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CASE REPORT

Morquio A syndrome: differential diagnosis of disproportionate short stature

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Abstract

Short stature is defined as a condition in which the height of the individuals is below the third percentile or two standard deviations below the expected average for children of the same age and sex. Bone dysplasias are an important group in the differential diagnosis in children with short stature and, among them, Morquio A syndrome, a genetic-metabolic disease, characterized by an enzyme deficiency and lysosomal accumulation with a direct impact on bone development and cartilaginous. Often, this pathology goes unnoticed by the endocrinologist or pediatrician when evaluating children with short stature, mainly because the classical signs and symptoms of the disease are not yet evident. Morquio A syndrome is not curable, but early diagnosis and treatment make it possible to prevent disease progression and provide better quality of life for patients. The currently available treatments are hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (TRE). In addition, due to the various disabling comorbidities that can arise with evolution, a multidisciplinary approach is essential. Knowledge of genetic causes of short stature due to alteration in bone development is fundamental for the clinical suspicion of this group of diseases. This article aims to report the case of three siblings with the syndrome, whose diagnosis of two of these patients took more than two decades to be established.

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INTRODUCTION

According to the World Health Organization (WHO), short stature is defined as a condition in which the height of individuals is below the third percentile or is two standard deviations below the expected mean for children of the same age and sex[1]. The minority of patients who seek medical care due to short stature have a primary organic cause, with the majority having a family stature and/or caused by extrinsic factors, such as the environment and nutrition, or idiopathic[2].

Among the pathological causes, the most common are of genetic and neuroendocrine etiology. From a genetic point of view, bone dysplasias constitute an important group in the differential diagnosis of stunting in children. Among them, Morquio A syndrome or mucopolysaccharidosis type IV A (MPS IVA) stands out, which has become a prototype of disproportionate short stature since its initial description by the Uruguayan pediatrician Morquio. It is a rare, autosomal recessive disease, with a prevalence of 1/210,000, characterized as bone dysplasia resulting from lysosomal deposits[3].

Often, the MPS IVA goes unnoticed by the endocrinologist or the pediatrician when evaluating children with delayed stature, since, often, the main signs and symptoms of the disease are not yet evident. For this reason, the history and physical examination must be detailed in order to look for clinical findings that may contribute to early diagnosis and treatment, in order to avoid complications of the disease and offer genetic counseling to families[4].

We describe a series of cases referring to three brothers with Morquio A syndrome, whose diagnosis in two of these patients took more than two decades to be established.

METHODS

Retrospective analysis of clinical, laboratory and radiological data from three patients with Morquio A syndrome in follow-up at a clinical genetics service.

RESULTS

case 1

Patient JRS, female, daughter of a non-consanguineous couple, born by normal delivery at term, with normal weight and height. She was referred, at the age of three, for evaluation with the pediatrics department because she showed signs of growth deceleration. Investigation for endocrinological causes was normal. (unfortunately, there is no record that upper-to-lower-segment body proportions were measured in these consultations). However, as a patient he continued to move away from the family channel and because he had an alteration in the rib cage (*pectus carinatum*) (Figure 1), was referred to an orthopedist. Signs of bone dysplasia were observed and spondyloepiphyseal dysplasia was hypothesized.



Figure 1. The image illustrates the three patients reported, index case aged ten years, brother (case 2) aged seven years and sister (case 3) aged eight months. It is observed that, up to the first year of age, the third case had no visible clinical manifestations of the disease, while the older siblings had evident bone alterations (keeled chest) (A, B).

With disease progression, the patient evolved with hearing loss, worsening ability to walk, in addition to moderate obstructive respiratory dysfunction, requiring follow-up with a pulmonologist. After two decades of evaluation, the patient was finally referred to the clinical genetics service to investigate suspected bone dysplasia.

His genetic-clinical examination revealed: height 94cm (below the 3rd percentile), weight 21kg (below the 3rd percentile), head circumference 54.8cm at the 50th percentile, infiltrated facies, moderate dextroflexion of the neck, corneal opacity , short nasal dorsum, flat nose, thick lips, reduced and spaced teeth, shortened chest with keeled sternum; bilateral genuvalgus (Figure 2), marked ligament laxity in the hands, grade 3 osteotendinous reflexes (ORT) in the upper and lower limbs.



Figure 2. Patients 1 and 2 aged twenty-six and twenty-three, respectively. Short stature (patient 1 with 94cm and patient 2 with 101cm) associated with bone alterations (bilateral genuvalgus, *pectus carinatum*), and facial (short nasal dorsum, flat nasal root, and thick lips).

As the findings were suggestive of type IVA mucopolysaccharidosis (Morquio A syndrome), diagnostic tests aimed at this suspicion were requested (Table 1).

case 2

JDSJ patient, male, brother of case 1, also born vaginally, at term, with adequate height and weight for his gestational age. He was referred for evaluation because of his short stature and also because of his sister's family history. Again, general biochemical and endocrinological exams were normal, which raised the need for evaluation for signs of bone dysplasia, which were confirmed by radiological exams (again, there is no record that upper segment body proportions were measured in relative to the lower segment in these queries). Diagnosis of spondyloepiphyseal dysplasia was affirmed. Similar to her sister, the patient developed sensorineural and conductive hearing loss, in addition to difficulty walking long distances, requiring a wheelchair.

He was referred for genetic evaluation with his sister. Her genetic-clinical examination revealed: height 101cm (below the 3rd percentile), weight 25kg (below the 10th percentile), head circumference 56.5cm between the 50th and 75th percentiles. in keel (Figure 1), bilateral genuvalgus and hyperactive ROT. Tests for Morquio A syndrome were also requested (Table 1).

case 3

Patient LCS, female, sister of cases 1 and 2, for having a positive family history for Morquio A syndrome, was diagnosed through an enzymatic study performed on amniocytes cultured from an amniocentesis procedure. The patient was also born vaginally, at term, without any complications at birth or any evidence of Morquio A syndrome. After birth, an enzyme assay for MPS IVA was performed on leukocytes extracted from peripheral blood, confirming the prenatal diagnosis previously made. Other tests were also requested according to the patient's evolution (Table 1).

Weight and height growth. However, at one year and eight months, he suffered a fall from the chair with trauma in

Table 1. Findings in complementary exams of the reported cases.

	PATIENT 1	PATIENT two	PATIENT 3
Presence of platyspondyly	+	+	+
C2 odontoid process dysplasia	+		
	+		
	+		
Osteopenic , hypoplastic, and irregular carpal and tarsal bones	+	+	+
Bilateral femoral varus accentuation ; tortuosity of the humerus, radius and ulna	+	+	+
Iliac wing hypoplasia, with irregular contours; shallow and irregularly contoured acetabulum	+	+	+
Thickening of the mitral and aortic valves	+	+	-
Evoked potential of upper and lower limbs	Unrealized	no response at the cranial level	no response at the cranial level
Sensorineural and conductive hearing loss	Moderate to severe grade	Moderate Degree	Moderate Degree
Combined pattern (obstructive and restrictive) ventilatory disorder	accentuated degree	accentuated degree	accentuated degree
Narrowing of the vertebral canal in craniovertebral and cervicothoracic transition areas	+	+	+
corneal pacification _	+	+	+
bilateral cataract	-	+	-
Presence of keratan sulfate in urine	+	+	+
Measurement of glycosaminoglycans in urine			
(NV= 13-45 microg GAGs /mg creatinine).	89	100	120
Enzyme assay of N-acetylgalactosamine-6-sulfatase in leukocytes (VN=0.44-1.89 nanomoles /h/mg prot)	not detectable	0.005	not detectable
Molecular study of the GALNS gene – pathogenic missense mutations in homozygosity: c.901 G>T (p.G301C) in exon 9.	+	+	+

NV = Normal value.

the occipital region. At that time, she was evaluated by the neurosurgical team, and C1C2 arthrodesis was performed with interposition of an iliac graft and ligation with steel wire.

At twelve years of age, he progressed with worsening gait, showing signs of spinal cord compression both clinically and on neuroimaging examination (Figure 3), requiring decompression of the posterior fossa. The patient subsequently presented new compression, after falling from his own height, evolving to quadriplegia and need for tracheostomy for continuous invasive ventilatory support. Patient evolved with disproportionate short stature similarly to siblings.

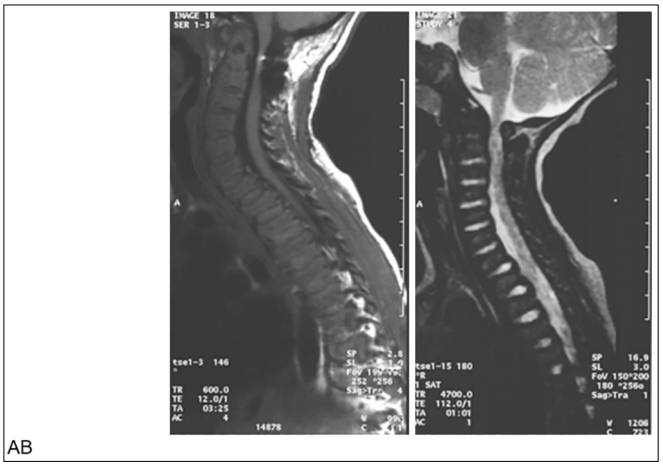


Figure 3. Narrowing of the spinal canal in areas of craniovertebral and cervicothoracic transition with foci of T2 hypersignal compatible with myelopathy in bulbomedullary transition (A, B).

Patients were referred to start enzyme replacement therapy (ERT) with elosulfase- alpha, but they had not started it until the end of this article.

DISCUSSION

Mucopolysaccharidosis type IVA (MPS IVA), also known as Morquio syndrome A (OMIM 253000), is part of a group of genetic-metabolic diseases, characterized by a deficiency of one of the eleven enzymes involved in the degradation of glycosaminoglycans (GAGs). Currently, seven types of mucopolysaccharidosis are known, classified from I to VII. In relation to MPS IVA, there is a deficiency of the enzyme N-acetylgalactosamine-6-sulfatase (GALNS), generating accumulation of two specific GAGs: chondroitin-6-sulfate and keratan sulfate , which are produced especially in cartilage. Therefore, non-degraded substrates are stored mainly in cartilage and its extracellular matrix (ECM), having a direct impact on bone and cartilaginous development[5,6].

It is an autosomal recessive disease, that is, couples heterozygous for mutations in the GALNS gene have a 25% chance of having an affected child. Both sexes are equally affected, and cases of MPS IVA in consanguineous marriages are common[3,7]. Our patients, however, although they were not the result of a consanguineous union, had the same homozygous mutation in the GALNS gene, suggesting the possibility of a kinship not recognized by family members or even a founder gene effect.

Patients with the syndrome are apparently normal at birth and exhibit preserved neuropsychomotor development throughout life. Symptoms begin to manifest from eighteen to twenty-four months of age and consist of a pattern of dysmorphic features that is suggestive but not diagnostic. Among them, skeletal and joint abnormalities (*pectus carinatum*, kyphosis, hyperlordosis, scoliosis, ovoid deformity of the vertebrae, genuvalgus, bilateral flat foot valgus, joint hyperextension), respiratory dysfunction (restrictive and obstructive lung disease), cardiac (valvular regurgitation and stenosis), auditory (conductive to sensorineural hearing loss), visual (corneal opacity), abdominal (hepatomegaly, hernias) and dental abnormalities (prognathism, spaced teeth and reduced enamel)[8].

Worth noting that the presence of stature disproportion is a relevant clue for the pediatrician and endocrinologist in the evaluation of these patients and also a warning sign that it may be a bone dysplasia, allowing a more targeted approach and, therefore, resulting in a diagnosis earlier[8].

Musculoskeletal changes, including growth retardation, gait disturbances and hip pain, are among the first clinical symptoms to manifest and are usually the causes that lead the patient or family to seek medical help[4]. In the reported cases, the complaint of short stature combined with rib cage deformities were the reasons for referral for initial evaluation.

The diagnosis requires the recognition of clinical and radiographic signs combined with laboratory confirmation, which often involves a radiologist, pediatrician and geneticist[4].

Radiological exams, such as X-ray and MRI, can corroborate the diagnostic suspicion. The possible findings to be found in the MPS IVA are described in Table 2.

Table 2. Radiological findings that may be present in patients with MPS IVA.

Skull	macrocephaly Sella turcica: flared, J- or omega-shaped thick cap Premature closure of sutures
Chest	Oar-shaped ribs Small, high-placed scapulae hypoplastic glenoid fossa Small, thick collarbones
Column	Platyspondyly dorso-lumbar kyphosis Hypoplasia of the anterosuperior portion of the vertebrae Projectile-shaped, ovoid and rectangular vertebrae
pelvis	Hypoplastic and irregular acetabular teats Thick small iliac wings Thick ischium and pubis
members	Ax-shaped proximal humerus Curved ulna and humerus Convergent distal epiphyses of radius and ulna Small and irregular carpal bones Short, thick phalanges

Source: Adapted from Lachman et al. (2014)[4].

Based on clinical suspicion, the patient should be referred for laboratory diagnostic tests with the determination of levels of GAGs in urine samples (which are usually elevated in MPS IV A, but not in all patients) and identification of the type of GAG through chromatography or electrophoresis (in this case, keratan sulfate)[9].

Morquio 's syndrome is confirmed. A[9].

Currently, the intrauterine diagnosis of MPS IVA is possible, which consists of the analysis of enzyme deficiency in the amniotic fluid or chorionic villus sampling. However, this research is reserved for pregnant women with a family history of MPS and/or gestational signs that suggest the disease, such as non-immune fetal hydrops[9]. In the case of patient 3, prenatal diagnosis was indicated, considering the family history of two brothers affected by Morquio A syndrome.

As it is a genetic disease, MPS IVA is not a pathology that can be cured, however, the treatment aims to prevent the progression of the disease and offer a better quality of life to patients[10]. Currently available treatments are hematopoietic stem cell transplantation (HSCT) and, more recently, enzyme replacement therapy (ERT)[11]. HSCT has been less indicated for Morquio A syndrome due to the high morbidity and mortality of this procedure[11].

The recent approval of ERT for MPS IVA (Vimizim®, elosulfase alfa) represented a significant advance for patients. Clinical studies have shown improvement in the respiratory capacity of patients, in the *hardness* and stability of cardiac lesions. Obviously, the impact on patients' growth now depends on early diagnosis, as bone changes in this disease begin in the first years of life[12].

In addition, due to the various disabling comorbidities that may arise with the evolution of the disease, a multidisciplinary approach is essential, covering physical therapy, occupational therapy, pulmonology, rheumatology, cardiology and orthopedics, according to the individual's needs[3,12].

Pediatricians and endocrinologists especially pay attention to the initial alterations presented by patients with growth deficits should not be restricted only to environmental/nutritional causes or hormone deficiency[12]. Knowledge of genetic causes of short stature due to changes in bone development is essential for clinical suspicion of this group of diseases to arise when the earliest signs appear, and not just when symptoms typically associated with the classic phenotype appear, ensuring, thus, an accurate diagnosis and that reverts to therapeutic benefit for these patients.

What this case teaches:

• In the investigation of short stature in children, it is necessary for the pediatrician to remember the group of bone dysplasias in their differential diagnosis.

• Among the different bone dysplasias that occur with short stature, Morquio syndrome A constitutes a peculiar group in which bone alterations become evident only at 2-3 years of age.

• In view of the possibility of recombinant enzyme therapy, early diagnosi

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