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Mucopolysaccharidosis type VI on enzyme replacement therapy since infancy: Six years follow-up of four children☆

Dafne D.G. Horovitz [a,*], Angelina Xavier Acosta [b], Liane de Rosso Giuliani [c], Erlane Marques Ribeiro [d]

[a] Centro de Genetica Medica, Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira/FIOCRUZ, Rio de Janeiro, RJ, Brazil
[b] Serviço de Genética Médica, Universidade Federal da Bahia, Salvador, BA, Brazil
[c] Faculdade de Medicina, Universidade Federal do Mato Grosso do Sul, Campo Grande, MS, Brazil
[d] Hospital Albert Sabin, Fortaleza, CE, Brazil

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ABSTRACT

Clinical and biochemical improvements are reported on Mucopolysaccharidosis type VI (MPS VI) patients on Enzyme Replacement Therapy (ERT) with rhASB (galsulfase, Naglazyme®), and preclinical and clinical studies have shown clinical benefits of early initiation. We report four unrelated MPS VI children who began ERT as infants (ages 5 days–10 months). The three older patients showed the first clinical signs of MPS VI at baseline, also presenting different degrees of dysostosis multiplex, and two had mild heart disease. The two oldest also had mild facial coarseness, one had hearing conduction deficit and sleep disorder and the other corneal clouding at baseline. After six years on ERT, all four patients have normal urinary GAG values. Although they all showed normal motor and mental development, brain and cervical spine MRI images available from two of the older patients showed abnormalities, while the youngest child continues having normal images. The four patients presented slower progression of bone and joint disease when compared to their affected older siblings. It should be noticed that only two patients in this sample are currently below the 3rd percentile for height: the youngest who has a constitutional factor associated and the eldest who already presented frank dysostosis at 10 months of age. These findings confirm previous studies that report that skeletal features of the disease cannot be completely prevented despite early ERT. Heart disease already present in two of the four infants at baseline got worse over time and appeared in another patient, but the youngest child on ERT introduction still has a normal echocardiogram at six years of age; he also is the only one without corneal clouding after six years follow-up. Our results also suggest that early ERT prevented storage in spleen and liver and may also have improved or prevented progression of facial dysmorphic features, corroborating similar findings seen in previous studies. No safety concerns were identified and none of the patients experienced a serious adverse event. The baseline severity of the disorder of these four infants seems related to age and it is tempting to say that severity on the first year of life is progressive and ERT effectiveness is indirectly related to it. Despite being known that MPS VI progresses differently among patients, the fact that these infants had a slower progression than their older siblings speaks in favor of a very early start of ERT. In conclusion, this report confirms the early manifestations of the disease and provides additional evidence on safety and of the beneficial effects of ERT in patients less than 1 year of age.

1. Introduction

Mucopolysaccharidosis type VI (MPS VI; Maroteaux-Lamy syndrome) is a multisystemic chronic and progressive lysosomal storage disease in which deficient activity of the enzyme N-acetylgalactosamine 4-sulfatase (arylsulfatase B) impairs the stepwise degradation of the glycosaminoglycan (GAG) dermatan sulfate. Partially degraded GAG accumulates in lysosomes in a wide range of tissues, causing significant functional impairment and shortened lifespan [1–3].

Severely affected MPS VI patients are usually diagnosed by 2 or 3 years of age, and develop severe skeletal and heart abnormalities, joint stiffness, and corneal clouding. Clinical improvement in MPS VI patients receiving enzyme replacement therapy (ERT) with recombinant human N-acetylgalactosamine 4-sulfatase, rhASB (galsulfase, Naglazyme®) is reported, although some of the pathological changes might not be reversed. [4–7].

Clinical trials and case reports have shown the impact of ERT treatment in growth (mainly in patients who started ERT before 16 years) [4–6], endurance and cardiovascular aspects of the disease, in particular

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* Corresponding author at: Centro de Genetica Medica, Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira — Fiocruz, Av. Rui Barbosa 716 — Flamengo, Rio de Janeiro, RJ 22250-020, Brazil.
E-mail address: dafne@iff.fiocruz.br (D.D.G. Horovitz).

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reducing intraventricular septal hypertrophy and preventing progression of cardiac valve abnormalities when administered to those <12 years of age ([7]). Additional evidence from animal studies suggests that the limited effect of ERT on growth might increase if treatment would be started at an earlier age [8].

Previous studies of Galsulfase ERT in MPS VI cat models from birth have indicated that very early initiation of ERT before signs and symptoms of the disease develops leads to better long-term outcomes [8]. A more recent study in mice model with a similar disease, Mucopolysaccharidosis type I (MPS I), also showed that ERT started at birth improves the outcome in difficult-to-treat organs [9].

Starting ERT for very young MPS patients has generated much recent interest concerning safety profile and the ability of ERT to modify the natural history of the disease. Due to the progressive nature of MPS VI, halting disease progression or even slowing the rate of deterioration would be beneficial for the patient. Case reports of Australian and Japanese MPS VI patients comparing siblings where one started on ERT in the first year of life and a Brazilian cohort of 34 patients that started ERT under 5 years of age demonstrated a clear benefit of early initiation of ERT to slow or prevent the development of significant pathological changes of MPS VI. [10–12].

Better outcomes are also observed in MPS I and MPS II patients that started enzyme replacement therapy early. [14–18].

A recent multicenter open-label study with four MPS VI infants to evaluate the efficacy and safety of two dose levels of galsulfase also showed the benefits of early ERT initiation on hearing, cardiac function, facial dimorphisms, hepatomegaly and physical development, although skeletal abnormalities and corneal clouding continued to progress. [19].

This report describes the six year follow-up of four unrelated MPS VI patients that were the first infants treated in Brazil to further discuss the effects of very early ERT.

2. Methods

Four patients (P1, P2, P3 and P4) that had started treatment as infants were identified from the previous Brazilian cohort study [12] and a protocol questionnaire was sent to the attending physicians at the four centers located in different cities in Brazil. The sites confirmed that they were following the patients and agreed to participate. Data was obtained from patients charts and complemented by the attending physicians' family interview when necessary. All four children had older siblings affected and in two cases (P1 and P4) siblings were also included in the Brazilian cohort of MPS VI patients treated before the age of five years [12]. Data from the siblings is presented in this report when available, as well as retrieved data from an older brother of P3, to compare the progression of disease between them and the younger brother/sister. Charts for height and weight and head circumference [20,21] were used for normal standards.

3. Results

The four unrelated MPS VI patients, three boys (P1, P2, P3) and one girl (P4) that started ERT for MPS VI in the first year of life received the recommended dosage of 1 mg/Kg IV weekly of Galsulfase (Naglazyme®) and have been under treatment for more than six years. In all cases a specific informed consent was obtained before starting ERT, as at that time only anecdotal reports of early intervention were available.

Demographic data, molecular studies, baseline and six years follow-up clinical data and urinary GAG levels are presented in Table 1. Some specific issues are highlighted below.

3.1. Enzyme replacement therapy: safety and compliance

P1 presented mild perioral cyanosis and hyperthermia during the 2nd infusion, and P2 has presented erythema at the infusion site at five infusions, now controlled with regular antihistamines premedication. This is further corroboration that ERT is safe in infants as it was reported by [19].

Compliance to treatment was very good for P2, P3 and P4, with less than 15% of the programmed infusions missed per year. P1, however, during his first year on ERT, missed 28/52 of the programmed infusions due to social issues; his siblings missed the same number of infusions. Compliance was good after that period.

3.2. Biochemical

Diagnosis had been confirmed by enzyme determination in leucocytes all patients, (performed in cord blood for the prenatally diagnosed child and later repeated in peripheral blood leucocytes and dry blood spot). All patients had another enzyme determined for control in the same sample. Three patients had very high levels of urinary GAG before starting ERT, and all four patients had normal GAG values (within upper normal limits) after six years on ERT.

3.3. Development and nervous system

During the six years under ERT, all patients had normal motor and mental development, tested with Denver Developmental Screening Test during regular pediatric visits. Brain and cervical MRI images of P2 and P4 have shown abnormalities, while P1 has normal cranial and cervical images. No brain/cervical imaging studies are available for P3.

P2 at 17 months of age already showed thick duramater with narrowing of spinal canal at C1 level, and at age 5 years, stenosis of foramen magnum, odontoid hypoplasia, narrowing of cervical spinal canal and normal brain image; P4 at 17 months had prominent perivascular spaces on semioval center, radiate crown and lateral periventricular white matter, minimal gliosis, normal sized ventricles and anterior subluxation of C1 on C2, absence of anterior and posterior arches of C1 and cranial–vertebral junction stenosis with bulbo-medular compression. As she presented symptoms of myelopathy, cervical laminectomy and fixation were performed at 20 months of age [13]. At five years of age MRI showed normal brain and ventricular images; cervical spine images revealed no myelomalacia.

P4 had surgical correction of carpal tunnel syndrome at 6 years and 4 months of age, while her brother already had to operate at age 4 years. P3 was recently diagnosed with carpal tunnel syndrome; P1 and P2 have not been specifically tested yet.

3.4. Orthopedic

During the six year follow-up all four patients presented progression of bone and joint disease: P1 had mild restrictions of fingers at age two years and lumbar vertebrae degeneration was seen at age four, a milder and slower progression of dysostosis when compared to his older brother who already presented frank dysostosis at baseline (35 months) and older sister (Fig. 2). P1 is presently 93 cm tall, below the 3rd percentile for weight and height. His affected older brother and affected older sister present heights, at ages 10 and 12 years, are 91 cm and 97 cm respectively (Fig. 1). Short stature in this patient cannot be considered as only caused by MPS VI disease, as constitutional short stature was expected (father is under 5th centile and mother's height is only 140 cm).

P2 presented mild gibbus, dysostosis on phalanges of fingers and toes, and tapering of proximal ends of metacarpals at 17 months of age, and at age five years platyspondyly and hip deformity were evident, although progression is slow and he has normal height and weight measurements up to the last follow-up at 6 years of age.

P3 already had typical MPS VI dysostosis multiplex at 18 months but shows slow progression of deformities, and at 6 years has normal height, weight and head circumference. His older brother was diagnosed at 3 years, but only started ERT at the age of six years and seven months, and presented severe dysostosis, height and weight were

Table 1
Baseline and follow-up clinical, anthropometric, familial, molecular and enzyme replacement therapy (ERT) data on the four MPS VI patients who began ERT as infants.

Patient Gender Birthdate Age 1st ERT	Consanguinity	Familial recurrence	Molecular studies	Baseline follow-up	Height (centile)	Weight (centile)	Head Circumference (centile)	Coarse facies	Hernia	Corneal clouding/ ophtalmology	Hearing deficit	Sleep apnea	Dysostosis multiplex	Gibbus	Claw hand	Cervical Instability	Echocardiogram	Urinary GAG (mg/g creatinine)	Surgeries	hospitalization clinical diseases	ERT adverse effects
P1 Male 14sept2008 5 days	Yes	2 affected siblings	IVS5–8t>g / IVS3–22 T>C polymorphism	Baseline (5 d)	46 cm (<p3)	2.88 kg (p10)	33.5 cm (p3)	No	No	No	No	NT	No	No	No	No	Normal	NT	Inguinal hernia (3 y)	No	Mild perioral cyanosis and hyperthermia 2nd infusion
				Follow–up	93 cm (<p3)	15 kg (<p3)	50.5 cm (p50)	No	bilateral Inguinal	No	Mild/ moderate conductive	Mild	Yes mild	No	Yes	No	Normal	213 (ref: 67–214)			
P2 Male 11mar2008 4 months	Yes	1 affected sibling (deceased)	D59N/?	Baseline (4 m)	69.5 cm (p50)	7.55 kg r (p50)	42 cm (p50)	No	No	No	NT	NT	No	Yes	No	No	Mild mitral insufficiency	1470 (ref:133–460)	Inguinal hernia and phymosis (18 m)	Allergic; GE reflux, recurrent Otitis Frequent urinary tract infections	Local erythema at venipuncture site on 5 infusions
				Follow–up	108 cm (p50)	18 kg (p50)	52 cm (p50)	No	Bilateral Inguinal	Mild clouding leucoma strabismus	Bilateral conductive	No	Yes mild	Yes mild	Yes	No	Ventricular wall thickening, mitral and aortic regurgitation (all mild)	242 (ref: 133–274)			
P3 Male 5apr2008 6 months	Yes	Several affected in family*	p.H178L/ p.H178L	Baseline (6 m)	68 cm (P50)	8.35 kg (p50)	NA	No	No	No	No	Mild	Yes	No	No	NT	Patent ductus arteriosus	1180 (ref:133–274)	No	Viral respiratory infection	No
				Follow–up	113 cm (p50)	19.5 kg (P50)	53.5 cm (P98)	No	Small umbilical	Mild clouding, strabismus	No	No	Yes mild	No	Yes	NT	Thickened mitral and aortic valves, mild egurgitation, dilated left chambers	260 (ref: 68–188)		No	
P4 Female 2dec2007 10 months	No	1 affected sibling	Unknown	Baseline (10 m)	69.5 cm (p75)	7.89 kg (p25)	49.3 cm (>p98)	No	No	mild	NT	No	Yes	Yes	No	Yes	Mitral regurgitation, moderate left ventricular dysfunction (both mild)	874,52 (ref: <21)	Cervical laminectomy and fixation (20 m); carpal tunnel syndrome and umbilical hernia (6 y4 m)	No	No
				Follow–up	100 cm (<p3)	15.7 kg (<p3)	52 cm (p90)	Very mild	Small umbilical hernia	mild	No	No	Yes	Yes mild	No **	No	Dilated left chambers, thickened mitral and aortic valves, mitral regurgitation	27.24 (ref: <66.2)			

Legend: NT — not tested; d — day, m — month, y — year, GE — gastro-esophageal; *patient belongs to endogamic population [22]; **normalized after carpal tunnel syndrome surgery.

Fig. 1. P1 (arrow) with older affected brother and sister, ages 4, 7 and 10 years.

below the 3rd percentile and head circumference was on the 98th percentile (Fig. 3).

Dysostosis that was present when P4 started ERT got progressively worse and height and weight are now below the third percentile. Her brother was 3 yrs. and 9 months when ERT was introduced and had dysostosis, height and weight were below the third percentile. P4 is now taller than her brother was at age 6 yrs. (Fig. 4).

3.5. Abdomen

The four children have not presented hepatosplenomegaly at any time, so storage in spleen and liver was prevented by early enzyme replacement. The siblings of P1, P3 and P4 had hepatomegaly at baseline and liver size progressively normalized with ERT.

3.6. Cardiac

Heart disease was already present in two of the four infants at baseline and got worse over time, but the youngest patient (P1) still has a normal echocardiogram at six years of age, while his older brother who only started ERT at 35 months presented thickening of the aortic valve at baseline.

P2 had mild mitral valve insufficiency at baseline that led to mild ventricular wall thickening and at five years of age mild aortic valve insufficiency was also present.

P3 had a persistent ductus arteriosus since birth but at age two years showed typical MPS VI heart disease with mild mitral valve regurgitation and dilated left chambers, and at four years, thickened mitral, aortic and tricuspid valves, mitral and aortic regurgitation. His affected older brother had only mild mitral regurgitation at 6 years and 7 months.

P4 had mild mitral regurgitation and moderate left ventricular dysfunction at baseline, At 25 months the mitral regurgitation was worse

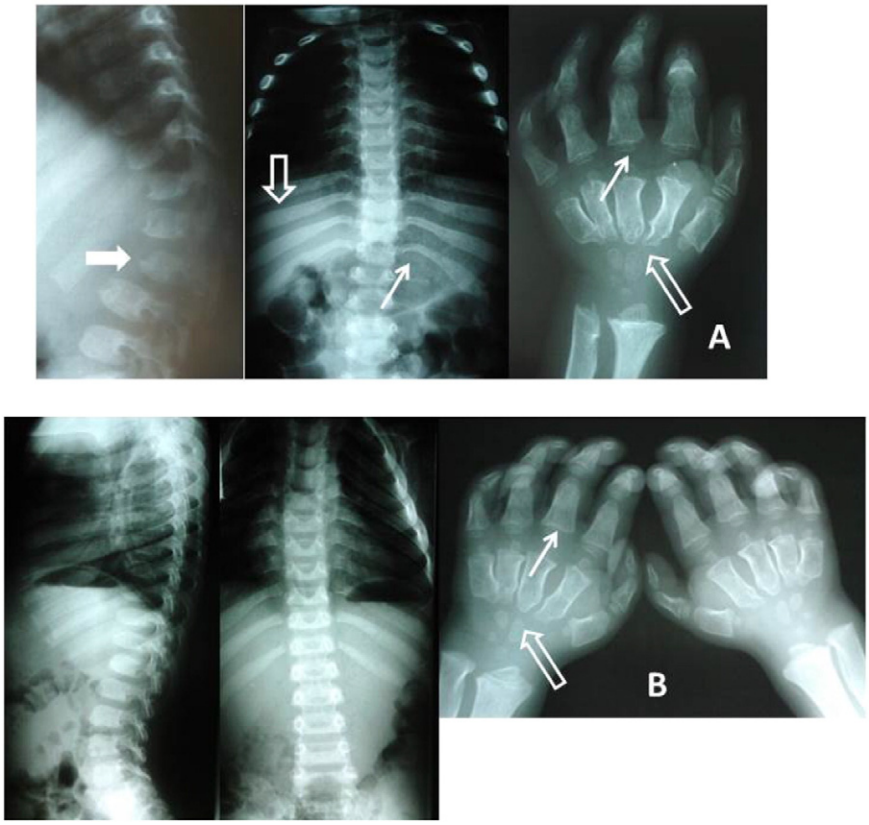

Fig. 2. Comparative X-rays at age 6 years. A — older sister of P1: note dysostosis multiplex, with abnormal vertebrae (rounded vertebral bodies with the "anterior beaking" aspect – white arrow – and posterior scalloping), abnormal ribs (tapered proximally — full arrow, and wider distally — empty arrow) and hands (broad and proximally pointed short metacarpals — empty arrow, bullet shaped phalanges — full arrow); B–P1: milder vertebrae abnormalities, dysostosis in hands (same pattern as sister, pointed by arrows).

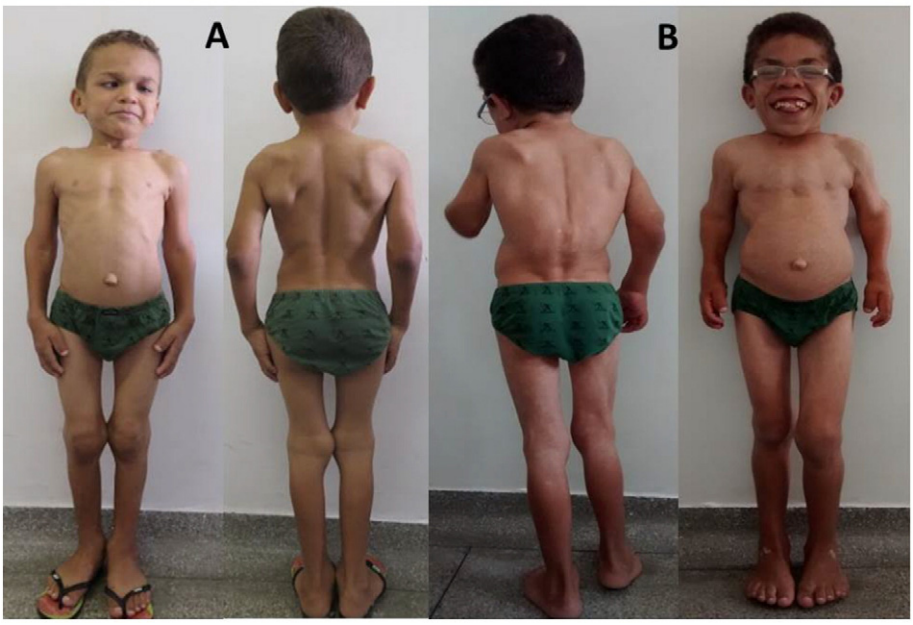

Fig. 3. P3 (A) and older brother (B), ages 6 and 12 years.

and she had dilated left chambers with normal ventricular function. At 6 years a dysplastic and thickened aortic valve was also present, while mitral regurgitation and ventricular function had slightly worsened. Her older affected brother had, at 5 years, mild mitral and minimal aortic thickening and regurgitation, dilated left ventricle and diminished ejection fraction.

3.7. Eyes

P1 corneas are still normal, P2 presented mild corneal clouding at age 17 months and now has moderate clouding, P3 had no clouding up to four years of age but at age 5 years it was detected. Only the oldest child (P4) had corneal clouding detected at baseline, although it continues to be mild.

3.8. Development and nervous system

During the six years under ERT, all patients had normal motor and mental development, tested with Denver Developmental Screening Test during regular pediatric visits. Brain and cervical MRI images of P2 and P4 have shown abnormalities, while P1 has normal cranial and cervical images. No brain/cervical imaging studies are available for P3.

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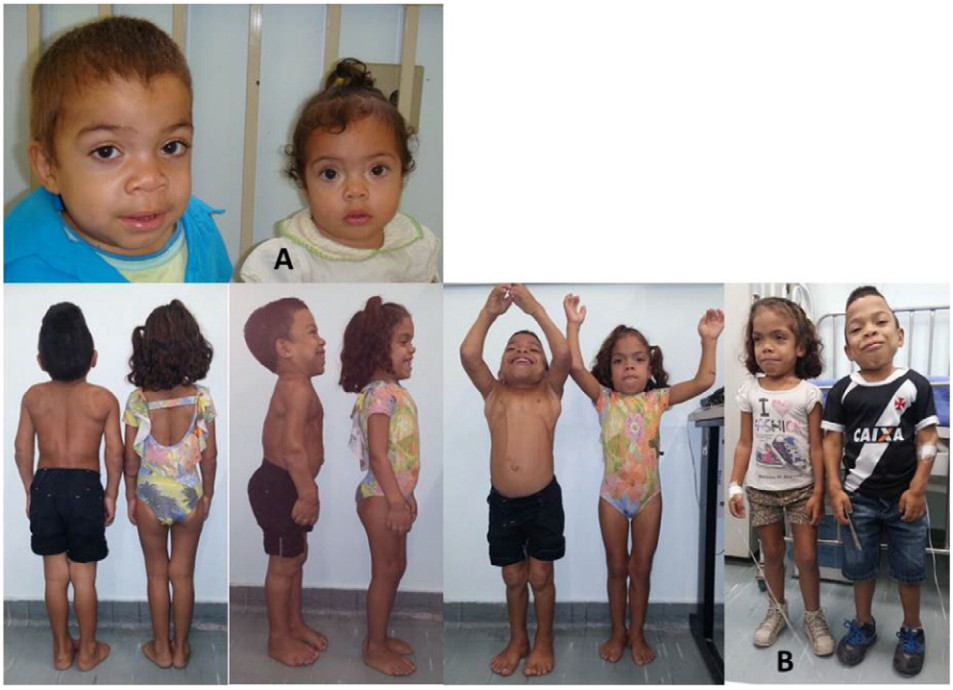

Fig. 4. P4 (the girl) and older affected brother. A — baseline, ages 10 months and 3 years; B — after 6 years on ERT, ages 7 and 10 years.

Fig. 5. Facial phenotype: MPS VI on ERT since infancy, 6 years under treatment, patients P1, P2, P3 and P4.

and normal brain image; P4 at 17 months had prominent perivascular spaces on semioval center, radiate crown and lateral periventricular white matter, minimal gliosis, normal sized ventricles and anterior subluxation of C1 on C2, absence of anterior and posterior arches of C1 and cranial-vertebral junction stenosis with bulbo-medular compression. As she presented symptoms of myelopathy, cervical laminectomy and fixation were performed at 20 months of age [13]. At five years of age MRI showed normal brain and ventricular images; cervical spine images revealed no myelomalacia.

P4 had surgical correction of carpal tunnel syndrome at 6 years and 4 months of age, while her brother already had to operate at age 4 years. P3 was recently diagnosed with carpal tunnel syndrome; P1 and P2 have not been specifically tested yet.

3.9. Hearing

P2 had conductive hearing deficit diagnosed at 4 years of age.

3.10. Sleep studies

P1 at 5 years has moderate sleep disorder while his brother already presented sleep apnea at 35 months of age. P3 had mild sleep apnea at baseline and had a normal polysomnography at age 5 years. His brother at ERT baseline (6 years and 7 months) had severe restrictive respiratory insufficiency and severe sleep apnea; after five years on ERT the brother's apnea is now mild although he still needs to use a CPAP. P4 at seven years of age has no sleep apnea; her brother had severe sleep disorder at 45 months of age that improved with ERT.

3.11. Surgeries

The three boys in the sample had inguinal herniae detected after age 18 months and had surgical corrections; the girl (P4) had a small umbilical hernia.

3.12. General phenotype

Our results suggest that early galsulfase therapy may also improve or even prevent progression of facial dysmorphic features in MPS VI patients, corroborating similar findings seen in previous MPS VI sibling studies and in the recent multicenter open-label study [10,11,19] (Fig. 5).

4. Discussion

Evaluating the effect of early ERT on individual patients is very difficult as MPS VI has a very large clinical spectrum in severity and progression of disease. Genotype–phenotype correlation is not possible [2]; furthermore, the patients whose molecular studies have been completed had different mutations so their clinical conditions should not be compared.

MPS VI is a progressive disease and the natural history is that patients typically appear normal at birth and the clinical features begin to emerge between the ages of 1 and 3 years [2]. The patients here reported showed the first clinical signs of MPS VI in the first year of life, with the exception of P1, who began treatment at the 5th day of life.

As for the other three patients, P2 started ERT later, at four months of age and already presented dysostosis on vertebrae and hips and mild mitral valve insufficiency. He also presented recurrent ear infections (that could be due to a gastroesophagic reflux) on the first four months of life, that resulted in a mild conductive hearing deficit, and had upper airways infections monthly up to one year of age. He is allergic and these situations often occur in children, but recurrent upper airway infection is one of the nonspecific clinical signs reported for MPS VI. Although the patient was on ERT, these cannot be excluded as disease manifestations.

Diagnosed at two months of age, P3 started ERT at six months of age and already had mild hearing deficit, mild sleep disorder and dysostosis of vertebrae, phalanges of fingers and toes, long bones and hips.

P4 started ERT at 10 months of age and already showed mild facial coarseness, mild corneal clouding and mild mitral regurgitation with moderate left ventricular dysfunction. She had mild elbow joint restriction, macrocrania, prominent frontal, pectus carinatum and vertebral dysostosis.

These findings point to the fact that skeletal features of the disease cannot be completely prevented despite early ERT. It is clear, however, that even though ERT treatment could not prevent the progression of dysostosis multiplex in our four patients, less severe radiographic involvement can be noticed when comparing the younger sibling with his older pair. Dysostosis multiplex changes were also seen in other young MPS VI patients (sibling studies and open label study), regardless early ERT treatment [10,11,19].

In summary, heart disease has progressed in all but in P1, who began ERT at 5 days, bone disease, although milder, still exists and several surgeries have been necessary. Unfortunately, not all subjects have followed the same protocol, and some evaluations are still missing. Compliance with enzyme treatment has been satisfactory, and the children are under strict follow up. Overall, health in the four patients has been good, although complications of MPS VI still occur.

5. Conclusions

The present study is subject to limitations, since the patients were treated in a “real world setting” and not part of a designed clinical trial and in different regions of the country, with great diversity on health care opportunities. No single endpoint could be specified other than safety aspects of early ERT treatment in very young patients. In addition, the variability between sites regarding timing and availability of exams, imaging procedures, echocardiography and also exam reading techniques presented challenges in overall interpretation. It must be pointed out, however, that the disease still exists despite early ERT, as has been shown regarding findings on nervous system, orthopedic and cardiac. Nevertheless, progression does seem to be at a different rate, and the

sibling comparison is an aspect that reinforces the clinical impact of early ERT, since differences on disease progression between sibs were obvious.

The severity of the disorder in these four infants seems related to age and it is tempting to say that severity on the first year of life is progressive and that ERT effect is indirectly related to baseline severity. As stated above, MPS VI patients do have different progression rate of the disease. By showing that these infants had a slower progression than their older siblings speaks in favor of a very early start of ERT. Beneficial results of very early ERT may also support the need to consider the inclusion of MPS VI disease in newborn screening programs, especially in known high risk populations [22].

Important to reinforce, no safety concerns were identified and none of the patients experienced serious adverse events related to therapy. In conclusion, this report on follow-up of four MPS VI patients whose treatment with galsulfase began in infancy and were not part of a specific clinical trial confirms the early manifestations of the disease and provides additional evidence of the beneficial effects of ERT in patients younger than 1 year of age.

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