



## Enzyme replacement therapy with galsulfase in 34 children younger than five years of age with MPS VI

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### ABSTRACT

**Background:** Mucopolysaccharidosis type VI (MPS VI) is a progressive, chronic and multisystem lysosomal storage disease with a wide disease spectrum. Clinical and biochemical improvements have been reported for MPS VI patients on enzyme replacement therapy (ERT) with rhASB (recombinant human arylsulfatase B; galsulfase, Naglazyme®, BioMarin Pharmaceutical Inc.), making early diagnosis and intervention imperative for optimal patient outcomes. Few studies have included children younger than five years of age. This report describes 34 MPS VI patients that started treatment with galsulfase before five years of age.

**Methods:** Data from patients who initiated treatment at <5 years of age were collected from patients' medical records. Baseline and follow-up assessments of common symptoms that led to diagnosis and that were used to evaluate disease progression and treatment efficacy were evaluated.

**Results:** A significant negative correlation was seen with treatment with ERT and urinary GAG levels. Of those with baseline and follow-up growth data, 47% remained on their pre-treatment growth curve or moved to a higher percentile after treatment. Of the 9 patients with baseline and follow-up sleep studies, 5 remained unaffected and 1 patient initially with mild sleep apnea showed improvement. Data regarding cardiac, ophthalmic, central nervous system, hearing, surgical interventions and development are also reported. No patient discontinued treatment due to an adverse event and all that were treatment-emergent resolved.

**Conclusions:** The prescribed dosage of 1 mg/kg IV weekly with galsulfase ERT is shown to be safe and effective in slowing and/or improving certain aspects of the disease, although patients should be closely monitored for complications associated with the natural history of the disease, especially cardiac valve involvement and spinal cord compression. A long-term follow-up investigation of this group of children

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will provide further information on the benefits of early treatment as well as disease progression and treatment efficacy and safety in this young patient population.

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## 1. Introduction

Mucopolysaccharidosis type VI (MPS VI; OMIM ID: #253200, Maroteaux-Lamy syndrome) is a 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 [1]. Partially degraded GAG accumulates in lysosomes in a wide range of tissues, causing a multisystemic chronic and progressive disorder with significant functional impairment and shortened lifespan [2,3]. MPS VI has a wide disease spectrum, with rapidly progressing patients generally presenting with coarse facies, short stature and dysostosis multiplex within the first year of life. Patients with more slowly progressing disease may not present with these classic symptoms, potentially delaying diagnosis until later in life.

Since the advent of enzyme replacement therapy (ERT) for MPS VI with recombinant human N-acetylgalactosamine 4-sulfatase, rhASB (galsulfase, Naglazyme®), several aspects of clinical improvement were reported [3–6]. However, published clinical studies that showed the efficacy and safety of enzyme replacement therapy for MPS VI with rhASB did not include younger children (less than 5 years). This may be due to the challenge of evaluating this age group using the defined clinical end-points such as the 12-minutes-walk test (MWT) and pulmonary evaluations, which require the children's understanding and cooperation.

In the initial clinical trials, ages in Phase I ranged from 7 to 16 years. In Phase II, ages were from 6 to 22 years and in the Phase III study the inclusion criteria specified patients to be at least 5 years of age [4–6]. Although significant clinical responses were observed in those trials, long standing organ damage could not be reversed by ERT, suggesting that early initiation of therapy could be the best treatment approach. This was demonstrated in some pre-clinical studies with MPS VI animal models treated since birth [7], yet there are only a few reports of implementation of ERT at an early age in MPS VI patients [8,9].

In one report, a pair of MPS VI siblings started galsulfase ERT at 41 months of age and at 8 weeks [8]. As compared to the older sibling at the same age, the younger sibling developed only mild symptoms (skeletal, corneal clouding and mitral valve dysplasia), demonstrating the benefits and safety of early treatment. This report also highlighted the older sister's outcome, with improvement in skeletal involvement, hepatosplenomegaly and joint mobility [8]. Similar findings in another sibling pair were recently reported comparing a 5.6 year-old boy and his 6 week-old sister [9]. Visual acuity has also been found to stabilize in 6 MPS VI patients on ERT [10]. Significant clinical improvement was shown even in a 3-year-old patient with severe disease who had to be managed for infusion associated events (IARs) and yet ERT was not discontinued [11]. However, to ensure that ERT can be safely initiated at an early age, it is important for physicians to become aware of all symptoms of MPS VI, even those that are not as clearly indicative of the disease.

As a number of our patients with MPS VI initiated ERT with rhASB before five years of age, we sought to determine common presenting features of these patients, as well as clinical outcomes post-ERT to provide clinical information regarding use of ERT in this young cohort of patients.

## 2. Methods

The National MPS Patient Association – *Aliança MPS Brasil* – provided the location of patients with MPS VI in Brazil and their physicians. A questionnaire (Supplementary Table 1) was developed and sent to

these attending physicians at reference centers for diagnosis and treatment of MPS in Brazil. Data were collected from patients' medical records after informed consent was obtained. Mean, median and range of reduction of uKS levels were calculated. Growth velocity was calculated and percentiles were charted. Disease progression was evaluated based on cardiac and central nervous system involvement, sleep study assessments and surgical interventions required for those with baseline and post-ERT assessment. Ophthalmic, developmental and hearing assessments were also evaluated at different time points throughout the review.

## 3. Results

Fifteen sites located in the five different regions of Brazil agreed to participate. 161 MPS VI patients were identified in Brazil; 144 (89%) of which have been on ERT. Of these, 58 (40%) patients started infusions before the age of five years, and 34 (59%) of this group agreed to be included in this survey. Although 21 were boys and only 13 were girls, the 1.6:1 sex ratio was not considered significant ( $p > 0.05$ ). Parental consanguinity was present in 18 (60%) of the 30 families involved. MPS VI clinical signs and symptoms were observed at baseline in all but the newborn patient (Table 1). Clinical and/or radiological evaluations were available for 32 patients, with dysostosis multiplex present in 31. No obvious skeletal abnormalities were seen on the newborn patient's skeletal survey, but no lateral thoraco-lumbar spine films were available for analysis. Some clinical information and additional exams were not available for all patients.

The median age of diagnosis was 28.5 months. One boy was diagnosed prenatally; the earliest postnatal diagnosis was at two months of age and the latest at 46 months of age. The youngest patient to start ERT was five days old, and the oldest, 58 months (Table 2).

### 3.1. Genotype data

Targeted mutation analysis for known mutations in the *ASB* gene was available for 12 patients. Six patients, from the same geographic location, were homozygous for a previously described pathogenic mutation, p.H178L [12]. Four patients had a common polymorphism on intron 3 (IVS3-22 T > C); two patients had none of these common mutations detected. Sequence analysis of *ASB* gene is currently in process.

### 3.2. GAG levels

All patients had been receiving weekly 1 mg/kg body weight of galsulfase intravenously, from 1 to 56 months (average 25.47; SD 13.17; median 29.50 months). Only five patients had been treated for

**Table 1**  
ERT-related adverse events presented in the sample.

Adverse event	Number of events	Number of patients
Pyrexia	3	2
Chills	1	1
Skin rash	1	1
Cyanosis	1	1
Nausea	3	2
Coughing crisis	2	1
Hypertension	1	1
Tachycardia	1	1

**Table 2**

Ages of patients at the time of diagnosis, ERT initiation and present age in MPS VI patients under five years of age.

N	Age at diagnosis (months) <sup>a</sup>			Age at 1st ERT (months) <sup>a</sup>			Present age (months)		
	All	Boys	Girls	All	Boys	Girls	All	Boys	Girls
	34 <sup>b</sup>	21 <sup>b</sup>	13	34 <sup>b</sup>	21 <sup>b</sup>	13	33 <sup>b</sup>	21 <sup>b</sup>	12
Average	25.94	24.75	27.85	35.06	35.66	34.08	59.88	59.24	61.00
SD	12.94	12.27	14.24	14.97	15.84	14.00	17.93	18.51	17.62
Median	28.50	29.00	28.00	38.50	40.70	35.00	62	64.00	56.50
Min	−2.00	−2.00	6.00	0.17	0.17	10.00	24.00	24.00	30.00
Max	46.00	40.00	46.00	58.00	58.00	53.00	90.00	87.00	90.00

<sup>a</sup> Includes a deceased patient.

<sup>b</sup> Includes 1 boy who was diagnosed prenatally.

less than one year. Six patients never missed the programmed infusions, 17 missed <10%, eight between 10 to 20%, and 3 missed >20% (Fig. 1). Baseline urinary GAG levels were available for 26 of the 34 patients. They were elevated when compared to normal values for age with an average of 553.35, SD 452.63, median 516.00 mcg GAG/mg creatinine; normal values range from 16 to 188 mcg GAG/mg creatinine [13]. A significant negative correlation was seen with urinary GAG levels and age at baseline ( $r = -0.46$ ;  $t = 2.538$ ;  $p < 0.05$ ).

For 11 patients with follow-up urinary GAG levels, 10 had reached normal levels and one patient, whose baseline GAG excretion was only slightly raised, remained stable with ERT. Length of treatment with ERT in this group of patients varied from 15 to 41 months.

### 3.3. Growth

Follow up growth data was available for 32 patients. Mean annual growth velocity in boys was 5.72 cm (median 4.65 with a range of 0.72 to 12.40 cm) and, in girls, 4.80 cm (median 4.87 with a range of 1.35 to

8.50 cm). Mean baseline height z-score was  $-1.76$  for the whole patient population studied, compared with  $-0.914$  in the  $\leq 2$  years old group and  $-2.033$  in the  $> 2$  years population. Baseline height for 20 boys ranged from 49 to 94.5 cm (median 88; average 84.13; SD 11.4) and for 12 girls 69.5 to 91.5 cm (median 88.5; average 84.85; SD 7.55) (Fig. 2). Seventeen of 32 (53.13%) patients (10 boys and 7 girls) were below the 3rd percentile for height, one girl was above the 97th percentile (Figs. 3, 4a and b). Short stature at baseline was present in only one patient under 2 years of age, but was present in 21 of 25 patients above the age of 2 years (Fisher Exact Probability = 0.014). Comparing baseline to present height data, 12 (37.5%) patients remained on the same growth curve, 3 (9.4%) went to a percentile curve above and 17 (53%) fell below their original percentile curve (Fig. 2).

Baseline weight ranged from 2.88 to 23 kg for boys and from 7.89 to 17.7 kg for girls. At baseline, 6 of 32 (18.75%) patients (3 boys and 3 girls) were below the 3rd percentile for weight and two patients (6.25%), a boy and a girl, were above the 97th percentile.

No patient under two years of age was underweight, while 6 of 25 patients above age two were below the 3rd percentile. No significant difference in frequency of underweight patients were found between the two groups (Fisher Exact Probability = 0.20). Comparing baseline and present weight data, 10 patients remained on the same weight percentile curve, 7 had increased to a higher percentile curve and 15 dropped to a lower percentile. Weight gain during treatment ranged in boys from 500 g to 13 kg and in girls from 1.3 to 6.3 kg. The median monthly gain for boys was 277 g (average 161; SD 98 g) and ranged from 45 g to 361 g. The median monthly gain for the girls was 146 g (average 133 g; SD 44 g) and varied from 54 to 200 g.

At baseline, 7 out of 30 patients (5 boys and 2 girls) had a head circumference (HC) above two standard deviations, 2 of these have now normal measurements for age and 5 continued on the same percentile curve. Two patients had HC less than two standard deviations at baseline and on follow-up, one is within normal standards for age and the other is slightly below. Three of the 20 patients, that had normal measurements at baseline, had HC two standard deviations above at follow-up.

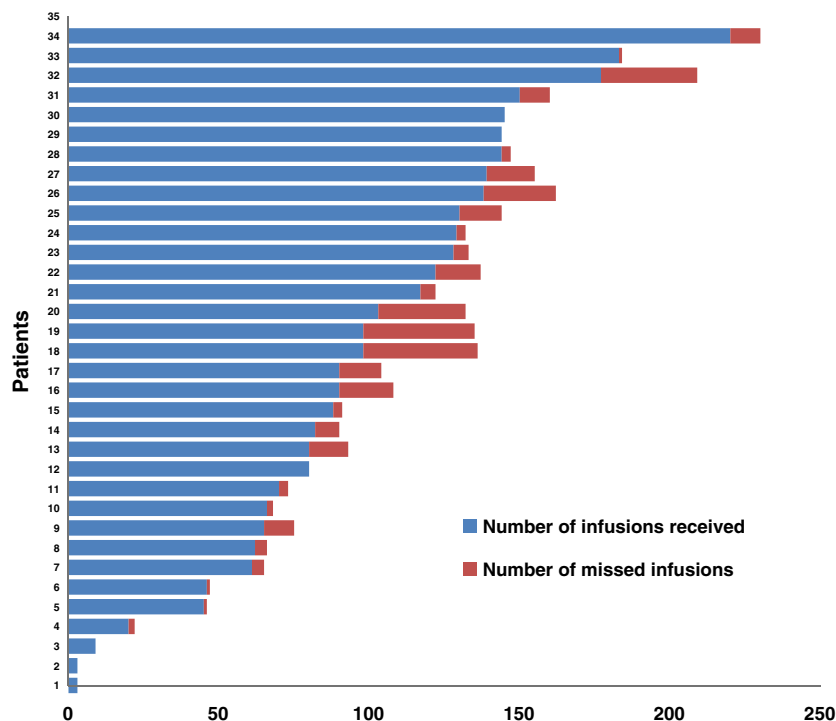


Fig. 1. Compliance to galsulfase ERT for 34 MPS VI patients under five years of age, ordered by total weeks on treatment.

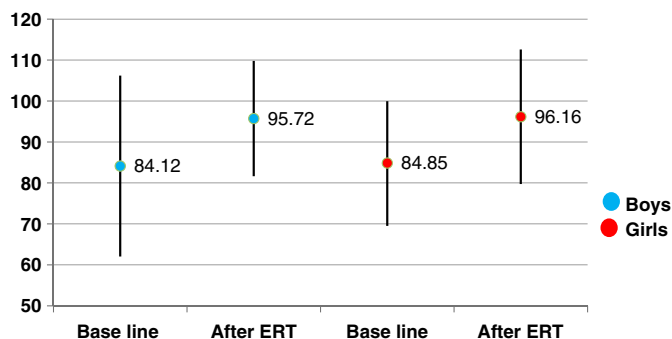


Fig. 2. Mean  $\pm$  SD baseline and present height (absolute measurement distribution) for 32 MPS VI patients, 20 boys and 12 girls who had ERT introduced before five years of age.

### 3.4. Safety/adverse events

No severe infusion-related reactions were observed. Despite the occurrence of adverse events (AE) considered treatment-related in 8 (24%) patients, all continued to receive infusions without further complications. During an infusion, one patient who had been on ERT for two years presented with skin rash and local edema (in the contralateral limb of the infusion site). This type of reaction persisted for 12 weeks, and was controlled with oral and intravenous antihistamines and intravenous steroids; he is now being pre-medicated with intravenous antihistamines before each infusion.

Four patients had one episode of mild AEs each (rise in blood pressure, tachycardia, skin rash and nausea), and the youngest patient (a neonate) had one episode of pyrexia with cyanosis. This episode resolved once infusion was halted and did not recur once infusion was restarted at a slower rate. Two patients presented with the same mild AE on 2 occasions (one had a coughing crisis with post-tussive emesis and the other developed transient pyrexia and shivering). Decreasing the rate of infusion and antipyretics were sufficient to control those AEs. The 34 patients had a total of 3325 galsulfase infusions in which 21 AEs were reported. (Table 3) One (3%) patient died from pulmonary hypertension at 6 years of age which was deemed not related to treatment.

### 3.5. Heart involvement

Of the 28 patients with baseline echocardiogram (echo) assessments, 18 (64%) had an abnormal echo; 7 had left ventricular hypertrophy (LVH) without ventricular dysfunction. Valve abnormalities were observed in 17 patients (mitral: 13; aortic: 6; tricuspid: 2). Aortic root dilatation was found in 2 patients. Twelve patients who had been on ERT for at least

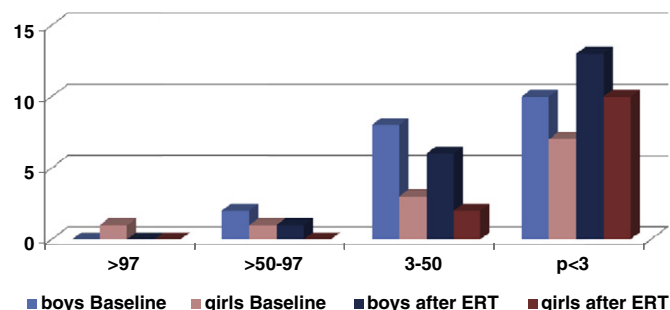


Fig. 3. Baseline and present height percentiles for 32 MPS VI patients, 20 boys and 12 girls who had ERT introduced before five years of age.

17 months had more than one follow-up echo exams. Valvular disease worsened in 11 patients, while the remaining showed no change. LVH improved in 4 patients over the treatment period, while 3 patients did not show further worsening. One patient had mitral valve regurgitation on diagnosis and severe pulmonary hypertension with dilated right chambers, severe right ventricular dysfunction and right to left oval foramen shunt upon follow-up. This patient died at six years of age due to pulmonary hypertension, considered not related to treatment.

The other 10 patients had normal echos at baseline. Two of these 10 remained normal on follow-up exam: the patient who started ERT as a neonate had normal echos at baseline and at follow-up at 27 months of age; the other patient that had a normal follow-up echo at 41 months of age started ERT when he was 26 months-old. One patient's echo at four months of age showed *ductus arteriosus*, while follow up exam at 23 months of age (17 months on ERT) showed mild mitral valve regurgitation, left ventricular and atrial dilatation with normal function. The other seven patients developed mitral regurgitation, three associated with aortic regurgitation and one with tricuspid regurgitation, and three of these patients also showed LVH. Among the six patients without a baseline echo, four were evaluated during treatment and all presented with mitral regurgitation, one combined with LVH. The remaining two patients had heart murmurs but have yet to be examined. In summary, when reviewing the most recent assessment of the 32 patients with an echo evaluation performed at any time, only two had normal exams, 30 had valve involvement and 11 had LVH.

### 3.6. Central nervous system, spinal cord and nerve conduction

Neuroimaging was undertaken in 11 patients: 5 had brain CT and 6 had brain MRI. Among those, 5 were reported as normal, 5 showed signs of hydrocephalus, 2 of these with white matter lesions and one was diagnosed as having brain atrophy. Two patients had measurement of intracranial pressure (ICP). One patient had elevated ICP and a ventricle-peritoneal shunt was placed.

Six patients underwent cervical MRI: 4 showed spinal cord compression at the cervical level and 2 of them had T2-hypersignal suggesting myelopathy. These patients had clinical signs of compression, with motor and sensitive deficits, 2 already at baseline and 2 developed clinical signs of compression during follow-up. The other 2 patients had reduction of intravertebral space, 1 with atlantoaxial instability, but with no clinical or radiological signs of compression or myelopathy.

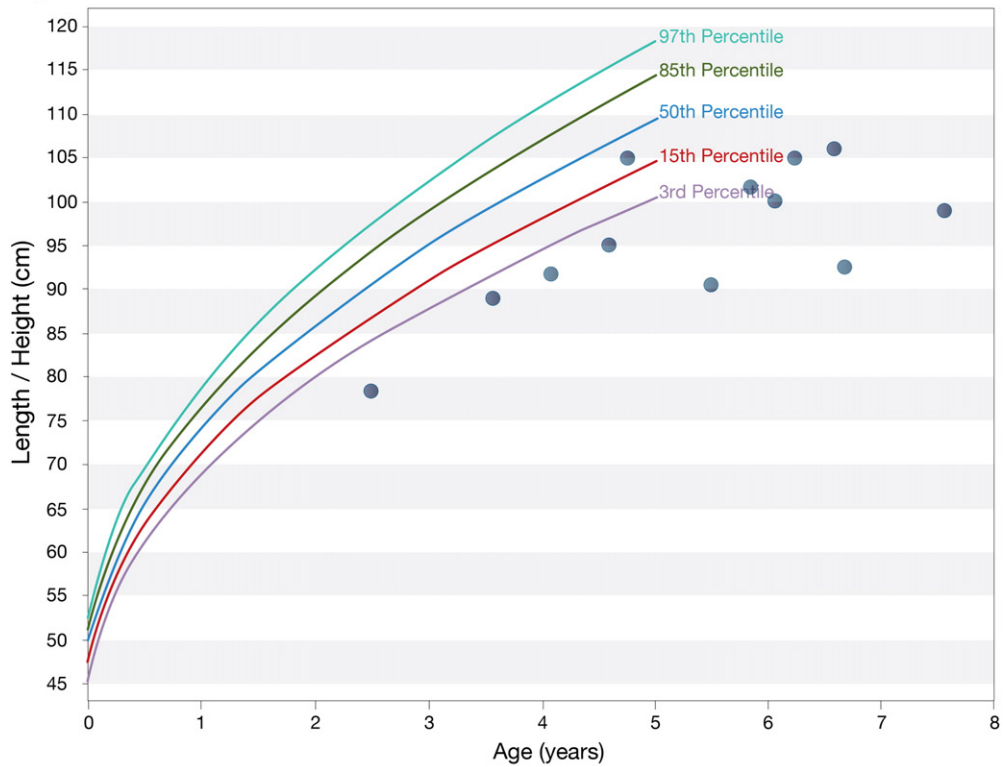
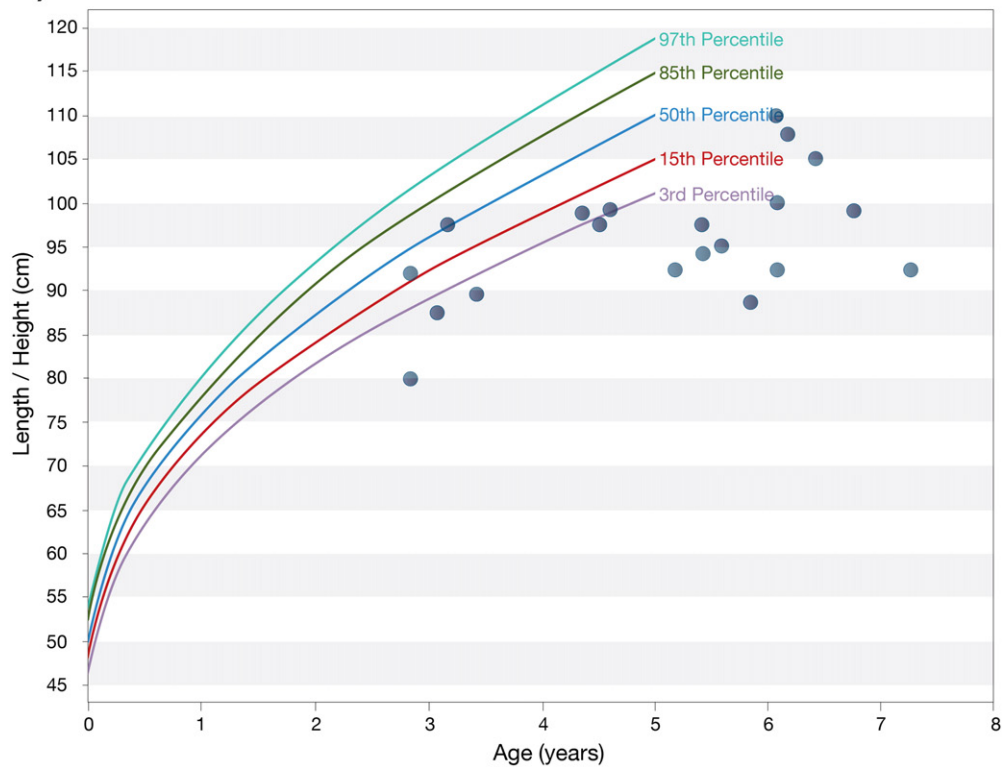
One patient in the cohort became paraplegic after a fall; unfortunately the cause has not yet been clarified, since no MRI has been performed. Three patients underwent neurophysiologic evaluations (SSEP, MEP and electroneuromyography), compatible with spinal cord compression at the cervical level, and one had a confirmation of bilateral carpal tunnel syndrome.

### 3.7. Surgery

Fourteen patients underwent a total of 18 surgical procedures: 8 for hernia repair (2 had recurrent hernia), 4 for cervical spinal cord decompression and one for carpal tunnel syndrome. One patient had an adenoidectomy, one had clubfoot surgical correction and one had a thoracic tube inserted due to pleural effusion. Six of these procedures were performed even before MPS was diagnosed, and one after diagnosis but before the patient began ERT. Two patients had infusion catheter implantation for administration of ERT.

### 3.8. Sleep studies

Sleep studies were performed at baseline in 17 patients, with follow-up studies available for 9 patients. At baseline, 12 of those assessed showed sleep apnea while the rest were unaffected. Of the

**A) Females****B) Males**

**Fig. 4.** A and B. Absolute present height (cm) of MPS VI patients compared to the World Health Organization (WHO) percentiles.

9 patients with follow-up data available, 5 that previously had normal sleep studies remained unchanged. One patient with severe sleep apnea at baseline remained stable. Interestingly, one patient with

mild apnea showed improvement with a normal follow-up study. Nevertheless, two patients had progression of sleep apnea from normal/mild to severe.

**Table 3**

Frequency of reported cardinal clinical signs at baseline evaluation for 34 MPS VI patients on ERT under five years of age.

Cardinal baseline signs <sup>a</sup>	Frequency of patients <sup>b</sup>
Dysostosis multiplex	31/32
Coarse facies.	18/27
Short Stature	17/32
Valvular Disease	17/28
Sleep apnea	12/15
Corneal Clouding	9/15
Auditive deficit	8/12
Head Circumference > 2 SD	8/30
Myocardiopathy	7/28
Hydrocephalus	7/11
Motor and/or speech delay	7/33
Cervical spinal cord compression	4/6

<sup>a</sup> Information or examinations were not available for all patients.

<sup>b</sup> Number of patients with cardinal base signs out of those with available data.

### 3.9. Ophthalmology

Ophthalmologic evaluations were performed in 15 patients at different time points relative to length of time on ERT in the study. Mild corneal clouding was observed in 9. Intraocular pressure examinations were measured in 4 patients – all of them had normal pressure. Fundoscopy was performed in only one patient and showed a very discrete retinal epithelial rarefaction.

### 3.10. Hearing

Hearing tests were performed at baseline in 11 patients and one only had it after introduction of ERT; 8 patients had bilateral mild or moderate conductive deficits. Follow-up studies were only possible in 3 patients: 1 had a normal evaluation and 2 remained unchanged.

### 3.11. Development

Out of the 34 patients, 7 had development delay at baseline, one probably due to perinatal hypoxia. A patient who presented initially with speech and motor delay had only mild speech delay at last follow up. Adequate motor and language development for age was noticed in 3 unrelated patients with previous features of motor delay and in 2 other patients with speech delay. Speech delay was observed in the patient treated since neonatal period at 32 months of age.

## 4. Discussion

The use of galsulfase in the Brazilian MPS patients with treatment initiation of <5 years of age in this study was found to be safe and effective in this young patient population and similar to that seen in clinical trials with older patients [4–6]. Diagnosis was confirmed earlier in families with a previously affected child than in those families without a previously diagnosed child. Among the non-familial cases, children were diagnosed only after the onset of clinical symptoms. Early treatment initiation with ERT was introduced under the rationale that no major contraindications for young patients were reported either in the literature or on the galsulfase prescribing information. Most physicians followed published guidelines for treating MPS VI and assessing disease progression and treatment efficacy [14].

The MPS VI patients presented in this report were treated in different clinical centers; all located within Brazil and were not involved in any clinical trials. As such, assessments used to assess disease progression and treatment efficacy may have differed slightly from those used in clinical trials, and were likely not as stringently implemented as done with clinical trials. Economic and geographic factors were obstacles for providing more complete evaluations. Some assessments were not available

in some settings, such as imaging exams and laboratory evaluations. Several exams that required sedation were not performed due to increased risks in relation to the benefits that would be provided. Furthermore, many children were too young to perform exams that required their comprehension and voluntary participation. These factors may result in variations in assessments used between and within clinics.

Mean baseline uGAG levels were 553.35 SD 452.63, higher than the 338 SD 111 reported by Decker et al. 2010, whereas mean baseline height z-score was –1.76, as compared to the –4.4 reported by Decker et al. 2010 in a cohort of 5–7 years [15]. Disparity in uGAG levels may be due to the increased severity of disease experienced in many Brazilian patients, whereas the disparity in height z-scores may illustrate the significant impact of disease individuals experience as they age. Although this is a retrospective study and measurements and evaluations were done by different physicians and no pre-treatment growth velocity is available for comparison, the calculated increase in height velocity during ERT was due in part to the treatment and cannot be considered only as an effect of joint restriction improvement as growth continued despite bone disease. Two patients moved to a higher height percentile curve and more than half of the patients dropped to a lower percentile, although still within the normal range, probably due to the limitation of ERT treatment for the bone disease in this disorder. We can only hypothesize how different these patients would have grown without ERT. Further follow up would be needed to determine what percentage of patients would achieve normal height and if their growth restriction is less severe than the untreated counterparts.

Frequency of drug-related AEs in these young children were similar to those seen in the clinical studies in subjects >5 years of age, and were isolated episodes of mild infusion reactions that did not require withdrawal of ERT [4–7]. Only one death occurred in this patient population, a female patient born to consanguineous parents, homozygous for the p.H178L mutation and diagnosed at 27 months of age with dysostosis multiplex, corneal clouding, mitral valve regurgitation and severe sleep apnea/hypopnea.

Treatment with ERT was initiated when the patient was 3.5 years of age. The patient gained weight and grew 14 cm in 33 months. Her cardiac involvement continued to progress and deteriorate and she continued to have chronic upper airway infections and severe sleep apnea/hypopnea throughout the time of treatment. Her last echocardiogram showed severe pulmonary hypertension with dilated right chambers, severe right ventricular dysfunction and right to left oval foramen shunt. She died from pulmonary hypertension at 6 years of age, at which time she had been on ERT for three years. However, she had missed 22% of scheduled infusions due to the distance to the treatment site. Other factors may have contributed to compliance problems resulting in missed ERT infusions for this and other patients, as well as being obstacles for providing complete evaluations. Common childhood illnesses, such as occurred with this patient, may be a frequent cause of missed infusions in this young patient population.

The fact that one patient of our cohort died of cardiorespiratory complications highlights the importance of close monitoring of cardiac disease in this population, especially as cardiovascular and respiratory complications are the main cause of death for MPS VI patients [1,16]. Cardiac involvement is a common finding in MPS VI patients, with almost two thirds of our study population presenting with cardiac valve abnormalities and/or myocardial involvement at baseline. Careful, ongoing assessment of heart disease is reinforced by the fact that only 2 patients continued with normal cardiac function at follow up (including the patient that started ERT in the neonatal period). In the other 10 patients with follow-up exams available, 6 presented with ventricular hypertrophy or dilatation at baseline, which was reduced in 4 and did not change in 2. Nevertheless, valvular disease continued to progress in 7 patients, seemingly not impacted by treatment with ERT. These results were also seen in young MPS I patients on ERT [16].

Despite the study including very young children, all but the patient diagnosed as a newborn presented with dysostosis multiplex. Short stature was present in more than half the patients at baseline and in 84% of patients >2 years, consistent with the natural history of the disease, with MPS VI patients usually achieving normal heights until 2–4 years of age and then fall off their growth curves [15]. It is important to note that only one of 7 patients <2 years of age at diagnosis were affected with short stature as this absence of growth restriction may delay the diagnosis of MPS VI.

Sleep disturbances and hearing deficits are probably underdiagnosed in our cohort since sleep studies and hearing evaluations were available only in a few of the centers. Still, more than one third of patients had apnea/hypopnea. This sign should be pursued as a clue to diagnosis, as with proper management hypoxia and even death can be prevented. Although the few follow-up studies were normal or remained unchanged, no conclusions on the effect of ERT on sleep disturbances or hearing capacity can be proposed based on our limited patients' data.

Macrocephaly was reported in a few patients, as head circumference was found to be greater than two standard deviations in 8 children, and continued to increase on follow-up in some of these patients as well as in several others who were considered normal at baseline. The data collected does not allow us to diagnose the etiology of the macrocephaly, as hydrocephalus cannot be excluded in those subjects where neuroimaging studies were not performed. For the 3 children whose head circumferences were normal at baseline and showed a rise on follow-up, bone dysplasia may be considered as the cause. Familial influences cannot be ruled out either, as parental measurements were not recorded.

Although MPS VI is not considered a neuropathic disease, the nervous system should be carefully followed and managed, as secondary lesions due to hydrocephalus, spinal cord or nerve compression may lead to severe sequelae [1]. Motor development and/or speech delay was reported in 6 patients (3 had normal neuroimaging and 3 had no investigation). Development delay can be expected in chronically ill patients. Children with joint limitations can have more difficulty to walk or to use their hands, which could explain the delay in some of our MPS VI patients. Interestingly, among the group of 5 patients that showed signs of hydrocephalus (2 with white matter lesions), no development delay or cognitive impairment were diagnosed. Another important symptom to be aware of is the early occurrence of myelopathy due to spinal cord compression, presenting both at baseline and also at follow-up. Four of 6 patients that had spinal MRI performed showed increased T2 signal intensity; the other 2 patients presented reduction of intravertebral space without any radiological signs of compression, which would most probably progress. This type of complication is seen most often in older MPS VI patients [17]. The early occurrence of such manifestations in this cohort may be related to an apparent increased MPS VI disease severity in Brazil probably combined with selection bias, due to a lack of diagnosis of the less severely affected patients that remain undiagnosed until older ages [18–20]. Enhanced cervical mobility possibly secondary to ERT leading to cervical instability and thus progressing to compression cannot be ruled out as an explanation [18], however one of the children in this cohort was found to have spinal cord compression upon diagnosis of MPS VI, potentially due to inadequate head positioning for intubation during an emergency surgery for intracranial hypertension at two years of age, before diagnosis, reinforcing the importance of early diagnosis and symptom awareness.

Lack of suspicion for this diagnosis can also lead to these types of complications. Not all individuals present with the classic symptoms of MPS VI. In our cohort, one third of the patients did not present with coarse facies and two thirds had no corneal clouding at baseline, two signs that could be an alert for the diagnosis. Considering this data, other early signs of the disease, such as frequent upper airway infections, joint and bone problems, among others should be considered important clues that can lead to early diagnosis and should not be overlooked by pediatricians. With the increased risk during anesthetics

for this patient population combined with the high occurrence of surgical interventions required, as illustrated by the six patients in this cohort who had surgical procedures before MPS VI was suspected, physician awareness of the signs and symptoms that can lead to diagnosis of MPS is imperative before submitting children to anesthetic procedures, as well as to ensure early initiation of treatment options currently available for MPS patients.

## 5. Conclusions

Enzyme replacement therapy with galsulfase in the prescribed dosage of 1 mg/kg body weight IV weekly has shown to be safe and effective in slowing progression and/or improving the burden of the disease for MPS VI in young children. As early treatment initiation results in improved patient outcomes in this young cohort, early recognition of the more subtle symptoms associated with slowly progressing disease should be a priority to ensure early diagnosis and treatment initiation. Patients should continue to be closely monitored, especially regarding cardiorespiratory involvement and spinal cord compression. Long-term follow-up of this group of children will provide us further information on the benefits of early ERT.

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## Conflict of interest

Drs. Horovitz, Acosta, Kerstenestzy, Martins Aranda and Llerena, Jr., report receiving educational travel grants and/or speaker honoraria from Shire, Genzyme and BioMarin. Drs. Magalhães, Giuliani, Palhares, Kim, de Paula, Costa, Santos, Holanda, Neto, Bonatti, de Freitas Rodrigues Ribeiro, and de Souza Rodrigues report receiving educational grants from Shire, Genzyme and BioMarin. In addition, Dr. Pianovski report receiving educational travel grants and/or scientific congress organizer honoraria from Shire and Genzyme. Dr. Ribeiro has received from BioMarin, Shire and Genzyme travel expenses as part of continuous medical education and grant as researcher for Hunter Outcome Survey. Drs. Cardoso, Jr., and da Silva declare no conflicts of interest.

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