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Long-term impact of early initiation of enzyme replacement therapy in 34 MPS VI patients: A resurvey study

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ABSTRACT

Patients with mucopolysaccharidosis type VI (MPS VI) present with a wide range of disease severity and clinical manifestations, with significant functional impairment and shortened lifespan. Enzyme replacement therapy (ERT) with galsulfase has been shown to improve clinical and biochemical parameters including patient survival, quality of life and growth. The present study is a resurvey of 34 Brazilian MPS VI patients with rapidly progressive disease (classical phenotype) who initiated ERT with galsulfase under five years of age and had been on ERT until data collection in 2019, with few exceptions ($n = 4$ patients who died before 2019).

Anthropometric measures, urinary glycosaminoglycans, and data regarding cardiac, orthopedic, neurologic, sleep apnea, hearing and ophthalmologic outcomes were filled in by specialists. Pubertal development, clinical complications, hospitalizations, and surgeries were also assessed.

In this resurvey study, treatment with galsulfase has shown to be safe and well tolerated in MPS VI patients who initiated ERT under the age of 5 years and who have been undergoing ERT for approximately 10 years. Mortality rate suggests that early initiation of ERT may have a positive impact on patients' survival, improving but not preventing disease progression and death. MPS VI patients on ERT also showed improved growth velocity and the pubertal development was normal in all surviving patients.

Follow-up data on pneumonia and hospitalization suggest that early ERT may have a protective effect against major respiratory complications. Cardiac valve disease progressed since their prior evaluation and spinal cord

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compression was observed in a large number of patients, suggesting that these disease complications were not modified by ERT.

1. Introduction

Mucopolysaccharidosis type VI (MPS VI) or Maroteaux-Lamy Syndrome (OMIM #253200) is an autosomal recessive lysosomal storage disorder caused by mutations in the *ARSB* gene. Pathogenic mutations in both alleles lead to deficient activity of *N*-acetylgalactosamine-4-sulfatase or arylsulfatase B (EC 3.1.6.12), a lysosomal hydrolase involved in the stepwise degradation of dermatan sulfate, a glycosaminoglycan (GAG). MPS VI is a multisystemic and progressive disease characterized by accumulation of undegraded or partially degraded GAGs inside cells and extracellular matrix of various tissues, and increased processing and urinary excretion of these molecules [1].

MPS VI patients present with a wide range of disease severity and clinical manifestations, with significant functional impairment and shortened lifespan. Clinical features usually include short stature, coarse facies, hepatosplenomegaly, dysostosis multiplex, restricted range of motion in joints, corneal clouding, cardiac abnormalities, and deficient pulmonary function [1,2].

Reduced lifespan is characteristic of MPS VI and patients with the classical phenotype (rapidly progressing) usually die before their second decade of life, whereas those with a more slowly progressing disease may live until their 40's or 50's [3].

Enzyme replacement therapy (ERT) with galsulfase (Naglazyme®, BioMarin Pharmaceutical Inc., Novato, California) has been shown to improve clinical and biochemical parameters including patient survival, quality of life and growth. Since MPS VI is a progressive disease, early and pre-symptomatic ERT is essential to improve prognosis, by slowing or preventing the development of significant pathological changes [4,5].

In 2013, Horovitz and colleagues [6] reported the outcomes of galsulfase administration in patients who started ERT under the age of five years (3.0 ± 1.3 years; mean ± standard deviation). The main results included a negative correlation between ERT and urinary GAGs (uGAGs) and the fact that no patient discontinued ERT due to adverse events, indicating the safety of treatment. Besides, ERT in young patients was shown to slow and/or improve certain aspects of the disease. However, it was suggested that patients should be closely monitored for complications associated with the natural history of the disease, especially cardiac valve involvement and spinal cord compression.

The present study is a resurvey of these Brazilian MPS VI patients, with the aim to evaluate a long-term follow-up of disease and treatment outcomes after early initiation of ERT.

2. Methods

This resurvey was a multicenter study comprising the Brazilian cohort of 34 MPS VI patients (21 males and 13 females) with rapidly progressive disease (classical phenotype) initially described by Horovitz et al., [6] and who had been undergoing ERT with galsulfase (1 mg/kg body weight, weekly) until data collection (performed from August through November 2019, with the exception of 4 patients who died before 2019).

All clinicians from the first study were contacted and agreed to fill in updated follow-up clinical information from the MPS VI patients. Patients were included in the study only after informed consent had been obtained. Additional fields were added to the same medical files used for the original publication data collection so that the same parameters could be analyzed. Anthropometric measures, uGAGs and data regarding cardiac, orthopedic, neurologic, sleep apnea, hearing and ophthalmologic outcomes were filled in by specialists. Clinical complications, hospitalization and surgeries were also assessed. Supplementary information regarding pubertal development was requested by email.

Qualitative and quantitative data were analyzed using Excel; descriptive results are shown as mean ± standard deviation. Growth analysis was performed using z-Score transformation, comparing the present cohort to healthy subjects and untreated MPS VI patients [7].

It is important to highlight that not all patients had undergone the same tests and exams, since this is a resurvey study which included 19 different medical centers throughout Brazil. Therefore, the denominator used for frequency calculations (total number of patients) varies according to available data and is always indicated between parentheses when appropriate.

3. Results

MPS VI patients were diagnosed at 2.1 ± 1.0 years and ERT was initiated early, at 3.0 ± 1.3 years of age (ranging from 0 to 59 months; Table 1). By the time of data collection, 4 patients had died (mortality rate = 12%); detailed mortality data are shown in Table 1. Anthropometric data from baseline evaluations, prior to ERT, are also shown in Table 1.

Causes of death were respiratory related in 3 out of 4 patients (i.e., pulmonary hypertension, bronchopneumonia, and acute respiratory failure – the latter possibly caused by cervical spine compression). The other patient died during an anesthetic procedure to perform an MRI.

Surviving patients ($n = 30$) were 13.1 ± 1.7 years-old (ranging from 10.2 to 15.8) and had been undergoing ERT for 9.8 ± 1.0 years (ranging from 8.4 to 12.2 years on ERT). Most patients (85%) had at least one period of ERT interruption (more than 1 month), mainly due to non-medical circumstances (e.g., drug unavailability). Infusion-related clinical complications were observed in 8 patients (24%) with urticaria as the most common side-effect. No patient permanently discontinued treatment.

By the time of data collection, mean patients' height was 115.2 ± 12.9 cm. The current height MPS VI z-scores, when plotted using MPS VI reference curves [7] were positive for 28 (82.4%) patients, negative in one (2.9%) patient, unchanged for 3 (8.8%) patients, and not available for 2 (5.9%) patients. Although still below normal growth parameters, patients with early ERT showed a better growth curve than non-treated MPS VI patients (Table 2), with an average gain of 3.1 ± 1.2 cm per year. Detailed data on growth according to patients' sex is shown in Table 3.

The pubertal development was normal in 88% (23 out of 26 patients with available data ($n = 3$ patients with late progression).

Table 1
Anthropometric, diagnosis, treatment and mortality data of MPS VI patients.

	All patients ($n = 34$)	Deceased patients ($n = 4$)
Current age (years)	13.1 ± 1.7[a] [10.2; 15.8][a]	11.4 ± 3.9[b] [6.9; 13.6][b]
Age at diagnosis (years)	2.1 ± 1.0 [0; 3.8]	2.5 ± 0.6 [2.0; 3.4]
Age at ERT initiation (years)	3.0 ± 1.3 [0; 5.0]	3.9 ± 0.4 [3.5; 4.3]
Years on ERT	9.8 ± 2.1 [2.7; 12.2]	6.4 ± 4.3 [2.7; 10.1]
Baseline weight (kg)	12.3 ± 3.3 [2.9; 23.0]	13.1 ± 1.1 [12.0; 14.5]
Baseline height (cm)	84.8 ± 9.7 [49.0; 97.0]	88.3 ± 2.5 [85.0; 91.0]
Baseline head circumference (cm)	50.2 ± 4.4 [36.0; 56.0]	52.7 ± 0.6 [52.0; 53.0]

Results are presented as mean ± standard deviation and [minimum; maximum].
[a] Current age of surviving patients (n = 30).
[b] Age of death.

Table 2
Z Score growth analysis of MPS VI patients with early initiation of ERT (under five years-old) and who had been undergoing ERT for 9.8 ± 1.0 years ($n = 30$). Reference growth charts were described by Quartel et al. [7].

	Compared to healthy subjects	Compared to untreated MPS VI patients
Baseline height (Z Scores)	−1.8 ± 1.8 [−5.3; 2.6]	0.2 ± 0.6 [−1.0; 1.0]
Current height (Z Scores)	−5.2 ± 1.6 [−8.8; −0.5]	0.7 ± 0.5 [−0.3; 1.5]

Results are presented as mean ± standard deviation and [minimum; maximum].

Table 3
Detailed data on growth of surviving MPS VI patients who started ERT under 5 years of age. ($n = 30$ patients).

Patient #	Sex	Baseline height (cm)	Current height (cm)	Age at measurement (years)	Growth per year (cm per year)
1	F	91.5	131.0	14.0	3.9
2	M	90.0	102.5	11.0	1.5
3	M	94.5	105.5	15.1	1.1
5	F	88.5	132.1	15.0	3.7
6	F	69.5	108.5	11.7	3.6
7	M	87.0	107.5	14.5	1.9
8	M	92.0	123.0	14.4	2.8
9	F	88.0	106.0	15.8	1.7
10	M	91.0	112.0	13.8	2.1
11	M	94.0	110.0	14.1	1.6
12	M	88.0	112.0	14.4	2.3
14	F	88.0	128.5	12.9	3.5
15	F	75.0	117.2	12.6	4.0
16	M	68.0	123.5	11.6	5.3
17	F	89.2	122.0	13.0	3.7
18	M	84.0	112.5	14.6	2.8
19	F	73.5	106.0	11.1	3.7
20	M	81.0	107.0	15.8	2.6
21	M	85.0	119.0	11.5	3.6
23	M	69.0	108.0	11.4	3.4
24	M	88.0	124.0	12.8	3.8
25	F	87.0	110.0	10.2	2.4
26	M	77.0	98.0	13.5	1.8
27	M	49.0	104.0	10.9	4.9
28	M	92.0	120.0	11.2	2.7
29	M	84.0	111.0	10.3	3.2
30	F	97.0	122.0	12.6	2.9
31	M	90.0	165.0	14.9	6.6
32	F	89.0	119.0	14.4	2.5
33	M	89.0	119.0	12.6	3.1

Levels of uGAGs decreased in all patients (except one) when compared to pre-treatment ($n = 23$ patients with pre-ERT and follow-up uGAGs results); mean reduction was 74% (± 23%). Despite this improvement, uGAG concentrations were still higher than normal range in 72% of patients analyzed.

Cardiologic evaluation through echocardiogram was recently performed in 90% of patients (27 out of 30). One patient was only evaluated through electrocardiogram, which showed normal results. Valvular disease was common, with valve insufficiency observed in 89% of patients (mainly mitral and/or aortic, present in 78% and 41% of patients, respectively), and valve thickening (70% mitral and 37% aortic) in 19 patients. Ventricular hypertrophy was observed in 10 patients (37%). When compared to data presented in the first publication [6], 20 patients (74%) had worsened cardiologic parameters since that evaluation. Interestingly, 2 patients from this cohort did not show any cardiac disease symptoms by the time of data collection in the present resurvey - one of them started ERT soon after birth and the other at 46 months of age.

After the original publication [6], 7 patients had upper airway infections, and only 1 patient was hospitalized during this period. Pneumonia was the most common clinical complication, observed in 7 patients (30% of patients with reported complications). A high prevalence of sleep apnea was observed – 68% of patients who underwent polysomnography (17 out of 25) had positive results for the disorder.

Hearing and ophthalmologic evaluations showed that hearing loss and corneal clouding were still common among patients (observed in 53% and 60% of patients, respectively).

Cervical spine imaging was performed by MRI in 16 patients (53%) and cord compression was observed in 11 patients (representing 32% of all patients and almost 70% of patients who underwent the exam). It is important to highlight that MRI was mainly performed in patients who had indications of possible lesions; overall frequency of spinal cord compression was 32% (11/34 patients, including those with no MRI).

Eleven patients presented with carpal tunnel syndrome (50% among the 22 patients who were evaluated). Reports on skeletal abnormalities were available for 20 patients, all presenting dysostosis at the time of this resurvey.

The total number of surgeries patients underwent since birth varies from none to 6, but most of MPS VI patients who started ERT under 5 years of age (70%) underwent 2 surgeries until adolescence. Umbilical and inguinal herniorrhaphy, followed by neurosurgeries were the most common (Table 4). Among neurosurgeries, 6 patients underwent cervical spinal decompression surgeries and 3 ventriculoperitoneal shunting.

4. Discussion

This resurvey study is the first long-term follow-up of a large cohort of MPS VI patients who started early treatment with galsulfase, under 5 years of age. None of the initial patients discontinued ERT throughout data collection and galsulfase has shown to be safe and well tolerated in MPS VI patients who had been undergoing ERT for a mean period of 9.8 years (Table 1).

In this current resurvey of MPS VI patients, the mortality rate observed (12%) was lower than previous reports. In 2014, Giugliani et al. [8] demonstrated that MPS VI patients who had been undergoing ERT for 10 years had a mortality rate of 16.5%, whereas for untreated patients the rate observed was 50%. After 15 years of ERT, the same cohort of patients was analyzed and mortality rate increased but it was still lower than that found in untreated patients (24% and 57%, respectively)

Table 4
Surgical procedures in MPS VI patients who started ERT with galsulfase under 5 years old ($n = 34$), reported since birth.

Surgery	Number of patients	Description
Umbilical and/or Inguinal herniorrhaphy	19	–
Neurosurgery	9	Cervical spinal cord decompression (6), ventriculoperitoneal shunting (3)
ENT, otorhinolaryngologic	7	Adenoidectomy (2), tonsillectomy (2), tracheostomy (3)
Orthopedic	5	Club foot correction, hip osteotomy (2), knee, cystic neurofibroma (foot)
Carpal tunnel	4	
Port-a-cath	3	
Cardiothoracic	3	Ductus arteriosus correction and mitral valve surgery, thoracic drainage
Tarsal tunnel	2	
Urogenital	2	Phimosis
Spinal	1	Thoracolumbar spine arthrodesis
Gastrointestinal	1	Appendicectomy
Ophthalmologic	1	Corneal transplant
Other	1	Removal of lumbar granuloma
TOTAL	58	

ENT: ear, nose, and throat.

[9]. The main differences between this study [9] and our current report is the age when patients started ERT (i.e., teenagers vs under five years of age), and mean age at death (23.3 ± 10 vs 11.4 ± 3.9), therefore, it is still unclear whether the lower mortality may be a positive impact of earlier ERT initiation or simply associated with the younger age of MPS VI patients in this resurvey.

Although the main causes of death in this resurvey were respiratory related, it is important to highlight the death of one patient during the anesthetic procedure to perform an MRI, since unfortunately it is not a rare event among MPS VI patients. In general, it is recommended that MRI should be performed without anesthesia, and it is not different for MPS VI patients as they are not intellectually impaired. However, if sedation would be necessary, it is recommended that intubation should be done with extreme caution by experienced professionals, and alternatives such as the use of laryngeal mask should be discussed.

Reduction of baseline uGAGs has been extensively reported as an important outcome of ERT in other types of MPS disease. In our cohort, reduction of uGAGs was observed in all patients except one, when compared to pre-treatment [10]. Unfortunately, uGAGs analysis had not routinely been performed in the medical center where this patient with no uGAGs reduction was treated, so this observation could not be further assessed and discussed in this report (this was the only uGAGs result available for the patient since the original publication [6]).

Even though uGAG results were still higher than normal range in 72% of patients analyzed, the relevant reduction in uGAGs may be associated with the lower mortality observed in the current study. This association is consistent with a previous study in which a greater reduction in uGAGs was associated with a substantial decrease in mortality in subjects older than 12 years [9]. In addition, in a recent review by Kakkis and Marsden [10], the authors reinforce the importance of uGAG reduction and suggest that although an individual correlation between uGAGs, clinical outcomes and mortality had not been assessed by Quartel et al., [9], a general association may be clearly inferred from their results, along with preclinical and Phase 3 studies.

In the original publication [6], patients were approximately 5 years-old and had been receiving galsulfase ERT for 2 years. Initial results showed that 12 (37.5%) patients remained on the same growth percentiles, 3 (9.4%) moved to higher percentiles, and 17 (53%) fell below their baseline percentiles. During the first year of life, MPS VI infants and toddlers are expected to have normal to accelerated growth velocity, followed by a decrease in growth rate after the second year. Reference growth charts for MPS VI patients were developed in 2015 [7] and used for analyses in this resurvey. By the time of data collection, mean patients' height was 115.2 ± 12.9 cm. The majority (82.4%) of patients showed positive growth using MPS VI reference curves [7]. Although still below normal growth parameters, patients with early ERT showed improved growth velocity when compared to untreated MPS VI patients. In accordance with our results, previous studies in infants with MPS VI suggest that early onset of ERT may prevent or limit deviation from normal growth curves [5,11–13].

Reports on skeletal abnormalities were available for 20 patients, all presenting dysostosis at the time of this resurvey, similar to observations of ERT in adults [13]. MPS VI patients who started ERT before one year of age presented slower progression of bone and joint disease when compared to their affected older siblings, showing that skeletal features of the disease may slowly progress but cannot be prevented [14]. Moreover, limited impact on bone development has also been observed in Japanese patients who initiated ERT as newborns [12], suggesting that even very early initiation of ERT is not able to prevent skeletal abnormalities in MPS VI.

Delayed onset or progression of puberty have been observed in a large percentage (42%) of untreated MPS VI patients [13], but the mechanisms that lead to these alterations are still unknown. In this resurvey, normal progression through puberty was observed in 80% (23 out of 26) of patients analyzed, suggesting that early initiation of ERT may have an important positive impact on pubertal development for most patients.

Pneumonia was the most common clinical complication, observed in 30% of patients with reported complications (7 out of 23 patients); overall frequency of pneumonia was 23%. It is important to point out that the number of patients with pneumonia in this resurvey is quite lower than described in untreated Brazilian MPS VI patients (16 out of 28 patients, 57%) [2] which, in turn, may be associated with a reduced need for hospitalization as well. After the original publication [6], 7 patients had upper airway infections, and only 1 patient had to be hospitalized during this period. In general, less clinical complications and hospitalizations until adolescence were observed in this cohort when compared to patients who started ERT later in life [8].

Cardiovascular and respiratory alterations are frequent and represent the main cause of death in MPS VI; cardiac disease (mainly mitral and/or aortic valve insufficiency) was a common finding in this resurvey. The most frequent alteration was observed in the mitral valve, which is similar to results found in a previous Brazilian study [2] and international literature [15]. The fact that the MPS VI patients in this present study were diagnosed early, their mean baseline uGAGs were > 200 μg/mg, and that cardiac alterations were similar to untreated Brazilian patients [2,8], reinforces that most of our cohort would represent the rapidly progressing MPS VI phenotype.

In addition, 74% of patients had worsened cardiologic parameters since their first evaluation for the original publication [6], suggesting that early initiation of ERT may not prevent this outcome in MPS VI patients, despite slowing or stabilizing overall disease progression [8]. Accordingly, it has already been shown that ERT did not improve or halt progression of cardiac valve disease in MPS VI patients with different phenotypes [16].

It is also important to point out that, as a resurvey, this present study was not designed to assess specific and/or subtle cardiologic alterations which may have been impacted by ERT, nor to evaluate the severity of valve disease or changes in severity over time. In addition, the fact that 2 patients from the cohort did not show any cardiac disease when resurveyed highlights possible limitations to conclude that there was no effect of early ERT on cardiologic features. Altogether, these results underline the importance of monitoring cardiovascular function in MPS VI patients.

It is recommended that the nervous system should also be closely monitored in MPS VI patients, because of secondary lesions that may arise from spinal cord compression and hydrocephalus [17]. However, in Brazil, MRI is not easily accessible within the public health system. Thus, in this resurvey only approximately half of the patients ($n = 16$) had cervical spine imaging results - from those who were able to undergo the exam, spinal cord compression was observed in 70%. The high percentage is likely biased by the fact that MRI was mainly performed in patients who had indications of possible lesions. Overall frequency of spinal cord compression (11/34 patients, which includes those with no MRI) was 32%, which is in accordance with findings from The MPS VI Clinical Surveillance Program [16].

The observation of hearing loss and corneal clouding in a high number of patients by the time of this resurvey (53% and 60%, respectively) indicates that the disease was still progressing on these systems, despite ERT, which is not unexpected considering the association of such signs / symptoms with the nervous system.

Most MPS VI patients who started ERT under 5 years of age had up to 2 surgeries until adolescence. Herniorrhaphies and neurosurgeries were the most common (Table 4); 6 patients underwent cervical spinal cord decompression, although 11 had surgery indications. Difficulties to schedule surgical procedures in the Brazilian public health system may explain the difference between the number of patients with MRI findings and surgeries. Besides, these difficulties are increased by the fact that surgeries in MPS VI patients should be ideally performed in reference centers, as they require trained and experienced professionals for intubation (possibly fiberoptic) and prevention of other operative complications. Another important issue is that families sometimes do not authorize surgical procedures in MPS VI patients due to anesthesia

related risks (one of the patients from this cohort died during an anesthetic procedure). Therefore, although important data are described in this resurvey study, conclusions regarding the association of early ERT and surgeries are limited.

It is also important to highlight that, as discussed in the first publication [6], MPS VI patients presenting with early signs and symptoms are usually associated with more severe or rapidly progressive disease, which is likely the case of most patients in this cohort. Hence, the effect of early treatment in slowly progressing patients still needs to be investigated.

The youngest patient to start ERT in this resurvey (age 5 days) still presents no cardiac involvement. Four patients in this cohort started ERT under one year (ages: 5 days, 4 months, 6 months, and 10 months). The disease also progressed in this subgroup, but despite having dysostosis, their bone disease is milder when compared to the older affected siblings, and three of them are presently taller than the affected siblings (one of the siblings has been deceased for a long time). Detailed information from this subgroup who started ERT before 1 year of age is shown on a previous paper published by Dr. Horovitz et al. [14].

Although the overall assessment of starting ERT in patients under 5 years-old may be positive, there are still unmet needs in MPS VI patients that should be addressed. In this sense, new strategies are currently being tested to overcome these limitations, mainly to enable the delivery or production of sufficient therapeutic enzyme levels to the central nervous system. In addition, recent advancements in the knowledge of lysosomal biology and function may bring complementary therapies for MPS [18,19].

Altogether, our results suggest that initiation of ERT with galsulfase up to the age of 5 years promotes positive impacts on important clinical manifestations of MPS VI, by delaying important aspects of disease progression and protecting against respiratory complications. Furthermore, considering the existing data on the benefits of very early initiation of ERT [5,12], they highlight the importance of early diagnosis of MPS VI and initiation of treatment as soon as possible to improve patients' prognosis.

5. Conclusion

In this resurvey study, treatment with galsulfase has shown to be safe and well tolerated in MPS VI patients who had been undergoing ERT for approximately 10 years, initiated under 5 years of age. The mortality rate observed suggests that early initiation of ERT may have an important positive impact on patients' survival, improving but not preventing disease progression and death. Also of note, MPS VI patients on ERT showed improved growth velocity and normal progression through puberty.

Follow-up data on pneumonia and hospitalization suggest that early ERT may have a protective effect against major respiratory complications. Cardiac valve disease progressed since their prior evaluation and spinal cord compression was observed in a large number of patients, suggesting that these complications were not modified by early initiation of ERT.

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Declaration of Competing Interest

AG, AMM, ASSP, AXA, BFFR, CML, FCS, JFSF, LCLL, LRG, TBT, JICFN: declared no conflict of interest. ACMS, ALB, CAK, DDGH, EKEAL, EMR, MCSR, MK, RCFB: received funds or reimbursement from BioMarin Brasil Farmaceutica LTDA for attending related symposia, or speaker honoraria. DDGH: received consulting fees from BioMarin Brasil Farmaceutica LTDA.

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