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SCIENTIFIC ARTICLE

Clinical and radiological findings in Brazilian patients with mucolipidosis types II/III

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Abstract

Objective The present study aims to provide orientation for clinicians and radiologists to recognize the most prevalent findings leading to diagnosis in mucolipidosis from a description of the natural history of five Brazilian cases.

Materials and methods We conducted an observational and retrospective study of five patients with clinical and radiological diagnosis of mucolipidosis. Clinical evaluation consisted of information obtained from records and including physical, neurologic, and dysmorphic evaluations. Radiologic studies consisted of complete skeletal radiographs of all patients. Enzyme assessment was performed for confirmation of the diagnosis.

Results The five patients were referred for genetic evaluation due to disproportionate short stature with short trunk accompanied by waddling gait. Age at referral varied from 11 months to 28 years. The most prevalent findings were joint restriction (4/5 patients), neuropsychomotor developmental delay (3/5), coarse facies (2/5), hypertrophic cardiomyopathy (2/5), and mental retardation (1/4 patients). The most common radiological findings were anterior beaking of the vertebral bodies (5/5), shallow acetabular fossae (5/5), epiphyseal dysplasia (5/5), platyspondyly (4/5), pelvic dysplasia (4/5), decreased bone mineralization (4/5), scoliosis (3/5), wide and oar-shaped ribs (3/5), generalized epiphyseal ossification delay (3/5), and hypoplasia of basilar portions of ilea (3/5). Enzyme assessment showed α-iduronidase, α-mannosidase, β-glucuronidase, hexosaminidase A, and total hexosaminidase increased in plasma and normal glycosaminoglycans concentration. One patient was clinically classified as ML II and four patients as ML III.

Conclusions The follow-up of five patients showed the typical clinical and radiological findings allowing the diagnosis, thus improving clinical management and providing adequate genetic counseling. Clinicians and radiologists can take advantage of the information from this work, enhancing their differential diagnosis ability.

Keywords Lysosomal storage disease · Mucolipidosis II · Mucolipidosis III · I-cell disease · Skeletal dysplasia · Dysostosis multiplex

Introduction

Lysosomal storage disorders (LSD) are a group of nearly 60 inherited metabolic diseases with organelle dysfunction causing pleiotropic functional impairment. When considered together, the frequency is nearly 1:7700 live births [1]. Within LSD, different forms of mucolipidosis (ML) are included, with an estimate prevalence of 0.16–0.8:100,000 live births for ML II and 0.08–1.89:100,000 live births for ML III [1]. ML are caused by defective trafficking of lysosomal hydrolases, divided in three subtypes according to the clinical presentation, although there is clinical and radiological overlap between these entities: ML II alpha/beta, ML III alpha/beta, and ML III gamma [2]. Moreover, there is clinical and radiologic overlap between the mucolipidoses, the mucopolysaccharidoses (MPS), and sphingolipidoses [3].

Mucolipidosis II

ML II alpha/beta, known as I-cell disease, is a progressive inborn metabolic disease with onset at birth [4]. Clinical

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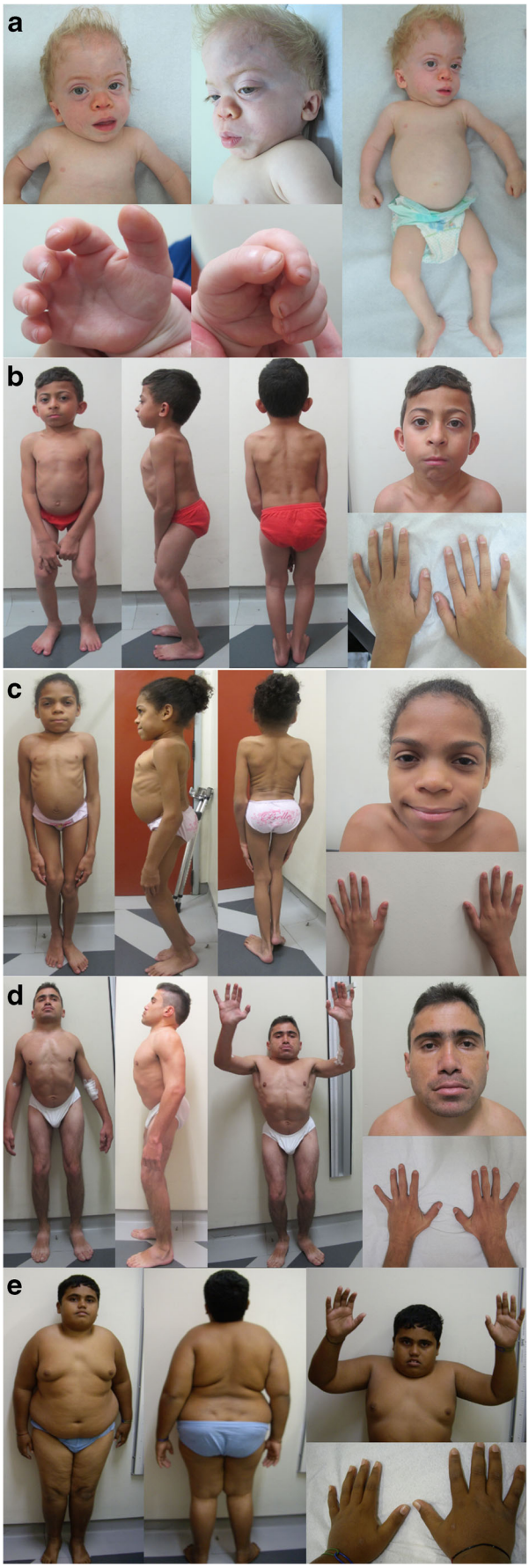

◀ **Fig. 1** Clinical findings of patients the five patients with ML. Patient **a** is affected by ML II. Patients **b** to **e** are affected by ML III; **a** 2-year-old male ML II patient (P1) showing premature graying of hair and coarse facies; **b** 9-year-old male ML III patient (P2) with evident trunk shortening and normal facies; **c** 12-year-old female ML III (P3) patient with evident trunk shortening; **d** 25-year-old male ML III patient (P4) with trunk shortening and joint mobility restriction; **e** 12-year-old male ML III patient (P5) with obesity, joint mobility restriction, and scoliosis

findings of ML II encompass short stature, gingival enlargement, hypertrophic cardiomyopathy, and facial dysmorphism reminiscent of MPS I, without mucopolysaccharidiuria. Patients are small for gestational age, hypotonic, and with dislocated hips. In infancy, there are recurrent upper respiratory tract infections, failure to thrive, and motor delay. Joint mobility restriction, thoracolumbar kyphosis, and pes valgus are also common findings [5].

Radiological findings in ML II in early infancy are compatible with dysostosis multiplex and commonly patients present hypomineralization, classic metaphyseal fraying, periosteal cloaking, diaphyseal expansion of the long tubular bones, short anteroposterior diameter of the vertebral bodies with anterosuperior hypoplasia of the upper lumbar bodies, pelvic dysplasia, and punctate calcifications with stippled epiphyses [6]. Premature synostoses of skull sutures have been reported [5]. In later infancy and early childhood, there is conversion to more typical dysostosis multiplex changes. The vertebral bodies show short anteroposterior diameter, biconvex upper and lower endplates, and concavity of the anterior aspects, with hook-shaped configuration at the thoracolumbar junction area, pelvic dysplasia, hypoplasia of the basilar portions of the ilia wings, distorted pubic and ischial bones, coxa valga, shortening and gross undermodeling submetaphyseal overconstriction, epiphyseal dysplasia of the tubular bones, shortening and diaphyseal expansion of the short tubular bones with gross retardation of the carpotarsal and epiphyseal ossification [6, 7]. The spine shows short anteroposterior diameter, biconvex upper and lower endplates and concavity of the anterior aspects of the vertebral bodies, with a hook-shaped configuration at the thoracolumbar junction. The pelvis is dysplastic and hypoplasic, most prominently in the basilar portions of the ilia, with marked flare of the iliac wings, distorted pubic and ischial bones, and coxa valga [6].

Mucolipidosis III

Maroteaux and Lamy [8] reported the first case of ML III as pseudo-Hurler polydystrophy syndrome. These patients showed mild mental retardation, early restriction of joint mobility, dysostosis multiplex, and normal mucopolysaccharidiuria. Indeed, ML patients show similar

Table 1 Clinical findings in patients with mucolipidosis II and III

Case register	P1	P2	P3	P4	P5	Total
Current age	5 years	11 years	18 years	35 years	22 years	Mean, 18 years Median, 18 years
Clinical - radiological diagnosis	ML II	ML III	ML III	ML III	ML III	ML II, 1/5 ML III, 4/5
Gender	Male	Male	Female	Male	Male	4/5, M 1/5, F
Onset of symptoms	11 months	4 years	3 years	4 years	4 years	Mean, 3.2 years Median, 4 years
Glycosaminoglycans chromatography (urine)	H/D	Normal	H/D	Normal	H	H = 1/5 H/D = 2/5
Glycosaminoglycans concentration (urine)	123 (133–274)	90 (26–97)	77 (26–97)	35.4 (13–45)	79 (26–97)	Normal 5/5
Enzyme activity α-iduronidase α-mannosidase β-glicuronidase hexosaminidase A Total hexosaminidase	Elevated	Elevated	Elevated	Elevated	Elevated	Elevated 5/5
Weight (kg) Z-score[a]	7.3	18.5	27.7	50.5	84.4	
Height (cm)/ (Z-score)[a]	69 (− 7.24)	110 (− 4.07)	131 (− 4.92)	141.5 (− 4.34)	151.1 (− 3.31)	Short stature 5/5
Motor delay	+	+	–	+	–	3/5
Mental retardation	NA	+	–	–	–	1/4
Premature lightening hair	+	–	–	–	–	1/5
Coarse face	+	–	+	–	–	2/5
Corneal clouding	+	–	–	–	–	1/5
Wadding gait	NA	+	+	+	+	4/4
Joint stiffness	–	+	+	+	+	4/5
Cardiomyopathy	–	+	+	–	–	2/5
Valvular insufficiency	+	–	+	+	–	3/5
Ventricular dilatation	–	–	–	–	+	1/5

M male, *F* female, *NA* not applicable, *H* heparan sulfate, *D* dermatan sulfate

[a] According to the last clinical evaluation at the Genetics Unit

clinical features of the mild forms of MPS I and VI, but milder and later onset of symptoms when compared to ML II [5].

The radiological aspects of ML III present a later course of dysostosis multiplex, when compared to ML II. The findings include mildly flattened vertebral bodies with irregular upper and lower endplates and accentuated dorsal scalloping, hypoplasia of the thoracic vertebral bodies and anterior hypoplasia, irregular narrowing of the intervertebral spaces, oar-shaped ribs, also wider then habitual, pelvic dysplasia, hypoplastic iliac bones, iliac flare, shallow acetabula, epiphyseal dysplasia of the proximal femora, coxa valga. The tubular bones show mild undertubulation and shortening [6]. Early craniosynostosis has been described [7].

The present study aims to provide orientation for radiologists to recognize the aspects of ML so that they can suggest appropriate genetic studies to the clinicians, from a description of the natural history of five Brazilian cases.

Material and methods

We performed an observational and retrospective study of five patients with clinical and radiological diagnosis of ML from 1994 to 2017. All patients attended the genetic ambulatory of the Genetics Unit.

Clinical evaluation was performed annually when possible and consisted of: assessment of prenatal and birth information obtained from records, review of the family history, anthropometric, neurologic and dysmorphic evaluations. Radiologic studies consisted of complete body radiographs of all patients. Biochemical enzyme assessment was performed using glycosaminoglycans chromatography and glycosaminoglycans concentration in urine and plasmatic evaluation of enzymatic activity of α-iduronidase, α-mannosidase, β-glucuronidase, hexosaminidase A, and total hexosaminidase.

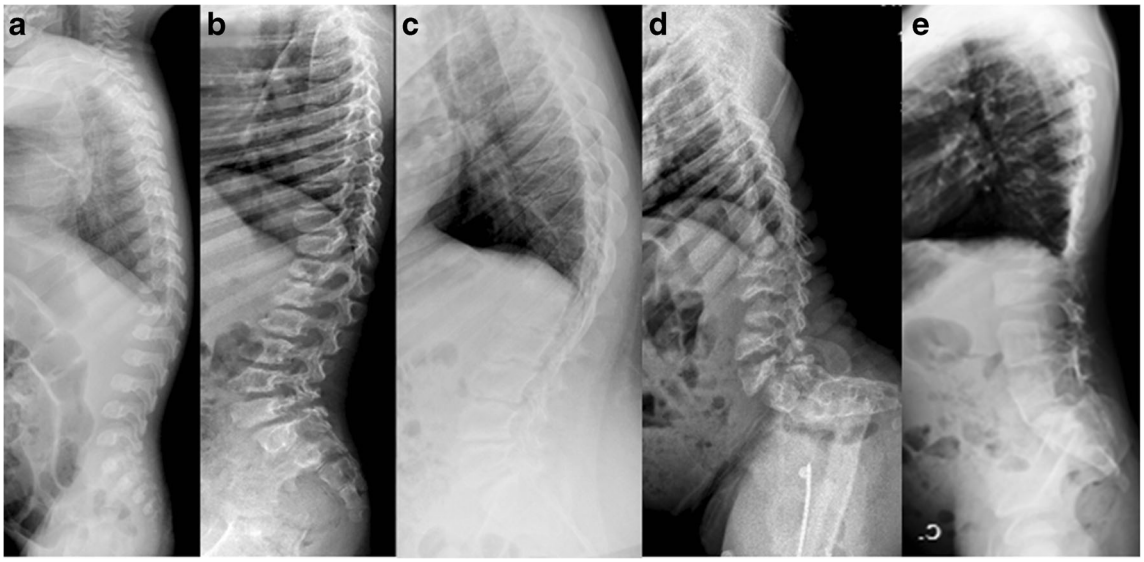

Fig. 2 Profile view of the spine radiographs of the five ML patients. Patient **a** is affected by ML II and patients **b** to **e** are affected by ML III; **a** 11-month-old male ML II patient (P1) showing dorsolumbar kyphosis, short anteroposterior diameter of the vertebral bodies with mild anterosuperior hypoplasia of the upper lumbar bodies more evident in T12; **b** 9-year-old male ML III patient (P2) showing short anteroposterior diameter of the vertebral bodies with mild anterosuperior hypoplasia of the upper lumbar bodies more evident in T11-T12, with endplate irregularities; **c** 17-year-old female ML III patient (P3) showing dorsolumbar kyphosis, short anteroposterior diameter of the vertebral bodies with mild anterosuperior hypoplasia of the upper lumbar bodies more evident in T12 with endplate irregularities from L1-L5; **d** 33-year-old male ML III patient (P4) showing kyphosis, platyspondyly, short anteroposterior diameter of C1, C1-C2, and C2-C3 with anterior wedging and lack of fusion from odontoid process and axis; **e** 18-year-old male ML III patient (P5) showing dorsolumbar kyphosis, endplate irregularities, and short anteroposterior diameter of the vertebral bodies with mild anterosuperior hypoplasia of the upper lumbar bodies

Results

Clinical aspects

First evaluation and current age of the patients: The five patients were referred for genetic evaluation due to disproportionate short stature with short trunk with waddling gait, with onset from 1 to 4 years (median 3.5 years; mean 3 years). Age at the genetic referral varied from 11 months to 28 years (median 15 years; mean 16 years). None of the patients had a history of consanguinity.

Neurologic and motor development: neuropsychomotor developmental delay was present in 3/5 patients. One patient had mild mental retardation.

Dysmorphic features: 2/5 patients presented coarse facies, 1/5 presented premature graying of hair, none had gingival hyperplasia, none had tongue thickening (Fig. 1).

Musculoskeletal: Joint restriction was present in 4/5 patients, most prominently in the lower limbs; none had gibbus; two patients underwent surgical procedures: patient 4 (P4) underwent five corrections, two for cervical spine, one for hip, and two for claw hands, and patient 3 (P3) underwent seven procedures on the pelvis.

Organic compromise: 2/5 patients had hypertrophic cardiomyopathy, and none presented with hepatosplenomegaly, hernias, or hearing impairment.

Other clinical findings are detailed in Table 1.

Radiological aspects

The most prevalent radiological findings are shown in Figs. 2, 3, and 4 and include: anterior beaking of the vertebral bodies 5/5, shallow acetabular fossae 5/5, epiphyseal dysplasia 5/5, platyspondyly 4/5, pelvic dysplasia 4/5, decreased bone mineralization 4/5, scoliosis 3/5, wide and oar-shaped ribs 3/5, epiphyseal ossification delay 3/5, hypoplasia of basilar portions of the ilea 3/5.

Other radiological findings are described in Table 2.

Enzyme assessment

All patients had normal glycosaminoglycans concentration in urine; glycosaminoglycans chromatography revealed heparan and dermatan traces in 2/5 patients and only heparan in 1/5 patient. Regarding serum enzymatic activity, α-iduronidase, α-mannosidase, β-glicuronidase, hexosaminidase A, and total hexosaminidase were elevated in all patients.

Diagnosis

Based on the clinical, radiological, and enzyme assessment assays performed, one patient (P1) was classified as ML II and four patients (P2-5) ML III.

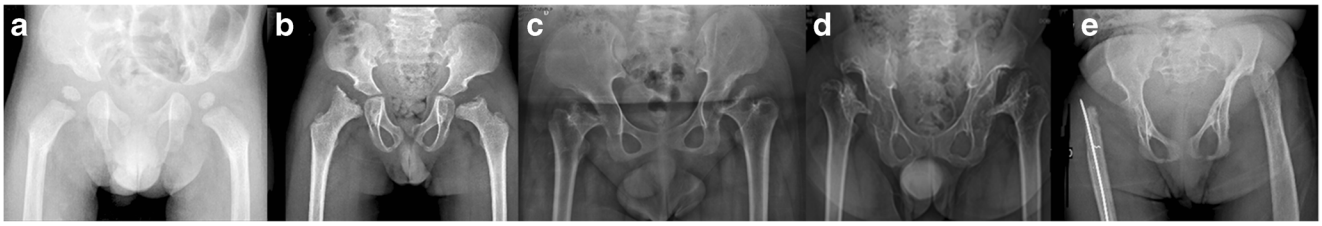

Fig. 3 Anteroposterior view of the pelvis radiographs of the five ML patients. Patient **a** is affected by ML II and patients **b** to **e** are affected by ML III; **a** 11-month-old male ML II patient (P1) showing decreased bone mineralization, coarse trabecular bone structure, characteristic slanting of the acetabular roofs and coxa vara; **b** 9-year-old male ML III patient (P2) showing fragmentation of the femoral epiphysis, coarse trabecular bone structure, slanting of the acetabular roofs, coxa vara; **c** 17-year-old female ML III patient (P3) showing proximal femoral dislocation which lacks epiphyseal ossification, iliac hypoplasia, coarse trabecular bone structure; **d** 33-year-old male ML III patient (P4) showing decreased bone mineralization, hip dislocation, and irregularities of the femoral epiphysis; **e** 15-year-old male ML III patient (P5), showing slanting acetabular roofs, narrowing of the pubic and ischial bones, hypoplastic femoral epiphyses

Discussion

The recognition of early signs and symptoms of genetic conditions is immeasurably valuable because it contributes to diagnosis, adequate clinical management, and genetic counseling of families. Importantly, the five ML patients were referred for genetic evaluation due to disproportionate short stature with short trunk accompanied by waddling gait. Together, these findings suggest that this association could be considered a red flag for both clinicians and radiologists to consider this diagnosis.

Indeed, ML is a genetic disorder that belongs to the group of LSDs, which includes MPS. Differently from MPS though, ML patients do not usually show evident facial dysmorphism—in our work, 2/5 patients presented coarse face and one patient had premature graying of hair; none had gingival hyperplasia, none had tongue thickening. Regarding neuropsychomotor development, 3/5 patients showed delay, in concordance with the literature. Mental impairment is often progressive and demands regular follow-up. By the last evaluation, only two patients presented hypertrophic cardiomyopathy and none had hepatosplenomegaly, hernias, hepatomegaly, or hearing impairment. Furthermore, bone pain was present in 1/5 patients—this symptom has been previously described as a major finding in ML patients by Robinson [9], which treated a series of patients with intravenous pamidronate improving bone pain, joint mobility, and bone density. None of our patients underwent this proposed approach.

The typical radiologic findings of ML (dysostosis multiplex) were present in all patients: beaking of vertebral bodies T12-L3, epiphyseal dysplasia and shallow acetabular fossae. Other findings that were present in the majority of patients, including platyspondyly, scoliosis, decreased bone mineralization and pelvic dysplasia – which includes flared iliac wings, horizontal acetabular roofs, supra-acetabular constriction, hip dislocation and irregular contours of pubis and ischium, may be observed later in follow-up due to the progression of the disease. In ML, there is compromise of hydrolases trafficking to lysosomes and subsequent lysosomal storage of glycosaminoglycans and sphingolipids in chondrocytes and osteoblasts,

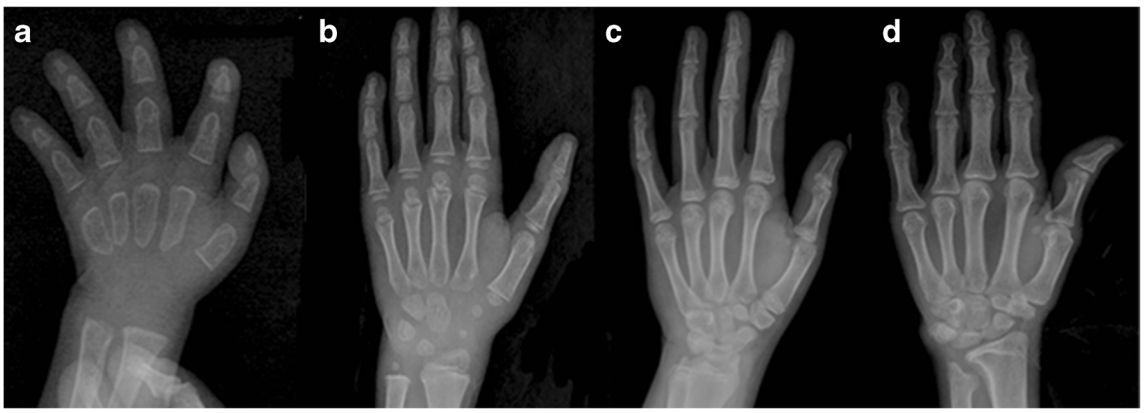

Fig. 4 Hand radiographs of four ML patients. **a** 11-month-old male ML II patient (P1) showing expansion of the shafts and proximal pointing of 2nd to 5th metacarpals, expansion of the middle phalanges, and lack of carpal nuclei ossification; **b** 9-year-old male ML III patient (P2) and **c** 15-year-old male ML III patient (P5), both with normal hand radiographs; **d** 17-year-old female ML III patient (P3) with shortening of the ulna, distal radioulnar joint dislocation, and hypoplasia of the radial epiphyses

Table 2 Radiological findings in patients with mucolipidosis II and III

Case number	1	2	3	4	5	Total
Clinical – radiological diagnosis	ML II	ML III	ML III	ML III	ML III	ML II 1/5 ML III 4/5
Age at radiological studies	11 months	9 years	17 years	33 years	15 years	NA
Thickened cranium	–	–	+	–	–	1/5
J-shaped sella turcica	–	+	+	+	–	1/5
Platyspondyly	–	+	+	+	+	4/5
Scoliosis	–	–	+	+	+	3/5
Beaking of vertebral bodies T12-L3	+	+	+	+	+	5/5
Ovoid vertebral bodies	+	–	–	–	–	1/5
Hook-shaped configuration of the vertebra	–	+	+	–	–	2/5
Wide, oar-shaped ribs	–	+	+	–	+	3/5
Hip dislocation	–	+	+	+	+	4/5
Hypoplasia of basilar portions of ilia	+	+	+	–	–	3/5
Shallow acetabular fossae	+	+	+	+	+	5/5
Coxa valga	–	–	+	+	–	2/5
Decreased bone mineralization	+	+	+	+	–	4/5
Widened metaphyses	+	–	–	+	–	2/5
Diaphyseal expansion	+	–	–	–	–	1/5
Epiphyseal dysplasia	+	+	+	+	+	5/5
Carpotarsal and epiphyseal ossification delay	+	+	–	+	–	3/5
Small, irregular carpal bones	–	+	–	–	–	1/5

NA not applicable

impairing bone formation [10]. The lysosomal impairment compromises the differentiation of osteoclasts, leading to increased expression of interleukin-6, which stimulates osteoclastogenesis, resulting in the appearance of destructive bone lesions [11].

High enzyme activity levels were present in all patients (Table 1). In the case of ML and MPS, two conditions that overlap clinical and radiological findings, laboratory assessments of enzyme activities are mandatory - in MPS, enzyme specific activity is low, depending on the MPS type, whereas in ML characteristically high levels are observed [5].

In summary, the clinical, radiological, and enzyme assessments of five ML Brazilian patients provided the diagnosis, improved clinical management, and allowed adequate genetic counseling of all five families. This specific strategy decreases costs and is relatively non-invasive. Therefore, clinicians and radiologists can take advantage of the information from this work, enhancing their differential diagnosis abilities.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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