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# Mucopolysaccharidosis VI: Evaluation After 2 Years of Treatment

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## Abstract

**Introduction:** Mucopolysaccharidosis VI (MPS VI) is the result of the absence of arylsulfatase B leading to the abnormal lysosomal accumulation of glycosaminoglycans. Two different phenotypes have been described to date, namely, rapidly progressive and slowly progressive. **Aim:** To present the evolution of a slowly progressive phenotype of MPS VI in a patient after 2 years of enzyme replacement therapy. **Case report:** A 26-year-old man diagnosed with MPS VI at 9 years of age started enzyme replacement therapy with galsulfase due to cardiac, pulmonary, neurologic, and joint involvement. After 10 months of treatment, improvement in quality-of-life scales and walk test was evident. Because of persistent symptomatology associated with narrow cervical spinal canal, decompressive surgery was performed. After 2 years of treatment, there was a clear improvement in the respiratory, motor, and cardiac functions as well as in the spinal symptoms. **Discussion:** The evolution of our patient leads to the conclusion that the combined treatment of galasulfase and decompressive surgery should be indicated at an early stage in order to achieve best outcome for the patient.

## Keywords

spinal compression, galsulfase, glycosaminoglycans, dermatan sulfate, mucopolysaccharidosis VI

## Introduction

Mucopolysaccharidosis VI (MPS VI) or Maroteaux-Lamy syndrome is an autosomal recessive disease determined by the presence of mutations in the arylsulfatase B (ASB) codifying gene located in chromosome 5 (5q13-5q14).[1]

The reduction in or absence of ASB activity results in an incomplete degradation and intralysosomal accumulation of the glycosaminoglycans (GAGs), mainly dermatan sulfate (DS), and, at a much lower concentration, chondroitin sulfate (CS) in connective tissue.[2]

The diagnosis of MPS VI is made through the analysis of the enzymatic activity in dry blood spot (filter paper technique), isolated leukocyte, or fibroblast culture. The presence of high levels of GAGs in urine must be first confirmed to go on to identify the DS as accumulated GAG[3] through thin-layer chromatography.

It is advisable to carry out the molecular test to identify the ASB gene when the enzymatic values are not conclusive.[3]

The enzyme replacement therapy (ERT) with galsulfase has been approved by the Food and Drug Administration and the European Medicines Agency (EMA) for the treatment of MPS VI in 2005 and 2006, respectively.[4] The aim of this study was to report the evolution of a patient with MPS VI after 2 years of treatment with ERT and cervical decompression surgery.

## Patient and Method

In this case, the patient was a 26-year-old man, with no cognitive involvement, 145-cm high, with confirmed MPS VI diagnosis at 9 years of age through the analysis of the ASB enzyme activity in leukocytes, 0.1 nmol/min/mg (Normal value (NV) 1.2 to 5.8 nmol/min/mg), and high level of

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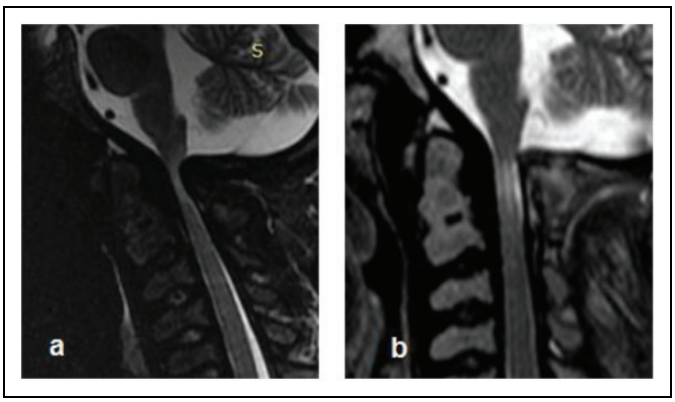


**Figure 1.** A, Short tau inversion recovery (STIR) sequence. Severe compression with myelomalacia signs at C1 to C2 levels. B, Postsurgery findings: normalization of cervical spine cord thickness with reappearance of cerebral spinal fluid at anterior and posterior areas and chronic central damage.

GAGs in urine. The patient had a history of bilateral hip dysplasia and umbilical hernia at birth. At 1 year of age, a delay in the pondostatural growth was detected, and at 3 years, restricted joint movement. The echocardiogram, prior to the beginning of ERT, reported mildly dilated left ventricle (LV) with a 60-mm left ventricle end-diastolic diameter (LVEDD) and asymmetric hypertrophy (Interventricular septum (IVS): 10 mm and posterior wall (PW): 7 mm) with a 154 $g/m^2$ left ventricular mass index (LVMI). The LV systolic function was preserved and the pulmonary artery systolic pressure was normal. The aortic valve was trivalve with mild systolic gradient (maximum gradient: 27 mm Hg and mean gradient: 14 mm Hg) and moderate degree of insufficiency. The mitral valve was also thickened with mild diastolic gradient (mean gradient 7 mm Hg and an area calculated in 2.9 $cm^2$) and mild insufficiency. The spirometry showed a forced vital capacity (FVC) of 45% and a forced expiratory volume in 1 second (FEV1) of 45%, with a severe restrictive pattern.

The physical and neurologic examinations showed cervical spine involvement through clinical signs of pyramidal involvement (clonus, Hoffmann, and Babinski signs) and posterior spinal cord injury (localized cervical pain, spontaneous propriospinal myoclonus, and Lhermitte sign). The magnetic resonance imaging of the cervical spine showed a severe compression with myelomalacia signs at C1 to C2 levels (Figure 1A). The ophthalmologic examination reported a 10 of 10 visual acuity for both eyes; biomicroscopy showed corneal clouding, corroborated by confocal microscopy, associated with intracytoplasmic deposits in the endothelium. The audiologic evaluation results were normal. Before the beginning of ERT, the 6-minute walk test (6MWT) reported a distance of 225 m and the 3-minute stair climb test (3MSC) reported a total of 88 steps.

## Results

After the first 10 months of ERT with galsulfase, 1 mg/kg every 7 days, there was no evidence of allergic reactions associated with the infusions. There was an increase of 35 meters (a total of 260 m) in the 6MWT and the 3MSC went up to 98 steps. There was a clear improvement in the quality-of-life scale (Short Form Health Survey (SF36)) associated with stability in the rest of the studies carried out. Although the benefits of the ERT were evident, the cervical pain persisted, associated with an increase in the propriospinal myoclonus. For that reason, a decompressive surgery was carried out at the craniocervical junction level with removal of the C1 posterior arch, widening of the foramen magnum, and followed by a prosthesis placement with upper occipital and lower C3 to C5 fixation. Immediately after recovery from the anesthesia, The patient reported cervical pain relief and disappearance of propriospinal myoclonus and Lhermitte sign (Figure 1).

Two years after starting the treatment, the patient showed a sustained improvement in 6MWT, reaching 328 meters, and an increase in steps climbed to 118 in 3 minutes. The new echocardiogram showed a significant reduction in LVEDD (from 60 to 53 mm), with a slight increase in thickness of IVS and PW (11 and 9 mm, respectively) and a slight decrease in LVMI (153 $g/m^2$). The ejection fraction remained normal (59%), with no structural or hemodynamic valve changes. The new spirometry reported a clear increase in FVC reaching 52% and FEV 53%.

## Discussion

Epidemiologic studies reported varied prevalence rates ranging from 1 in 43261 births in Turkish immigrants living in Germany to 1 in 1505160 births in Sweden,[2] and it is not possible to establish the prevalence rate of MPS VI in Argentina. Two phenotypes have been established for MPS VI, namely, slowly progressive and rapidly progressive.[5]

The rapidly progressive phenotype is characterized by presenting urinary GAG levels higher than 200 μg/mg creatinine and not exceeding 120 cm in height. Usually, the onset of signs and symptoms occurs before 2 or 3 years of age, with evident skeletal alterations, characteristic coarse facies, and restricted joint mobility, mainly in the hands. Associated with these, there is also delayed puberty, hepatoesplenomegaly, umbilical and/or inguinal hernia, stunted stature growth with percentiles lower than 50 since 2 years of age.[1] The otorhinolaryngological engagement implies hearing impairment, otitis media, and recurrent sinusitis as well as obstructive apnea syndrome. The pulmonary involvement that has been described includes restrictive and obstructive features.[6] The obstructive pulmonary disease is the result of airflow limitation and the presence of tracheobronchomalacia, while restrictive pulmonary disease is due to small and stiff thoracic cage, combined with kyphosis, scoliosis, and increased lumbar lordosis.[6] The neurologic complications have been divided into central and peripheral types. The latter results from the compression of the medial (carpal tunnel) and posterior tibial nerves (tarsal tunnel), which frequently leads to the recommendation of decompressive surgery. The central complications are as follows: bulbospinal compression at cervical level (less frequent at dorsolumbar level) and hydrocephalus. It should be stressed

that MPS VI does not entail intellectual or cognitive involvement as has been described for other MPS.[7] The cervical compression has been described since the age of 3 years for patients with rapidly progressive phenotype and it is the result of the deposit of GAGs in transverse, cruciate, and posterior and anterior longitudinal ligaments, periodontoid soft tissue, and dura.[7]

The patient in this report meets the criteria associated with the slowly progressive type, which is characterized by reaching a height over 140 cm and urinary levels of GAGs below 100 μg/mg of creatinine. These patients may develop the same skeletal involvement as the rapidly progressive phenotype but in a milder form.[8]

The first controlled, randomized, double-blind, and multicenter ERT clinical study included 39 patients. Those who received galasulfase presented a significant improvement in the 6MWT and 3MSC[4] tests after 24 weeks. Associated with this benefit, the urinary GAG levels decreased significantly and there were no severe adverse reactions. Results of long-term follow-up for pulmonary and cardiac functions have been published to date, and both studies show positive outcomes with stabilization of the systolic function, no progression of valve involvement, and improvement in FVC and FEV in many patients.[9,10] There is no evidence that the ERT improves or stops spinal cord injury when cervical compression is already present. Two years after starting ERT associated with craniocervical decompression, we have confirmed a clear improvement in 6MWT (45%), 3MSC (34%), ventilatory capacity, cardiac function, and quality-of-life scales. The benefit in the functional motor scales 6MWT and 3MCS seen in our patient resembles the results previously described in phase III, which led to the final approval of ERT.[4] Cardiac improvement in our patient is made evident by the stabilization of LVMI and of parietal thickness with significant decrease in the end-diastolic diameter. The systolic function of the LV remained normal with 59% ejection fraction. There was no evidence of progression of the valve involvement existing before the ERT. These results are in agreement with those reported in multicenter studies assessing the cardiac effects of galsulfase, where there was a clear reduction in LVH in patients younger than 12 years of age after 96 weeks of treatment, while in patients who were $\geq$12 years of age, stabilization of the myocardial and valvular[10] involvement was achieved.

Finally, the improvement in the respiratory function has been reported mainly after 72 weeks of treatment. Mean improvement in FEV1 and FVC in these cases was 11% for both the parameters.[9] Our patient presented a 15% improvement in FVC and 17.7% in FEV1.

The increasing bibliographic evidence and the evolution of our patient lead us to the conclusion that the combination of ERT and decompressive surgery must be indicated at an early stage to achieve the best benefits for patients. However, in patients with moderate or severe spinal compression, decompressive surgery should be indicated in specialized centers to prevent quadriplegia, and possibly provide some clinical benefits.

## Declaration of Conflicting Interests

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