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Corrections of diverse forms of lower limb deformities in patients with mucopolysaccharidosis type IVA (Morquio syndrome)

Ali Al Kaissi[1,2], Vladimir Kenis[3], Eugeniy Melchenko[3], Maher Ben Ghachem[4], Robert Csepan[2], Franz Grill[2], Rudolf Ganger[2]

ABSTRACT

Background: Thoracolumbar kyphosis has been considered as the first presenting deformity and is often a key diagnostic clue noted in children with mucopolysaccharidosis (MPS) type IV (Morquio's syndrome). However, we observed that the progressive irregularities of the epiphyses of the long bones were the most prominent skeletal pathology, causing effectively the development of diverse forms of lower limbs deformities with extreme variation in age of onset. **Materials and Methods:** Ten patients (seven children and three adults) with an average age of 15 years have been enrolled in this study. Age of diagnosis of MPS IVA has a variable age of onset and a MISLEADING rate of severity. Hip dislocations, genu valgum, protrusio acetabuli and osteoarthritis were the most common lower limbs deformities in these patients. Clinical and radiographic phenotypes were the baseline tools of documentation. Urinary screening and genotypic characterizations have been applied accordingly. **Results:** Combined pelvic and femoral procedures for hip dislocation, epiphysiodeses and supracondylar osteotomy for genu valgum and hip arthroplasty for protrusio acetabuli have been performed. All patients manifested insufficient activity of *N*-acetylgalactosamine-6-sulphate sulphatase, an enzyme that degrades keratin sulphate and chondroitin-6 sulphate. **Conclusion:** The extensive clinical heterogeneity contributed significantly in the delay in establishing the diagnosis particularly in adult patients with MPS IV. The epiphyseal irregularities of the long bones and the progressive flattening pathology of MPS IV A were the reason to falsely diagnose some patients as spondyloepiphyseal dysplasia congenital and/or tarda. Proximal femoral osteotomy, realignment osteotomy and total hip arthroplasty have been performed for coxa vara, genu valgum and protrusio acetabuli, respectively, in children and adult group of patients. The importance of early diagnosis on MPS IV A is to receive enzyme replacement therapy and plan for other therapeutic measures.

Key words: Insufficient activity of *N*-acetylgalactosamine-6-sulphate sulphatase enzyme, mucopolysaccharidosis type IV A, realignment, reconstruction

INTRODUCTION

The mucopolysaccharidoses (MPS) are a lysosomal storage disorder caused by defects in glycosaminoglycan (GAG) catabolism and are classified under the dysostosis multiplex group of skeletal dysplasias.[1] Morquio[2] and Brailsford[3] described the entity, now known to result

[1]First Medical Department, Ludwig Boltzmann Institute of Osteology, The Hanusch Hospital of WGKK and AUVA Trauma Centre Meidling, Hanusch Hospital, Vienna, Austria, [2]Department of Paediatric, Orthopaedic Hospital of Speising, Vienna, Austria, [3]Department of Foot and Ankle Surgery, Pediatric Orthopedic Institute n.a. H. Turner, Neuroorthopaedics and Systemic Disorders, Pushkin, Saint Petersburg, Russia, [4]Department of Paediatric Orthopaedic Surgery, Children Hospital, Tunis, Tunisia

Address for correspondence:
Dr. Ali Al Kaissi, First Medical Department, Ludwig Boltzmann Institute of Osteology, The Hanusch Hospital of WGKK and AUVA Trauma Centre Meidling, Heinrich Collin Street 30, 1140 Vienna, Austria Orthopaedic Hospital of Speising, Paediatric Department, Speisinger Street 109, 1130 Vienna, Austria.
E-mail: ali.alkaissi@oss.at

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from a deficiency of galactosamine-6-sulphatase.[1] Notable features included osseous dystrophy, corneal clouding, aortic valve disease and urinary excretion of keratosulphate.[2,3]

Morquio's syndrome is an autosomal recessive dysplasia caused by a deficiency in the enzyme *N*-acetylgalagtosamine-6-sulphate sulphatase (GALNS gene), which is essential for the degradation of keratan sulphate and chondroitin-6-sulphate on chromosome 16q24.

The intracellular degradation of micromolecular compounds by lysosomal enzymes is abnormal in this group of diseases, leading to intracellular accumulation of semidegraded compounds. The GAGs heparan sulphate, dermatan sulphate and keratan sulphate are the mucopolysaccharides that accumulate and are excreted by the urine. Biochemical analysis of the urine can lead to the diagnosis of specific MPS. Identification of the MPS is also possible through the skin fibroblast culture.[4,5] Morquio's syndrome is a multisystem disease that manifests clinically as a disproportionate dwarfing dysplasia and hypermobility of the joints. The disease usually becomes detectable between the 1st and 3rd year of life with remarkable clinical heterogeneity.[6] Skeletal abnormalities are common initial presenting symptom, though patients with slowly progressing disease and non-classic phenotypes can be particularly challenging to diagnose.[7] The recent emergence of specific therapies for some of the MPS disorders has brought to the forefront the importance of early diagnosis.[8,9] This paper describes the diversity of the lower limb deformities that can manifest itself in the course of the disease. Early recognition is the corner stone for proper management and the treatment plan accounts heavily on definite diagnosis.

MATERIALS AND METHODS

In this study, 10 patients have been enrolled. (Seven children and three adults with average age of 15 years.) Age of diagnosis of MPS IVA has a variable age of onset and a MISLEADING rate of severity. Signed consents were obtained from the guardians. The study protocol was approved by the Medical University of Vienna (Ethics Committee, EK Nr. 921/2009). Patients were of different ethnic origins. Patients with MPS IV usually appear normal at birth but they exhibited growth failure and features akin to spondyloepiphyseal dysplasia, especially in their first 2 years of life. Incorrect diagnoses resulted from a number of factors including the incorrect interpretations of radiographs, lack of disease awareness, broad spectrum of the clinical phenotype because of clinical heterogeneity, phenotypic overlap with other disorders and limitations of urinary GAG screening. In the classic forms of MPS IV, patients usually become symptomatic between 3 and 6 years of age. Generalized joint laxity (a unique feature mostly caused by progressive metaphyseal dysplasia with simultaneous degradation of connective tissues near the joints) was a feature in the paediatric group of patients, making it distinctly different from the other types of MPSs. Cervical spinal cord disorders have the priority for assessment via lateral flexion-extension radiographs. Translation of the anterior arch of C1 or splaying of the posterior elements with flexion indicates instability. In addition, GAG accumulation behind the odontoid process may result in progressive stenosis and spinal cord compression at the occipitocervical junction. Therefore, computed tomography scans were obtained in flexion and extension to delineate instability and spinal cord compression. Our strategy is to perform magnetic resonance imaging (MRI) of the cervical spine on annual basis; also MRI evaluation of the thoracic-lumbar spine was performed in patients manifested gibbus deformity. Two male patients underwent cervical spine fusion and decompression. The rest of the patients received regular MRI, and no prophylactic surgical operations have been performed. Electrocardiogram showed one girl with sinus arrhythmia and Doppler echocardiography revealed one boy with valvular heart disease and another adult male with thickened interventricular septum. (This is highly likely because of the progressive nature of MPS IV.) Conductive hearing loss has been encountered in two boys. (Both had a history of recurrent respiratory tract infections and secretory otitis media.) One girl and another adult patient showed mixed hearing loss (combination of secretory otitis media and sensorineural hearing loss). All our patients manifested insufficient activity of GALNS gene.

In accordance with the clinical presentations, we divided our patients into three main categories:

a. Hip dysplasia/dislocation,
b. Genu valgum and
c. Protrusio acetabuli.

Hip dysplasia/dislocation

Three male children with average age of 5 years developed noticeable limping and waddling gait. The waddling gait was associated with frequent falls. Duchene muscular dystrophy was suspected and these children underwent a series of neuromuscular investigations that were proved normal. Pain was an additional complaint and at this stage, they

were referred to the Rheumatology Department. No abnormal rheumatologic parameters were detected. Finally, they were referred to our department. Clinical examination showed short stature mostly because of short trunk (−2 standard deviation). Craniofacially, they did not manifest any profound facial dysmorphic features, apart from wide frontal areas and depressed nasal bridges. Thoracolumbar kyphosis and a pigeon chest associated with pectus carinatum were the most prominent features and the necks were short. The hips were flexed in a crouched position and the heads were thrust forward. The constellation of these abnormalities resulted in the development of a waddling gait. The radiographic features were distinctive. The vertebral bodies in the thoracic and the lumbar spine were platyspondylic. A central tongue/anterior beaking associated with narrow discs was evident. Irregular ossification of the epiphyses was generalized. The acetabuli were poorly developed in these patients and showed underdevelopment of the medial portion of the proximal femoral epiphyses thereby effectively causing the development of coxa valga. Defective ossification of the lateral acetabular corner, leaving a significant cartilaginous anlage was confirmed by the arthrogram images [Figure 1]. These pathological changes resulted in progressive hip instability and dislocation [Figure 2].

Genu valgum

The lower limbs malalignment is evaluated via anteroposterior standing radiograph, and the lateral distal femoral angle, the medial proximal tibial angle (MPTA) and the measurements of the mechanical axis deviation (MAD) were determined. Five patients manifested typical valgus deformity of the tibia and they manifested MPTA > 90° [Figure 3]. Four children (three males and one female) were referred because of progressive genu valgum.

Protrusio acetabuli

Three adult patients (two females and one male; aged 15-17 years) developed protrusio acetabuli. Prolonged protrusio acetabuli resulted in secondary osteoarthritic changes in the hip joint. Radiographic criteria for protrusio acetabuli included an abnormally positioned acetabular line, a centre-edge angle of Wiberg >40° and the crossing of the teardrop by the ilio-ischial line (arrow) [Figure 4].

SURGICAL INTERVENTIONS AND RESULTS

Hip dislocation

Surgery for hip subluxation and dislocation was carried out in four patients (six joints). The age at the time of surgery ranged from 6 to 7 years. Combined pelvic and femoral procedure was done in three patients (five joints) and isolated pelvic correction in one patient. Pelvic procedures included Salter innominate osteotomy (four joints) and triple osteotomy (two joints). Femoral procedure considered shortening, derotation and varus. Restoration of angular relations and coverage of the femoral head (Wiberg angle >20°) were achieved in all cases. Improvement in ossification pattern of the femoral head noticed in two cases was attributed as a consequence of improved containment [Figure 5a and b].

Genu valgum

Surgical management for genu valgum was carried out in three children (five legs, four — primary, one — secondary for recurrent deformity after primary surgery in another clinic).

In one of the patients who manifested bilateral and symmetrical genu valgum, excellent results were achieved via successful correction of the deformity

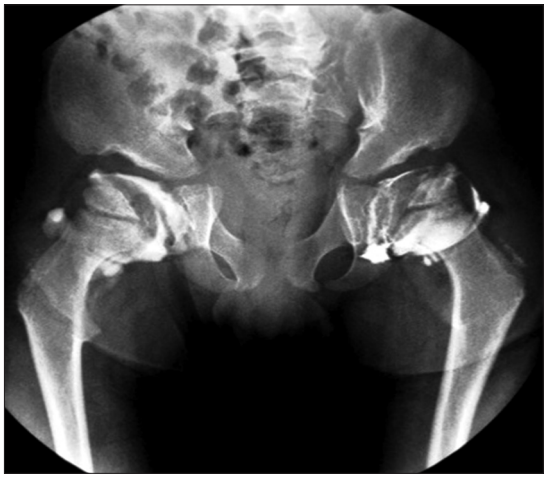

Figure 1: Pelvis arthrogram showed defective ossification of the lateral acetabular corner, leaving a significant cartilaginous anlage

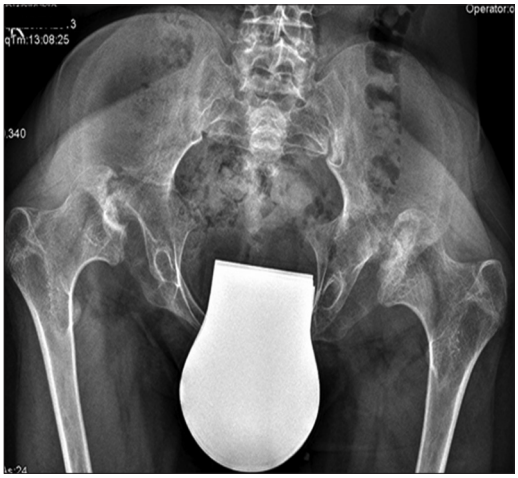

Figure 2: AP pelvis radiograph showed the acetabulo-femoral pathological changes which resulted in progressive hip instability and dislocation

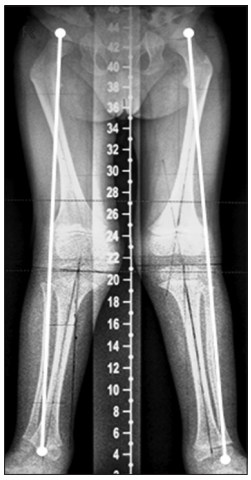

Figure 3: Anteroposterior standing radiograph, and the lateral distal femoral angle (LDFA) and the medial proximal tibial angle (MPTA) and the measurements of the mechanical axis deviation were determined. Five patients manifested typical valgus deformity of the tibia and they manifested MPTA>90

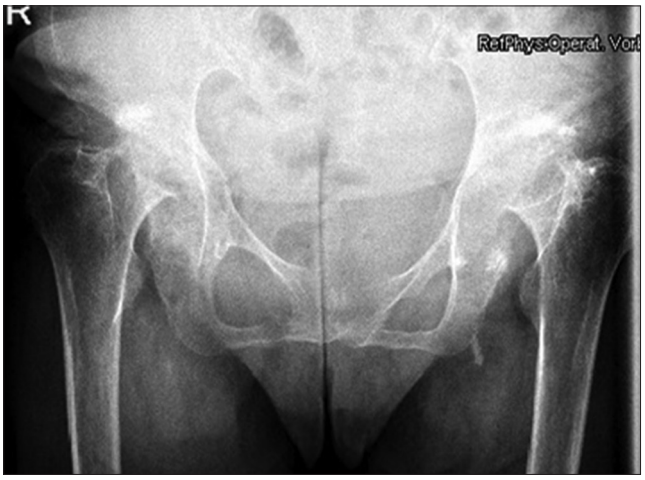

Figure 4: Radiographic criteria for protrusio acetabuli included an abnormally positioned acetabular line, a center-edge angle of Wiberg of >40°, and the crossing of the teardrop by the ilio-ischial line (arrow)

after 18 months of epiphysiodesis being impelmented. Medial axis deviation (MAD) shifted from zone 3 to the 0 point, demonstrating improvement in knee loading pattern [Figure 3]. Secondary improvement of hip joint parameters (increase of acetabular coverage and decrease of pelvic anterior tilting) reflects optimization of general biomechanics of the lower limbs after correction of genu valgum.

In the second case of bilateral asymmetrical genu valgum in a 10-year-old girl, the final result of correction was unsatisfactory because of progressive paraparesis due to spinal stenosis. Progressive flexion contractures of the knee joints led to inappropriate position of the loading axis. Muscle weakness developed as a consequence of medullary compression has led to loss in walking ability.

The third case was a 10-year-old boy with bilateral genu valgum operated in another clinic by corrective supracondylar osteotomy. The correction recurred on the left side after a period of 1 year postoperatively. Clinical and radiological examination revealed patellar dislocation on the left side. Single-stage combined procedure (supracondylar corrective osteotomy with fixation by locking plate accomplished by patellar realignment) was performed in our clinic [Figure 6].

Hip arthroplasty

We considered hip arthroplasty as a salvage procedure in the cases of severe osteoarthritis accompanied by pain, severe contractures and stiffness as well as acetabular protrusion. The procedure is challenging and technically demanding because of poor bone quality and severe residual deformity of both femoral and pelvic components. Total cementless arthroplasty was the method of choice. Early physical therapy and gradual weight bearing after surgery are crucial for functional restoration [Figure 7].

DISCUSSION

The MPSs constitute the largest group of lysosomal storage diseases and considered heterogeneous disorders, and patients present with a wide spectrum of clinical manifestations. Most MPS patients appear normal at birth, but patients with severe phenotypes typically develop clinical signs and symptoms before the age of 2-4 years and die before the age of 10 years. Patients with severe forms of MPS I, II and VII, and all MPS III patients[1] will also develop cognitive impairment. Patients with an attenuated phenotype can develop all of the somatic signs and symptoms seen in the severe phenotype, but never develop cognitive impairment. The onset of somatic symptoms is generally later and the disease progression is slower. Such patients may live well into adulthood. While the cognitive involvement is the hallmark of the severe phenotype in MPS I, II, III and VII, it is often difficult to determine whether or not a patient is experiencing cognitive decline until an age at which somatic disease is well established. Young patients with MPS may thus have an indeterminate phenotype. Growth in MPS can be difficult to predict, and, as such, criteria for intervention cannot necessarily follow those of normal children. Experience with hip surgery has shown osteotomies heal well in children with MPS.[1-3,7,10]

Morquio's disease (MPS type IV) is an inherited connective tissue disorder caused by the absence or

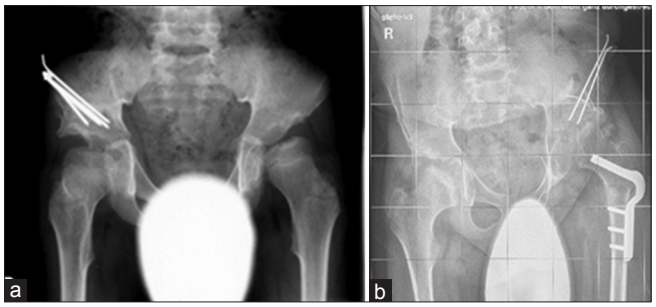

Figure 5: (a) The age at the time of surgery was from 6 to 7 years. Combined pelvic and femoral procedure was done in 3 patients (5 joints) and isolated pelvic correction – in 1 patient. Pelvic procedures included Salter innominate osteotomy (4 joints) and triple osteotomy (2 joints). Femoral procedure considered shortening, derotation and varus. Restoration of angular relations and coverage of the femoral head (Wiberg angle more than 20 degrees) achieved in all cases. Improvement in ossification pattern of the femoral head noticed in 2 cases was attributed as a consequence of improved containment (b)

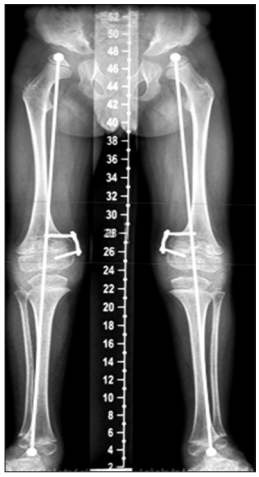

Figure 6: Single-stage combined procedure (supracondylar corrective osteotomy with fixation by locking plate accomplished by patellar realignment) was performed in our clinic

reduction in activity usually of one of two ubiquitous lysosomal hydrolases, *N*-acetylgalactosamine-6-sulphatase (MPS type IV A) and B-galactosidase (MPS type IV B). It manifests clinically as a disproportionate dwarfing dysplasia with hypermobility of the joints due to laxity of restraining ligaments and numerous other features. Cardiac defects and spinal cord compression are major causes of disability and death. Spinal cord compression in the thoracolumbar and sometimes also in cervicothoracic regions is due to kyphosis and narrowing of the spinal canal, and is usually less severe at the thoracolumbar and cervicothoracic regions than at the craniovertebral junction where localized soft tissue thickening is the dominant compressing agent. The delayed ossification of the odontoid process is one of the reasons behind C1-2 instability plus the defective ligamentous connections (ligamentous instability). The persistence of the cartilaginous anlage has a great affinity to repetitive trauma and possibly fractures might ensue. Spinal cord injury has resulted from the two existing abnormalities in patients with MPS IV A (the atlantoaxial instability and the cartilage/fibrocartilage reactive hypertrophy around the odontoid process).[11]

Axial and appendicular deformities in patients with MPS IV A are extremely a common complication. The severity of the deformities varies among patients, who manifest the same genetic pathology. Involvement of the cervical spine was the least among our group of patients. Thoracolumbar kyphosis was evident in 4 patients out of 10. The skeletal appendicular involvement was the most common complication of the disease.[11-15]

Hip dysplasia is common in patients with Morquio disease. Both femoral and pelvic components are usually involved. Acetabular dysplasia characterized radiologically by increased acetabular index should be interpreted carefully because of delayed ossification of the lateral aspect of the acetabulum. Arthrography and MRI are helpful in the assessment of the true condition. Femoral anatomy is also characterized by delayed ossification of the epiphysis as well as coxa valga. Thus, both femoral and acetabular component demonstrate features, characteristics for progressive hip dysplasia (subluxation leading to dislocation). Femoral head collapse and protrusio acetabuli develop later thereby leading to severe incongruence.[16]

As far as surgical management of hip dislocation is challenging in terms of technical difficulties and long-term results, progressive subluxation should be considered as the most preferable stage for surgical correction. Combined femoral and pelvic procedure is the preferred method.[16-19]

Progressive genu valgum develops in most of the patients with Morquio disease. Compromised ossification of metaphyseal region leading to static deformity is the most possible reason for the development of particular deformity. Soft tissue retraction (fascia lata) is also a potential reason for valgus deformity. In severe cases, patellar subluxation and dislocation occurs later and worsens the condition. Deformities accompanied by significant MAD to third zone of valgus should be corrected surgically. Guided growth is an effective tool for correction of mild and moderate deformities. Because of relatively slow growth, the average rate of correction is about 1° per month of epiphysiodesis. Thus, the expected amount of correction is not more than 30° because of recommended limitation of temporary epiphysiodesis by 2-2.5 years. In more severe cases, corrective osteotomy

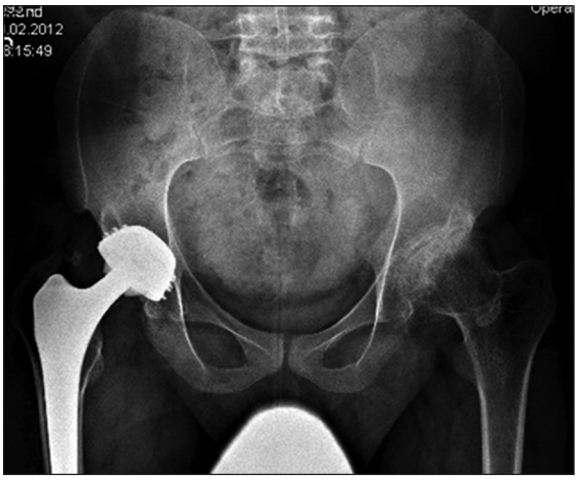

Figure 7: Total cementless arthroplasty was the method of choice. Early physical therapy and gradual weightbearing after surgery are crucial for functional restoration

should be the preferred procedure. If valgus deformity is accompanied by patellar instability, the latter should be improved simultaneously.[20]

Protrusio acetabuli is clinically characterized by hip/joint stiffness and pain, associated radiologically by narrowing of the acetabular teardrop sign reflecting diminished thickness of pelvic bone. Steel has described surgical closure of the triradiate cartilage in skeletally immature patients who were symptomatic or in whom increasing acetabular deeping was demonstrated radiologically.[21] Höhle discovered protrusio acetabuli in two of his patients who had arachnodactyly, keel breast, ectopia lentis and a familial incidence of protrusio acetabuli.[22] Nevertheless, he stated that the aetiology and pathogenesis of idiopathic protrusio acetabuli is not yet explained in all aspects. Later on, Steel reported seven cases of protrusio acetabuli, five of which were in patients who had all of the clinical manifestations of Marfan's syndrome. Do *et al*. reported that the occurrence of protrusio acetabuli in patients with Marfan's syndrome is correlated to disturbed bone mineral density and that it is as high as 31%.

Prolonged protrusio acetabuli may result in secondary osteoarthritic changes in the hip joint.[23] In the 1980s, treatment of MPS with bone marrow transplantation/hematopoietic stem cells transplantation was proposed and in the 1990s, and enzyme replacement therapy (ERT) began to develop and was approved for clinical use in MPS I, II and VI in the first decade of the 21st century. Giugliani *et al.* suggested that a better future for patients affected by MPS depends upon identifying, understanding and appropriately managing the multisystemic manifestations of these diseases.[10]

Recently, Vimizim™ (elosulfase alfa), developed by BioMarin Pharmaceutical Inc. (San Rafael, CA, USA), is the ERT for individuals with MPS IV A (Morquio A syndrome.) Vimizim improved endurance in clinical trials and is administered weekly via intravenous infusion. Preliminary studies are promising and indicate that Vimizim™ candidate binds naturally to bone matrix and can adequately reach the growth cartilage after IV infusion.[15]

SUMMARY

This study is based on 10 patients (seven children and three adults). The variablility of age of onset and the diversity of clinical manifestations was a noticeable feature in our group of patients. Patients were of different ethnic origins. Patients with MPS IV usually appear normal at birth but they exhibited growth failure and features akin to spondyloepiphyseal dysplasia, especially in their first 2 years of life. Our baseline tools of diagnosis are the clinical and radiographic phenotypes and a structured family history questionnaire.

Classically, MPS IV manifests clinically as a disproportionate dwarfism with generalized ligamentous hyper laxity associated with variable clinical deformities. However, the diversity and the wide range of the clinical presentation is a confusing element in detecting the disorder at an early age. The severity of skeletal involvement can be diverse among and within the same group of MPS IV because of the extensive clinical heterogeneity. Due to the misconception in reading the clinical and radiographic phenotypic characterizations in a remarkable number of patients, misdiagnoses were the results. Spondyloepiphyseal dysplasia congenita and tarda were the most common applied terms.

The necessity of early and definite diagnosis in MPS IV is a fundamental tool for maximizing the potential usefulness of implementing specific enzyme therapy to improve and prevent the dreadful outcome of this disorder.

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Conflicts of interest

There are no conflicts of interest.

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