcotic analgesics fentanyl (1-10 µg/kg/h). At the stage of intubation, the muscle relaxant Esmeron of medium action was used (Fig. 4,5) (Table 1,2).

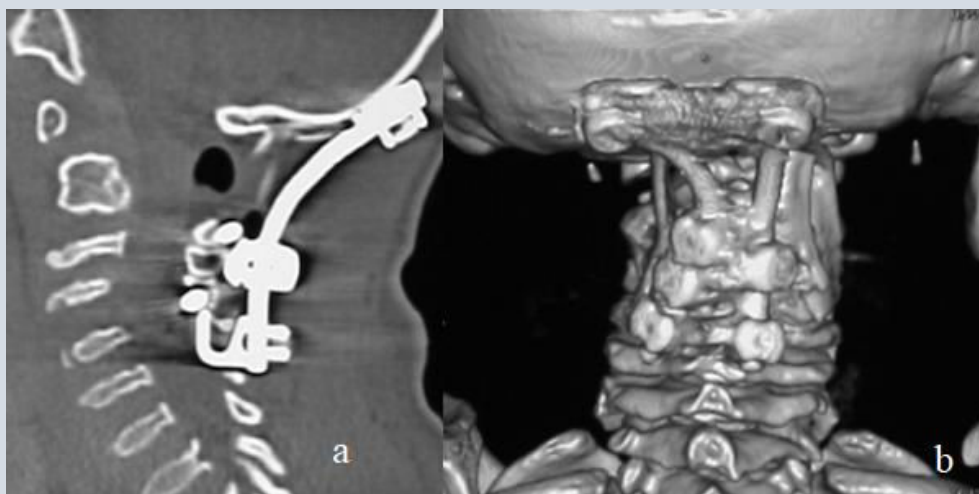


Figure 4: (a) The 7-year-old-girl underwent occipito fusion of C0-C5 and decompression of C1-2 via autorib boneplastic (fixation was performed to avoid the development of instability and cicatricial stenosis of the trachea (b).

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Figure 5: Photos of the same girl showed complete recovery, 6-months after the surgical intervention, there was no any trace of neurological deficits. She regained her full activity and normal life.

Patient's sex	Age when MPS was detected (years)	Age when targeted therapy was started	mJOA (start of follow-up)	Type of thoraco-lumbar deformity	Cervical spine pathology	Surgery in thoraco-lumbar level	Surgery in cervical level	Follow-up	mJOA (end of follow-up)
Female	Six months	--	18 months	Lumbar kyphosis	-	-	-		
Male	3 yrs	--	18 months	Lumbar kyphosis	-	-	-		
Female	7 yrs	--	7 yrs	Thoraco-lumbar kyphosis	C1-C2 stenosis	Yes	Yes	10 year	14
Male	13 yrs	2017 year	5 yrs	Thoraco kyphosis	Odontoid hypoplasia, C2-3 kyphosis and stenosis	No	Yes	patient was died in 2019 year	--

Male	7yrs	2019 year	9 yrs	---	Odontoid aplasia, C1-C2 stenosis	No	Yes	4 year	16
Male	7 yrs	2020 year	6 yrs	Thoracolumbar kyphosis	C1-C2 stenosis	Yes	Yes	8 year	14
Male	7 yrs	2020 year	9 yrs	Thoracolumbar kyphosis	Odontoid aplasia, C1-C2 stenosis	Yes	Yes	3 year	16
Male	6 yrs	2021 year	12 yrs	---	Odontoid aplasia, C1-C2 stenosis	No	Yes	3 year	16
Male	4 yrs	2019 year	8 yrs	Thoracolumbar kyphosis	Odontoid aplasia, C1-C2 stenosis	No	Yes	After 19 days - sudden death (according to autopsy, cardiovascular failure)	--

Table 1: Illustrates the clinical phenotypic characterizations of all patients.

Sex	Age of first surgery (years)	Type of first surgery	Complications	Age of second surgery (years)	Type of second surgery	Complications
Female	7 yrs	C1-2 laminectomy, C0-C3 screwing	-	7	Fusion «growing rods» 04,5	No
Male	15 yrs	C2-4 laminectomy, C0-C5 screwing	Paraplegia	-	-	-

Male	9 yrs	C1-2 laminectomy, C0-C3 screwing	-	-	-	-
Male	3 yrs	C2 laminectomy, C0-C2 screwing	-	3,7	Fusion Th10-L2	-
Male	8 yrs	C0-C3 laminectomy, C0-C5 screwing	-	11	Fusion Th10-L2	-
Male	7 yrs	C0-Th1 laminectomy, C0-Th5 screwing	-	-	-	-
Male	11 yrs	C0-C3 laminectomy, C0-C3 screwing	Tetraparesis	-	-	-

Table 2: Illustrates the type of surgical intervention and the prognosis.

Discussion

The Mucopolysaccharoidoses (MPSs) share a chronic progressive course with multisystem involvement, eventually lead to numerous skeletal and extra-skeletal pathologies. Patients with Morquio syndrome usually manifest a specific clinical phenotypic characteristics, through which differential diagnosis with other types of MPSs can be made. In their first year of life, children with Morquio syndrome usually manifest the triad of, marked ligamentous hyperlaxity (loose joints), growth deficiency and lumbar kyphosis. Walking is delayed and waddling gait is the paramount feature. Waddling gait occurred because of progressive dysplasia of the acetabulae. Later on in life, apparent growth deficiency, dolichocephaly and or scaphocephaly can be noticeable. Knock knees is a well-established deformity. Cranio-cervical junction is at risk for the development of vertebrogenic disorder because of, ligamentous hyperlaxity of the craniocervical junction, C1-2 instability and the accumulation of GAGs which can result in gradual onset of myelopathy. The Morquio syndromes belong to a family of a long list of

lysosomal storage disorders, which are known as Mucopolysaccharidoses (MPSs). MPSs are characterized by the pathological accumulation of certain complex carbohydrates (Glycosaminoglycans-GAGs) in connection with heritable deficiency in lysosomal enzymes. The outcome is dreadful through the pathological skeletal and extra-skeletal involvement. Onset may be in the first two years of life with genu valgum, a short trunk and neck, pectus carinatum and coarse facies. Painful waddling gait because of undiagnosed/overlooked acetabular dysplasia associated with generalized ligamentous hyperlaxity, can lead to clinical misconception [1-10]. In Morquio syndrome, both mortality and morbidity are strongly related to a constellation of craniocervical abnormalities. A simple trauma of the craniocervical junction can lead to a dreadful neurological deficits and possibly death. Although the skeletal changes may result in neurologic complications, but patients with the severe phenotype usually do not survive past the second or third decade of life. Spinal pathology is one of the prominent devastating manifestations of MPS IV A [11-13].

Comprehensive assessment of the patient's neurological and motor status is a key component of early screening of upper spine pathology. The modified Japanese Orthopedic Association mJOA (JOAScore), Nurick scale, 6-minute walk test and 3-minute walk test refer to the most valid scales. Burden of the neurological status and the confirmed stenosis/ instability are the major hazards of MPS IV. All the aforementioned elements are basic parameters in favor of a mandatory surgical intervention. Decompression and occipitospondylodesis are indicated in the patients with instability and stenosis at the level of the craniovertebral transition [14-18].

Summary

Difficulty in walking and the commencement of waddling gait has been the most confusing element to approach for the proper diagnosis in some patients with MPS IV A. Paediatricians and orthopaedic surgeons' first conception towards waddling gait is the diagnosis of Duchenne Muscular Atrophy (DMD). This sort of misconception emerged when consanguinity of the parents is confirmed. Particularly in the autosomal recessive type of Duchenne muscular dystrophy. A girl and boy were cousins and both underwent, the long vicious series of profound investigations to confirm or rule out DMD. Fallacy in diagnosis can cause a tremendous harm to the child and his family. As we have defined the purpose of the present study, the onset of the disease as manifested by waddling gait and frequent falls which might soon followed by the development of vertebrogenic myelopathy. All the aforementioned stages of the disease require appropriate knowledge and mandatory interventions to halt the massive axial and the appendicular skeletal abnormalities in patients with MPS IVA.

Conflict of Interest

The authors verify that there is no conflict of interest.

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