Original Article

Impact of Enzyme Replacement Therapy in a Patient Younger Than 2 Years Diagnosed With Maroteaux-Lamy Syndrome (MPS VI)

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Abstract

Introduction: Mucopolysaccharidosis type VI, also known as Maroteaux-Lamy syndrome (#OMIM 253200), is a rare autosomal recessive genetic disorder due to deficient activity of the enzyme N-acetylgalactosamine 4-sulfatase (arylsulfatase B) required for the breakdown of dermatan sulfate and chondroitin sulfate. **Patient:** Report of a female patient started on enzyme replacement therapy at 17 months of age. At the time of diagnosis (14 months), the patient presented mild corneal opacity and significant thoracolumbar kyphosis, but no visceral involvement or growth arrest. At 73 months of treatment, weight was normal, although the patient was in a low height percentile. The patient showed adequate neural development, with improvement in lumbar spine and joint involvement. Corneal compromise or valvular disease progression was not evident. **Conclusion:** Early and timely diagnosis and treatment with enzyme replacement therapy are essential, as the means to change the natural history of the disease, avoiding comorbidities and improving final prognosis.

Keywords

mucopolysaccharidosis type VI (MPS VI), Maroteaux-Lamy syndrome, enzyme replacement therapy, glycosaminoglycans

Introduction

Mucopolysaccharidoses (MPS) are a group of innate errors of metabolism of the complex molecule catabolism type. They are caused by a deficiency of a specific lysosomal enzyme that affects the normal catabolism of glycosaminoglycans (GAGs), leading to their accumulation in different organs and tissues and resulting in a number of complex signs and symptoms of multisystem disease.[1-3] Mucopolysaccharidosis type VI (MPS VI) or Maroteaux-Lamy syndrome (OMIM #253200) is a rare genetic disease of autosomal recessive inheritance caused by a deficiency of the N-acetylgalactosamine-4-sulfatase enzyme, also known as arylsulfatase B (ARSB), which hydrolyzes the sulfate fraction of the dermatan GAG.[1,2,4]

It is estimated that the incidence of MPS VI in the world ranges between 1 in 248 000 and 1 in 300 000 live births.[5] Nevertheless, Orphanet (http://www.orpha.net) reports a prevalence of 1 to 9 per 1 000 000. In Brazil, population data reveal that the incidence may be higher. A screening of a high-risk population with a diagnosis of MPS showed that 19% of this high-risk population was with MPS VI, although no ethnic group or founding effect was observed in the population.[6-8] In Colombia, there are no updated epidemiological data regarding the incidence of the disease in the population.

Patients with MPS VI exhibit a wide range of multisystem symptoms as part of a characteristically progressive and chronic course, affecting mainly their cardiorespiratory and skeletal systems, cornea, skin, liver, spleen, meninges, and brain.[3] The systemic involvement is very similar to the one observed in MPS I but, unlike that form of the disease, intelligence is not affected.

At present, galsulfase (recombinant form of human N-acetylgalactosamine [rhASB]; Naglazyme), an enzymatic replacement therapy (ERT), is the sole treatment approved for patients with MPS VI. Galsulfase has been approved by the regulatory agencies of the United States, the European Union,

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Australia, Brazil, Colombia, and other countries. The international management guidelines for MPS VI recommend galsulfase ERT as first-line treatment for patients with MPS VI.[7] In 2014, Giugliani et al, in a study about the natural history and treatment with galsulfase in patients with MPS VI, concluded that long-term galsulfase ERT improves survival, continued growth, endurance, and lung function. The treatment was also shown to help stabilize cardiac function and improve quality of life in patients with this disease. Even in patients with the most severe form of the disease, galsulfase ERT stabilizes endurance and lung function and improves survival. Early initiation of ERT may improve the clinical benefits in patients with MPS VI.[9]

This article reports the case of a 13-month-old Colombian patient with a clinical and biochemical diagnosis of MPS VI, started on ERT at 17 months of age. The article highlights the importance of early diagnosis for timely initiation of treatment, which results in a significant change in the progression of the disease and the quality of life for patients and families alike.

Case Report

This is a 13-month-old female patient born in Bogota, Colombia, to nonconsanguineous parents. The patient was the fourth pregnancy and received antenatal care. Ultrasound scans were within normal limits. The mother was delivered by cesarean section (37 weeks' gestation) due to preeclampsia. Weight and length at birth were 3200 g and 49 cm, respectively. Due to early jaundice, the neonate required admission to the neonatal care unit for management with phototherapy. From the time of birth, lumbar spine deformity prompted the mother to visit several pediatricians. Nevertheless, no workup or treatment was indicated. A pediatric orthopedic surgeon diagnosed hyperlordosis and scoliosis. The patient was referred to the medical genetics service. Parents reported normal neural development. The patient was asymptomatic at the time of the initial visit.

Family History

The patient has a half maternal sister, healthy; had a brother diagnosed with intrauterine growth restriction died at 18 days of birth of no clear cause; had a second sister died in uterus, at 7 months, with no cause of death identified. The mother reports no fetal hydrops or phenotypical abnormalities in either case.

Initial Physical Examination Findings

Weight (10 kg) and size (76 cm) were normal for age (Table 1). The patient had macrocephaly, broad forehead, mid-face hypoplasia, mildly coarse facies, thick eyebrows, anteverted nostrils, broad nasal bridge, epicanthal fold, mild corneal opacity, gingival hypertrophy, tonsillar hypertrophy, short mobile symmetrical neck, short chest, mild pectus excavatum, soft abdomen with no visceral enlargement, small reducible umbilical hernia, and bilateral reducible inguinal hernias. Joint mobility mildly impaired for elbow extension, and the patient had brachydactyly, no evidence of claw hand, no lower limb range of motion limitation, and evidence of lumbar kyphoscoliosis (Figure 1A). Several mongoloid spots located in the back and lumbar region.

Neurological Examination

Patient was alert with normal tone, normal gait, preserved strength, and sensation in the 4 limbs. Electrophoresis for MPS was performed with reported dermatan sulfate excretion, enzymatic activity for ARSB on filter paper was reported as 0.0, and leukocyte arylsulfatase at 0.71 (reference value of 115-226 nmol/mg/protein/h), confirming the diagnosis of Maroteaux-Lamy syndrome (MPS VI). Molecular sequencing of the ARSB gene identified the mutations giving rise to the disease on allele 1: c.1143-1G>C (IVS5-1g>c), as reported by Garrido et al,[10] and on allele 2: c.332 A>C (p.H111P), as reported by Giraldo et al[11] in patients with the severe phenotype.

Baseline Tests (Prior To Treatment Initiation)

Lumbar spine X-rays showed oval-shaped vertebral bodies and lumbar hyperlordosis. Echocardiography revealed mitral valve dysplasia with grade I prolapse and mild regurgitation, with mild aortic and tricuspid regurgitation. Total abdominal computed tomography scan showed no findings of enlarged organs. Brain magnetic resonance imaging (MRI) revealed enlarged perivascular spaces; brainstem auditory evoked potentials were within normal limits. Long-bone X-rays showed widening of the proximal and distal metaphyses. Cervical spine MRI and ribcage X-rays were normal (Table 2).

The ERT was initiated 3 months after diagnosis (17 months of age) using N-acetylgalactosamine 4-sulfatase, rhASB (galsulfase, Naglazyme) 1 mg/kg/wk intravenously (IV; total dose of 10 mg/wk). To date, there have been no reports of adverse reactions associated with the ERT. After 50 ERT infusions, the patient was within the normal percentiles for weight and height (87 cm, 12 kg) and head circumference was 48 cm. After 62 weeks of treatment, height, weight, and head circumference were 88 cm, 12.5 kg, and 48 cm, respectively, all within the low normal range. Later, there was a dip in height (Figure 2), but on the last follow-up (6 years of age), there is a trend toward recovery in the growth curve, with height, weight, and head circumference of 98.5 cm, 16.5 kg, and 48 cm, respectively (Figure 3). The patient has achieved therapeutic targets of improved joint mobility, corrected kyphoscoliosis with the use of a brace, and significantly improved corneal opacity, apnea/hypopnea syndrome, and adenoid infiltration. There is no evidence of valvular disease progression.

In summary, ERT has modified the natural history of the disease. Growth curves are within normal ranges and there is no organ enlargement (Figures 1 and 4). X-rays at 6 years of age show mild bony changes, but there is no evidence of severe bone disease such as dysostosis multiplex (Figure 5).

Table 1. Clinical Variants During the Course of the Treatment.

Parameter	Onset	49 Weeks ERT	62 Weeks ERT	98 Weeks ERT	110 Weeks ERT	122 Weeks ERT	133 Weeks ERT	136 Weeks ERT	149 Weeks ERT	160 Weeks ERT	172 Weeks ERT	196 Weeks ERT	206 Weeks ERT	219 Weeks ERT	231 Weeks ERT	270 Weeks ERT
Age	14 months	26 months	29 months	38 months	41 months	44 months	47 months	47.8 months	50 months	53 months	56 months	62 months	65 months	67 months	70 months	73 months
Weight	10 kg	12 kg	12.5 kg	13.2 kg	13.1 kg	12.2 kg	13.8 kg	14.2 kg	14 kg	14.4 kg	14 kg	14 kg	14.7 kg	14.7 kg	15.4 kg	16.5 kg
Size	76 cm	87 cm	88 cm	90 cm	91.5 cm	92 cm	94 cm	94.5 cm	94.5 cm	94.5 cm	94.5 cm	96.5 cm	96.5 cm	96.5 cm	96.5 cm	98.5 cm
Head circumference	46 cm	48.5 cm	48 cm	49.4 cm	47.5 cm	47.6 cm	47.5 cm	48 cm	49 cm	49 cm	49 cm	49 cm	48.5 cm	48.5 cm	48.5 cm	48 cm
Facial appearance	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies	Mild coarse facies
Chest	Mild pectus excavatum	Mild pectus excavatum		Mild pectus excavatum			Mild pectus excavatum			Mild pectus excavatum		Mild pectus excavatum				Bell-shaped chest, prominent inferior costal arches
Major joints	Mild limitation of elbow extension	No changes	No changes	No changes	No changes	Mild range of motion limitation at the elbows	No changes	No changes	No changes	Mild range of motion limitation at the elbows	No changes	No changes	No changes	No changes	Extension limitation at the elbows, mild gene valgum	No changes
Hands	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Mild interphalangeal contractures in fourth digit of the right hand	No changes	Mild bilateral contractures in third, fourth, and fifth fingers	No changes	Mild bilateral contractures in third, fourth, and fifth fingers

Abbreviation: ERT, enzymatic replacement therapy.

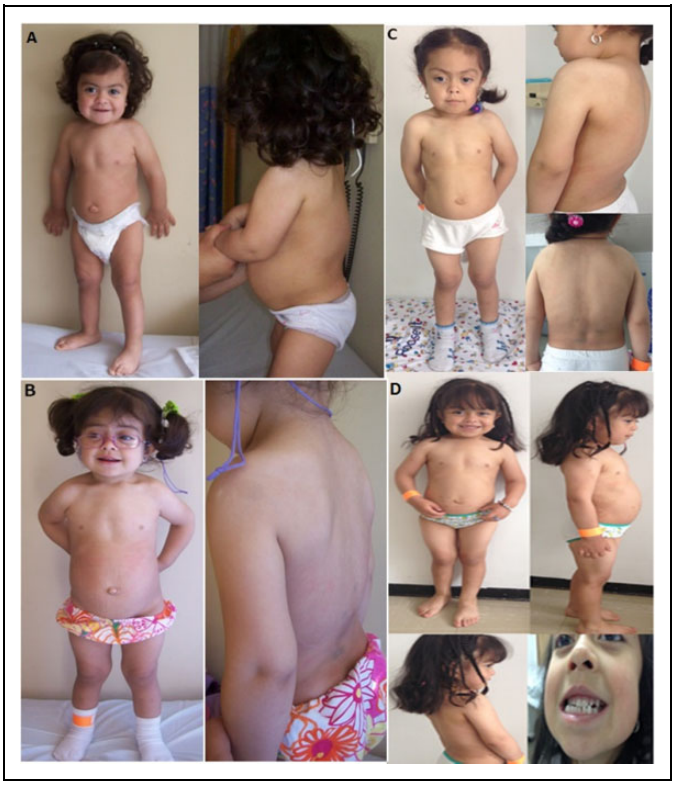

Figure 1. A, Patient at the time of diagnosis (16 months old), before initiating enzymatic replacement therapy (ERT). B, Patient at 28 months with no evidence of disease progression. C, Four-year-old patient: slow progression of the disease. D, Five-year-old patient: mild progression of the disease (without gingival hypertrophy or skeletal abnormality).

These changes include mild acetabular dysplasia, mild camptodactyly, and mild metaphyseal widening. Follow-up imaging tests have shown no evidence of hepatomegaly or splenomegaly, with oval-shaped vertebral bodies, and absence of scoliosis. Audiometry is normal. Brain MRI is normal and full spine MRI shows hyperlordosis and scoliosis. Echocardiography shows dysplastic aortic valve, mild aortic root dilatation, mitral dysplasia with regurgitation, and mild prolapse, with no improvement, but no worsening of cardiac involvement either. Follow-up parameters remained stable, but there was a small progression of clinical and paraclinical findings (Tables 1 and 2).

The patient has been followed up regularly by a multidisciplinary group. She goes to school and has a normal neurological development according to her age. The natural history of the disease was modified, and the patient showed improvement in airway and visual involvement, no progression of the valvular or skeletal disease, no visceral enlargement, and no changes in her facial phenotype.

Discussion

Doctors Maroteaux and Lamy first described MPS VI or Maroteaux-Lamy syndrome in 1963.[12] It is caused by mutations in the N-acetylgalactosamine-4-sulfatase or ARSB gene. This enzyme is responsible for removing the C4 ester sulfate group from the N-acetylgalactosamine sugar of dermatan sulfate and chondroitin 4-sulfateglycosaminoglycans (GAGs). Mutations in this gene cause ARSB enzyme deficiency and inadequate lysosomal GAG breakdown, eventually leading to GAG intralysosomal storage and urinary excretion.[8]

Patients with MPS VI exhibit a wide range of multisystem symptoms, including tracheobronchomalacia that contributes to respiratory problems, with frequent findings of obstructive sleep apnea. Cardiac compromise is responsible for morbidity and mortality in the vast majority of patients with MPS VI.[13]

Genotype identification may be important for predicting phenotype and therapeutic decision-making in some cases of MPS. Additionally, it can be used to provide genetic counseling on reproductive risks, thus contributing to lowering the recurrence of the disease.[3]

Before the advent of stem cell treatment and, in particular, ERT, treatment of patients diagnosed with MPS VI was palliative and symptomatic, aimed at managing and preventing complications.[3] The ERT with human recombinant N-acetylgalactosamine-sulfatase (rhASB) has shown to be effective in human phase II and phase III clinical trials, with significant improvement in endurance tests (12-minute walk, 3-minute stair climbing), increased joint range of motion, improved respiratory function tests, and reduced urine GAG excretion.[14,15] Enzyme replacement treatment was administered as a single dose of 1 mg/kg/wk infusion over a 4-hour period with antihistamine premedication in order to diminish the risk of secondary adverse events.[16] All clinical trials were done in patients older than 5 years to assess efficacy and safety. Since 2009, some papers have been published describing treatment in patients younger than 5 years,[16] with significant improvement in paraclinical parameters and in bone and joint parameters (scoliosis and joint mobility).

McGill et al described the case of 2 siblings with a diagnosis of MPS VI in utero. The first started treatment at 3.6 years, and the second at 8 weeks of life. At present, the first sibling has coarse facies, visceral enlargement, and bone and joint compromise, whereas the second patient shows mild signs and symptoms of the disease after 182 weeks of treatment (moderate pectus excavatum, mild restriction of shoulder flexion, normal hands and facial appearance).[16] Safety of the medication was demonstrated in patients younger than 5 years. Ribeiro et al have demonstrated the safety of ERT in patients younger than 1 year, with improvement in urine GAG excretion and functional status and a reduction of disease burden.[17]

In 2013, a study by Horovitz et al described 34 patients (21 males and 13 females) with MPS VI who started galsulfase ERT before 5 years, with a mean age at diagnosis of 28.5 months and a mean age at the start of therapy of 38.5 months. The study concluded that ERT with galsulfase at the prescribed dose of 1 mg/kg/wk IV was shown to be safe

Table 2. Laboratories and Imaging Studies During the Course of the Treatment.

Parameter	Onset	49 Weeks ERT	98 Weeks ERT	110 Weeks ERT	122 Weeks ERT	136 Weeks ERT	149 Weeks ERT	196 Weeks ERT	219 Weeks ERT	231 Weeks ERT	270 Weeks ERT
Age	14 months	26 months	38 months	41 months	44 months	47.8 months	50 months	62 months	67 months	70 months	73 months
Spine X-ray	Hyperlordosis, oval-shaped vertebral bodies	Oval-shaped vertebral bodies, improved hyperlordosis	Not done	No scoliotic curve, significant improvement of kyphotic curve, oval-shaped vertebral bodies	Not done	Not done	Not done	Significant improvement of scoliosis and lordosis oval-shaped vertebral bodies	Not done	Not done	No evidence of scoliosis, oval-shaped vertebral bodies
Echocardiogram	Mitral dysplasia, grade I prolapse, mild mitral, tricuspid, and aortic regurgitation	Mild aortic root dilatation, mitral valve dysplasia with regurgitation and mild prolapse, mild left ventricular dilatation	Not done	Moderate left ventricular hypertrophy and dilatation, grade II aortic insufficiency, mitral valve with grade II-III insufficiency	Left ventricular hypertrophy and dilatation, mitral valve prolapse, mild grade II insufficiency, grade II aortic insufficiency, left atrial dilatation	Not done	Moderate concentric left ventricular hypertrophy, mild aortic insufficiency, mild mitral prolapse and moderate insufficiency	Mild-to-moderate concentric left ventricular hypertrophy, thickened tricuspid, mild insufficiency, mild compromise of thickened, myxomatous anterior mitral leaflet, mitral prolapse, mild tricuspid regurgitation, FEV1 65%	Mild compromise of thickened, myxomatous anterior mitral leaflet, severe regurgitation, thickened tricuspid aortic valve severe, mild insufficiency, severe left atrial and ventricular dilatation, left ventricular diastolic diameter 4, 3 cm, mild-to-moderate left ventricular concentric hypertrophy	Not done	Moderate mitral insufficiency; ring diameter 2.4 cm, tricuspid 2.32, mild left heart dilatation, tricuspid aortic valve, mild insufficiency, no stenosis, mild tricuspid regurgitation FEV1 79%
Audiometry	Normal	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Normal
Liver on abdominal ultrasound	Normal liver size	Not done	Liver slightly increased in size	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Normal
Brain MRI	Enlarged perivascular spaces	Not done	Not done	Not done	Not done	Not done	Normal	Not done	Not done	Not done	Within normal limits
Spine MRI	Radiology report within normal limits	Not done	Not done	Not done	Not done	Not done	Mild cervical spine stenosis of the foramen magnum odontoid peg hypoplasia, dural thickening, hypoplasia of the posterior arch of C1. Lumbar hypoplasia of L1 and L2. Mil thoracic spine scoliosis	Not done	Not done	Not done	Not done
Auditory evoked potentials	Normal	Not done	Not done	Not done	Not done	Not done	Normal	Not done	Normal right ear. Prolonged absolute latencies of the left ear conductive hearing loss	Not done	Normal
Hip X-ray	Not done	Mild bilateral acetabular dysplasia	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Mild bilateral acetabular dysplasia	Not done
Others						Gait analysis: Gait pattern with minor abnormalities of joint kinematics with no significant functional impact	Polysomnography: IAH 2 still mild		Normal liver and kidneys on abdominal CT scan		Normal bone density according to age

Abbreviations: MRI, magnetic resonance imaging; LVE, Left ventricular ejection fraction; AHI, Apnea hypoapnea index.

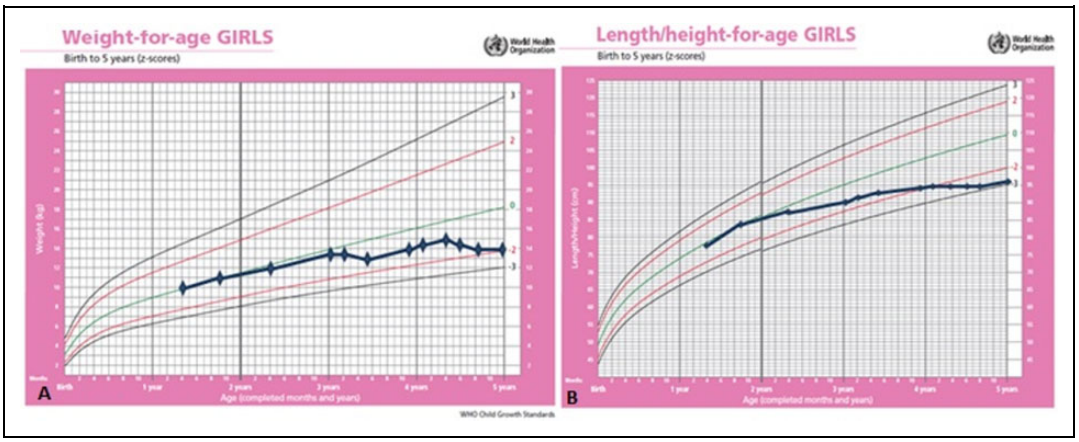

Figure 2. World Health Organization growth tables for girls 5 years of age. A, Weight curve for the patient from 5 years. B, Height curve for the patient from 5 years.

Figure 3. World Health Organization growth tables for girls up to 5 years of age. A, Weight curve for the patient from 16 months to 5 years. B, Height curve for the patient from 16 months to 5 years.

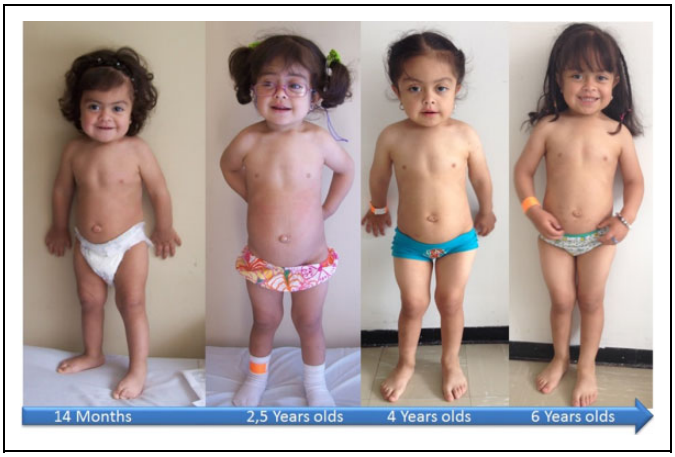

Figure 4. At different time points, the patient did not show significant progression of the disease.

and effective in slowing the progression and/or improving the burden of the disease in small children with MPS VI. The results of the study in this young cohort of patients include early recognition of the subtler symptoms associated with the slowly progressing form of the disease, which must be a priority to ensure early diagnosis and treatment. Patients must be followed closely, particularly in relation to cardiorespiratory compromise and spinal cord compression.[18]

In this case report, early diagnosis (biochemical) was made at 13 months and treatment was started at 17 months. Later, the molecular diagnosis identified c.1143-1G>C (IVS5-1g>c) and c.332 A>C (p.H111P) mutations, which have been reported in patients with the severe phenotype.[10,11] However, timely and adequate management has led to a clear arrest in the progression of the disease. Although the patient does not have a normal height, she is still within her growth percentile, but there is evidence of visceral, ocular, respiratory, and skeletal impact.

Lysosomal storage diseases are progressive, multisystem, and degenerative genetic disorders characterized by chronic deposit of macromolecules. The importance of an early initiation of ERT in patients diagnosed with lysosomal storage diseases is increasing, as ERT clearly avoids the progressive accumulation of metabolites, which could lead to cellular

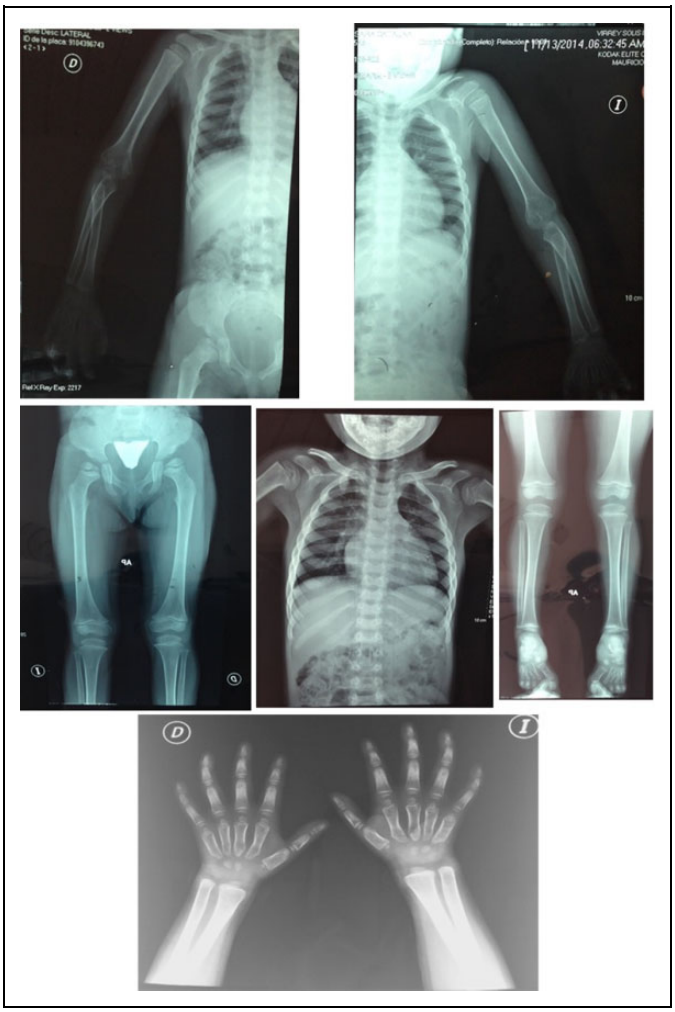

Figure 5. X-rays of the long bones and chest showing evidence of thickening of the clavicles, ribs, with slight paddle deformity due to proximal thinning and distal widening, acetabular hip dysplasia, and hand camptodactyly with mild widening of the proximal metacarpal metaphysis.

death. Thus, early initiation of ERT prevents disease progression and clinical and functional deterioration of the patient.

There are only a few reports in the indexed medical literature about MPS VI treatment. Among these reports, the one published by Lin et al stands out. It reports a case series of Taiwanese patients treated long term with galsulfase. One of the patients started the treatment at a similar age (16 months) as the one mentioned in this report.[19]

It is important to emphasize that this is the first case of MPS VI, treated before 2 years of age, reported in Colombia. This case demonstrates the importance of an early diagnosis and brings up the discussion about the convenience of performing newborn screening for lysosomal storage diseases.[20]

Conclusion

As has been shown in prior studies, and in this case report, ERT with galsulfase in patients younger than 5 years diagnosed with MPS VI is safe and effective and has a favorable impact on the natural course of the disease. This therapy has shown to improve bone and joint involvement, maintain an adequate growth curve, and frequently prevent visceral, respiratory, and cardiac compromise. The article emphasizes the importance of initiating ERT as early as possible in order to achieve the therapeutic objectives described above.

This is the first article on the Colombian population, and one of the very few published regarding the Latin American population, that reports early management of a lysosomal storage disease.

Ethical Considerations

The patient's guardian signed the informed consent for making pictures and visual recording of medical genetics with the support of Roosevelt Institute. He authorizes their use in medical publications (including articles, books, and online publications) and accepts that images may be seen by the public, besides medical and scientific researchers, who use these publications as part of their professional training.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Biomarin Colombia LTDA sponsored the translation and publication of this article.

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