

# Management Guidelines for Mucopolysaccharidosis VI

Roberto Giugliani, MD, PhD<sup>a</sup>, Paul Harmatz, MD<sup>b</sup>, James E. Wraith, MD<sup>c</sup>

<sup>a</sup>Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; <sup>b</sup>Children's Hospital and Research Center Oakland, Oakland, California; <sup>c</sup>Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester, United Kingdom

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## ABSTRACT

Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) is a lysosomal storage disease that is characterized by systemic clinical manifestations and significant functional impairment. Diagnosis and management are often challenging because of the considerable variability in symptom presentation and rate of progression. The optimal standard of care should be based on evidence from randomized, controlled trials, meta-analyses, systematic reviews, and expert opinion. In support of this goal, comprehensive management guidelines have been drafted by an international group of experts in the management of patients with mucopolysaccharidosis VI. The guidelines provide a detailed outline of disease manifestations by body system, recommendations for regular assessments, and an overview of current treatment options.

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### Key Words

mucopolysaccharidosis, Maroteaux-Lamy syndrome, lysosomal storage disease, *N*-acetylgalactosamine-4-sulfatase, arylsulfatase B, galsulfase, hematopoietic stem cell transplantation

### Abbreviations

LSD—lysosomal storage disease  
MPS VI—mucopolysaccharidosis VI  
ASB—arylsulfatase B  
ERT—enzyme-replacement therapy  
FDA—Food and Drug Administration  
HSCT—hematopoietic stem cell transplantation  
rhASB—recombinant human arylsulfatase B  
12MWT—12-minute walk test  
3MSC—3-minute stair climb  
SAE—serious adverse event  
CPAP—continuous positive airway pressure  
IOP—intraocular pressure  
ICP—intracranial pressure  
CTS—carpal tunnel syndrome  
CSP—Clinical Surveillance Program

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Address correspondence to Paul Harmatz, MD, Children's Hospital and Research Center Oakland, 744 52nd St, Oakland, CA 94609. E-mail: [pharmatz@mail.cho.org](mailto:pharmatz@mail.cho.org)

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THERE ARE >40 known lysosomal storage diseases (LSDs), which are rare but serious disorders in which a genetically transmitted enzyme defect causes intracellular accumulation of cellular debris within the lysosomes. Mucopolysaccharidosis VI (MPS VI), otherwise known as Maroteaux-Lamy syndrome, named after Drs Maroteaux and Lamy who first described the disorder in 1963,<sup>1</sup> is an LSD caused by a decreased amount and/or function of the enzyme *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B [ASB]).<sup>2</sup>

With the successful completion of clinical trials for an enzyme-replacement therapy (ERT) for MPS VI and anticipation of a future Food and Drug Administration (FDA)-approved therapy, we met in 2004 at the Eighth International MPS Symposium in Mainz, Germany, to initiate a plan for development of management guidelines for MPS VI. We identified a consensus panel of international consultant specialists in medicine, genetics, and biochemistry to review and approve the guidelines that we prepared. Assisted by Celeste Decker, MD, clinical director at BioMarin Pharmaceutical Inc, who coordinated meetings and discussions, we individually prepared sections of these management guidelines. These drafts were circulated via e-mail and reviewed in person at the 2005 American Society of Human Genetics meeting in Salt Lake City, Utah. After the guidelines were mostly complete, they were submitted to the individual consensus panel members. Their substantial comments and revisions were integrated into final guidelines and resubmitted to panel members for approval before submission to *Pediatrics* for publication. BioMarin Pharmaceutical Inc provided significant administrative support including coordinating meetings, assisting in editing of guidelines, and submitting comments to us for review.

#### OBJECTIVE OF THE CONSENSUS PANEL AND MANAGEMENT GUIDELINES

In the past, limited treatment options for MPS VI led many practitioners to adopt a palliative approach and focus primarily on management of individual disease complications. However, the availability of treatments such as ERT and hematopoietic stem cell transplantation (HSCT) has generated hope for significant improvement in the outlook for patients with MPS VI. Our objective for these guidelines was to provide an overview of the assessment, management, and treatment of affected individuals as a reference for health care providers, patients and their families, and reimbursement agencies.

#### SPECTRUM OF DISEASE AND DISEASE PROGRESSION

As with other mucopolysaccharidosis disorders, MPS VI is a clinically heterogeneous condition.<sup>3</sup> Case studies reported in the literature have identified subjects who presented with marked disease in the first year of life<sup>4,5</sup> and those who presented with slowly advancing disease that progressed over many decades.<sup>6,7</sup> Typically, the rap-

idly advancing form presents with progressive deceleration of growth rate, skeletal and joint deformities, dysmorphic facial features, upper-airway obstruction, recurrent ear infections, and joint deformities (Fig 1). Later, affected individuals often become wheelchair bound or bedridden secondary to skeletal deformities, joint disease, cardiopulmonary disease, blindness, or spinal cord compression. Individuals with rapidly advancing disease usually die in their teens or early 20s from infections, complications related to surgical procedures, or cardiopulmonary disease. Individuals with the slowly progressing form of the disease may live into their 40s or 50s. MPS VI is not typically associated with progressive impairment of mental status, although physical limitations may impact learning and development of motor skills. Both the slowly and rapidly progressive forms result in a significant decline in physical and functional well-being and, ultimately, a shortened lifespan.

#### Inheritance and Incidence

The disease is inherited in an autosomal recessive pattern. Estimates of MPS VI incidence range from 1 in 238 095 to 1 in 1 300 000.<sup>8-13</sup> On the basis of these incidence surveys, it is estimated that there are between 50 and 300 patients in the United States and ~1100 patients in the developed world with MPS VI.<sup>14</sup> Although birth incidence is not available from Brazil, selective screening of a high-risk population in Brazil showed that 19% of identified patients with mucopolysaccharidosis had MPS VI.<sup>15</sup> Although no associated ethnic group has been identified with MPS VI, a local founder effect has been suggested for northern Portugal and areas of Brazil.<sup>16</sup>



FIGURE 1  
Photograph of 3 patients with MPS VI (16, 30, and 12 years old, left to right) with typical features such as short stature, skeletal and joint abnormalities, coarse facial features, and tracheostomy.

### Disease Pathophysiology

MPS VI is characterized by an inherited deficiency of ASB, 1 of 5 enzymes required for the degradation of dermatan sulfate,<sup>1</sup> an important component of connective tissue. As such, it plays a structural role throughout the body, especially in the skin, tendons, blood vessels, airways, and heart valves. The progressive accumulation of dermatan-sulfate-breakdown products in the lysosomes of all cells can lead to irreversible cellular and tissue damage and organ-system dysfunction.

Pathophysiology in MPS VI has been best studied in the skeleton and joints of mice, rats, and cats with MPS VI.<sup>17–22</sup> These studies suggest that dermatan sulfate is an endotoxin-like molecule that incites an inflammatory response via the tumor necrosis factor pathway and promotes apoptotic cell death of chondrocytes. Progressive arthropathy develops in response to these 2 processes.<sup>17,18</sup>

### Molecular Correlates

There is considerable variation in the onset and severity of symptoms in patients with MPS VI. Disease manifestations are observed only in individuals with severe deficiency in enzyme activity (usually <10% of lower limit of normal). Carriers of 1 abnormal allele retain sufficient production of active enzyme to avoid any biochemical or clinical evidence of disease. The presence of a large number of mutations<sup>23</sup> and inconsistent phenotype testing have limited the ability to predict phenotype from genotype. A search of the Human Gene Mutation Database presently lists 54 mutations.<sup>24</sup> Most of these mutations are missense mutations ( $n = 35$ ) or small deletions or insertions ( $n = 9$ ), which can give rise to the full range of disease expression. A smaller number includes nonsense mutations ( $n = 10$ ) that, when present in homozygosity, give rise to the severe form.

Early studies by Jin et al<sup>25</sup> and Litjens et al<sup>26</sup> and 2 recent studies by Karageorgos et al<sup>27,28</sup> based on the phase 1/2 and phase 2 galsulfase clinical trials have reported a wide range of disease manifestations and provide genotype-phenotype correlations in a limited number of patients. The large variation in clinical phenotype could be related, in part, to different combinations of *ASB* gene mutations, severity of the mutation, and its effect on enzyme production and activity. The effect of a specific mutation on the gene and enzyme function has been tested for a number of mutations<sup>26–28</sup> by establishing the mutant gene as a stable transfectant in nonproducing cell lines. Bradford et al<sup>29</sup> have used this methodology to examine the biosynthesis, cellular trafficking, and enzyme activity for the Y210C mutation, a common mutation that is seen in 10% of cases and associated with a clinically attenuated phenotype.

Further application of this methodology conducted in specialized research laboratories has been applied to a large population of patients with MPS VI, as described by

Karageorgos et al.<sup>16</sup> Their study included 105 patients worldwide and identified 83 different mutations, 62 of which were previously unknown. The authors suggested that a correlation between certain genotypes and urinary glycosaminoglycan levels exists and may be used to predict clinical outcome.

### Diagnosis and Genetic Counseling

The diagnosis of mucopolysaccharidosis disease is generally suspected on the basis of clinical presentation. An affected child may show decreased growth velocity, coarse facial features, skeletal deformities, frequent upper-airway infections, enlarged liver and spleen, hearing loss, joint stiffness, or coarse hair. An elevated level of urinary glycosaminoglycan suggests a mucopolysaccharidosis disorder but does not provide a specific diagnosis.<sup>30</sup> Thin-layer chromatography or electrophoresis showing an increase of dermatan sulfate reinforces the suspicion of MPS VI, although false-positive and false-negative results may occur.<sup>30,31</sup> Diagnosis has generally been accepted with an ASB enzyme activity of <10% of the lower limit of normal in cultured fibroblasts or isolated leukocytes in an accredited laboratory with the presence of clinical findings consistent with MPS VI disease. However, Brooks et al<sup>32</sup> reported a patient with no obvious MPS VI clinical signs with slight dermatan sulfaturia, 2 mutant *ASB* alleles, and 5% of the lower limit of the normal range of ASB-catalytic capacity. They suggested that this patient represented an index case of the attenuated end of the MPS VI clinical spectrum.

Multiple sulfatase deficiency should be excluded by documenting normal levels of a second sulfatase.<sup>33</sup> Prenatal diagnosis is available for families with an affected child. Newborn screening programs are under development and may be available in the foreseeable future now that an FDA-approved treatment is available.<sup>34</sup>

Genetic counseling is recommended for parents and siblings of patients with MPS VI to explain the relative risk of having another child with the disease or passing MPS VI-related mutations to their children. When both parents are heterozygous carriers of MPS VI, each pregnancy carries a 25% chance of the child having MPS VI, a 50% chance of the child being a heterozygote carrier, and a 25% chance of the child inheriting 2 normal alleles of the *ASB* gene. Genetic counselors assist families with referrals to diagnostic facilities and medical centers with experienced subspecialty physicians. They will also introduce families to community and state support services and patient advocacy and support organizations.

### SPECIFIC THERAPIES TO PROVIDE DEFICIENT ENZYME

Historically, HSCT had been the only specific therapy available for MPS VI, but now ERT has been accepted as the safer option when available.<sup>35–37</sup> The physician must evaluate the risks, benefits, and availability on an individual basis to select the appropriate therapy for each

patient, including the risk of medical complications and death from bone marrow transplantation.

In contrast, ERT has a lifetime requirement of weekly intravenous infusions that carry a risk of allergic reaction and may require a central venous access port with its inherent risk of infection and subsequent risk of endocarditis. Naglazyme (galsulfase; BioMarin Pharmaceutical Inc, Novato, CA) ERT has been approved by the FDA and European Medicines Agency and is available in the United States, Europe (including Norway and Iceland), and Australia. When available, ERT is recommended as the first-line therapy for MPS VI.

Because Naglazyme is administered intravenously, it is unlikely that the enzyme reaches poorly vascularized sites such as the cornea and joint cartilage, and the blood-brain barrier prevents delivery into the central nervous system. Long-term follow-up data regarding this treatment are not yet available; however, existing study results have demonstrated improved walking endurance and stair-climbing capacity.

### Hematopoietic Stem Cell Transplantation

Successful HSCT has the potential to provide physiologic levels of the deficient enzyme over the long-term<sup>35</sup> as described for a small number of patients with MPS VI who have benefited from HSCT.<sup>35,38</sup> However, HSCT is not universally available because of a lack of suitable donors and is associated with significant morbidity and mortality. The European Group for Bone Marrow Transplantation reported a transplantation-related mortality risk from 10% (HLA-antigen identical) to 20% to 25% (HLA-antigen mismatched) for 63 cases of patients with LSD.<sup>38</sup>

Herskhovitz et al<sup>39</sup> published long-term outcomes of HSCT in 4 patients with MPS VI. The patients showed reduction of facial dysmorphism and improvement or stabilization of cardiac manifestations of the disease. However, skeletal changes persisted or progressed, although posture and joint mobility seemed to improve. Summers et al<sup>40</sup> reported initial improvement in electroretinograms over 1 to 2 years after HSCT, but a follow-up study reported slowly progressive worsening.<sup>40</sup> Corneal clouding and visual acuity have shown variable long-term changes after HSCT.<sup>41</sup>

With improvement in transplantation protocols, Staba et al<sup>42</sup> recently suggested that cord-blood cells from unrelated donors can be transplanted successfully into patients under 2 years of age with the severe form of MPS I (Hurler syndrome). An 85% event-free survival rate and reports of improved growth velocity and neurocognitive performance were observed along with stabilization of bone disease. Several aspects of cord-blood transplantation may affect outcome, including the donor's enzyme level (if the donor is a carrier-sibling), degree and persistence of donor chimerism, and post-transplantation complications, especially graft-versus-

host disease.<sup>43</sup> Experience with cord-blood transplantation in MPS VI has not been reported, but results should be comparable to those of HSCT.

### Enzyme-Replacement Therapy

A therapy for LSDs that has been shown to be effective in animals and in human clinical studies is ERT. ERT has been approved for human use for several LSDs: Gaucher disease,<sup>44</sup> Fabry disease,<sup>45</sup> Pompe disease,<sup>46</sup> MPS I,<sup>47</sup> MPS II,<sup>48</sup> and MPS VI.<sup>49</sup> ERT with recombinant human ASB (rhASB) in a feline model for MPS VI disease demonstrated clearance of glycosaminoglycan from storage organs and improved joint mobility,<sup>50</sup> and it prevented or slowed skeletal dysplasia in cats treated from birth.<sup>51,52</sup> Clinical trials in patients with MPS VI have addressed the safety and efficacy of ERT in the form of rhASB (Naglazyme, galsulfase).

#### Phase 1/2 and Phase 2 Clinical Trials

Two clinical studies of ERT in 16 patients with MPS VI using rhASB demonstrated a dose-response biochemical efficacy with decrease in urine glycosaminoglycan levels, an acceptable safety profile, and improved endurance on the 12-minute walk test (12MWT) and 3-minute stair climb (3MSC).<sup>53,54</sup>

#### Phase 3 Clinical Trial

Efficacy and safety were evaluated in 39 patients with MPS VI in a randomized, double-blind, placebo-controlled, multicenter, multinational study for 24 weeks.<sup>37</sup> The primary efficacy variable was the distance walked in a 12MWT, and the secondary efficacy variables were the number of stairs climbed in a 3MSC and the level of urinary glycosaminoglycan excretion. All patients received drug in a 24-week follow-on open-label extension period.<sup>37</sup>

For the placebo-controlled portion of the study (weeks 1–24), the 19 patients who were receiving galsulfase (galsulfase group) showed a significantly greater improvement in the 12MWT than was observed in the 20 patients who were receiving a placebo (placebo group). For the 3MSC, those in the galsulfase group also demonstrated greater improvement after 24 weeks than was observed in those in the placebo group. After receiving galsulfase, all patients exhibited rapid declines in their urinary glycosaminoglycan level.

During the first 24 weeks of the study (the double-blind, placebo-controlled phase), most of the adverse events experienced by patients in the galsulfase and placebo groups were consistent with the complications of the underlying disease and were considered unrelated to the study drug. Fifteen serious adverse events (SAEs) occurred during this period. Three of the SAEs were experienced by patients in the galsulfase group, and 12 were experienced by patients in the placebo group. Only 1 of the 15 SAEs, apnea, was considered to be possibly

related to galsulfase. That patient had a history of sleep apnea and had received diphenhydramine, which was considered a co-suspect medication in this event. The same patient tolerated ERT in the subsequent week, receiving a lower dose of antihistamine and a slower rate of ERT infusion, with no further reactions.

Ten patients who received galsulfase experienced infusion-associated reactions; the most frequent symptoms were rigors, dyspnea, and pyrexia. Five of these patients experienced anaphylactoid reactions, characterized by symptoms such as conjunctivitis, dyspnea, pyrexia, rigors, nausea, exanthem, urticaria, chest pain, edema, and abdominal pain. These reactions were managed by use of additional antihistamines, antipyretics, or steroid pre-treatment for 12 to 18 hours before the infusions.

#### *Immunogenicity*

Immunogenicity was examined for all patients in the clinical trials.<sup>37,53–55</sup> Of 54 patients, 53 developed immunoglobulin G antibodies to galsulfase.<sup>49</sup> Immunoglobulin E antibodies were not evaluated because they were not part of the clinical trials or reported data. Antibodies typically appeared after 4 to 8 weeks of treatment. Antibodies from 1 patient were analyzed for neutralizing effect and showed evidence of in vitro inhibition of galsulfase activity. Because only 1 patient's sample was analyzed for neutralizing activity, the effects of neutralizing antibodies were unclear. No association was observed between antibody development and urinary glycosaminoglycan levels or measures of endurance outcome in the studies.

### **MANAGEMENT GUIDELINES**

Because MPS VI affects multiple body systems, management of a diverse spectrum of disease manifestations is an important part of providing integrated care. Management may include use of adaptive or supportive devices, physical and occupational therapy, symptom-based medications, surgical interventions, and therapies to provide the deficient enzyme. To address this complex disease, these guidelines focus on management of symptom presentation by body system.

### **SYMPTOM PRESENTATION AND SUPPORTIVE CARE**

#### **Ear, Nose, and Throat and Respiratory System–Related Symptoms**

##### *Overview*

Glycosaminoglycan accumulation in the oropharynx and throughout the airway, combined with the typical dysmorphic features (including midfacial hypoplasia and dental abnormalities),<sup>56,57</sup> are commonly associated with persistent thick/viscous nasal discharge, recurrent and chronic rhinitis, enlargement of the tonsils and adenoids, narrowing of the trachea and bronchi, thickening of the epiglottis and vocal cords, and enlargement of the

tongue (Fig 2), obstructing the upper airway.<sup>58</sup> In addition to this obstruction, restrictive lung disease can be seen in patients with MPS VI. A small and stiff thoracic cage combined with kyphosis, scoliosis, and increased lumbar lordosis are the primary features related to the restrictive lung disease.<sup>59</sup> Disease complications are described below.

##### *Obstructive Sleep Apnea*

Upper-airway obstruction and decreased pulmonary reserve often lead to obstructive sleep apnea. Clinical features include mouth-breathing, snoring, apnea, and restless sleep. Less frequently, daytime somnolence, failure to thrive, pulmonary hypertension, and cor pulmonale may be noticed. Behavioral and learning problems may also occur secondary to disrupted sleep.<sup>60</sup>

##### *Pneumonia*

Recurrent pneumonia may be secondary to increased volume and poor clearance of airway secretions.

##### *Hearing Loss*

Hearing loss is common in MPS VI, and in most patients deficits are conductive in nature.<sup>58</sup>

##### *Evaluation*

Polysomnography can be used to assess sleep apnea. Hearing should be monitored regularly by audiometric testing.

Evaluation of pulmonary function by forced spirometry and flow-volume expiratory and inspiratory loops should be performed regularly to assess changes in lung volume and obstruction. It is not meaningful to evaluate results of pulmonary-function tests of patients with MPS VI in the context of reference values for the normal population, but it is useful to follow absolute values longitudinally in a single patient. To evaluate the extent or severity of airway infiltration and anesthetic risk, fiber-optic bronchoscopy can also be performed.



**FIGURE 2**  
Photograph of mouth with enlarged tongue, abnormal dentition, and gingival hyperplasia.

### *Interventions*

Surgical interventions such as adenotonsillectomy are sometimes performed to remove upper-airway obstruction. In addition, the use of continuous positive airway pressure (CPAP) or bilevel positive airway pressure to maintain the patency of the airway has been beneficial for some patients. Tracheostomy may be necessary for some patients with MPS VI either as a treatment for severe obstructive sleep apnea that is unresponsive to CPAP or, in rare cases, to facilitate safer anesthesia. It may also be required as an emergency procedure to treat anesthesia complications during surgical procedures.

Currently, there are no specific treatments for lower respiratory tract abnormalities; aggressive management of the airway secretions is highly recommended. Antibiotics may also be necessary. Vaccinations against respiratory pathogens such as influenza and pneumococcus should be considered.

### **Cardiac Symptoms**

#### *Overview*

Cardiac abnormalities are frequent in patients with MPS VI<sup>14,61,62</sup> and are an important cause of morbidity and mortality. Progression of cardiac disease in patients with mucopolysaccharidosis disease is related to abnormal storage of dermatan sulfate in the heart and blood vessels<sup>63</sup> and the secondary effects of pulmonary disease and chronic hypoxia on the heart.<sup>64</sup> Heart disease has been shown by serial echocardiography<sup>65</sup> to progressively worsen, and the severity has been found to correlate with age.<sup>61</sup> Specific cardiac manifestations may include the following.

#### *Valve Disease*

The primary cardiac manifestation of MPS VI is progressive valve degeneration with stenosis and/or insufficiency. Pathology seems to be more pronounced in the mitral and aortic valves, although all valves may be affected. Azevedo et al<sup>62</sup> reported mitral valve regurgitation (96%), tricuspid regurgitation (71%), and aortic regurgitation (43%) in 28 patients with MPS VI disease. Stenosis occurred in mitral and aortic valves in 7% of their patients.

#### *Electrocardiographic Abnormalities*

Electrocardiograms are frequently abnormal in patients with MPS VI.<sup>14</sup> The most common abnormalities are sinus tachycardia, right-axis and left-axis deviations, and atrial enlargement.

#### *Coronary Artery Disease*

Although coronary artery disease has been described only for MPS I,<sup>66,67</sup> its presence establishes a high risk for surgery and, therefore, should be considered in patients with MPS VI until more information is available. Identification of these stenotic lesions in patients with MPS I

has been problematic, and no specific method for screening can be recommended at this time.

#### *Systemic Vascular Narrowing and Hypertension*

Systemic hypertension is common (~30%) in patients with MPS I<sup>68</sup> and should be considered in those with MPS VI. Hypertension may develop in relation to aortic or renal artery narrowing or chronic intermittent hypoxia.<sup>68</sup>

#### *Cardiomyopathy*

Hayflick et al<sup>5</sup> reported cardiomyopathy and cardiac failure in a 5-month-old infant with MPS VI, and Miller and Partridge<sup>69</sup> reported endocardial fibroelastosis and cardiac failure that presented in a 9-month-old with MPS VI. Although these 2 reports are noted, cardiomyopathy is uncommon in patients with MPS VI, and the incidence rate is unknown.

#### *Endocarditis*

Bacterial endocarditis has not been reported in patients with MPS VI despite the presence of abnormal cardiac valves. With the recent increased use of indwelling central venous access ports to provide ERT, bacterial endocarditis on native or prosthetic valves may become a significant problem. Examination of the incidence of endocarditis in hemophiliacs with central venous access ports<sup>70</sup> shows a low (0.45 per 1000 catheter-days) rate of infection, although a high percentage of patients do ultimately develop such infections (44%).

#### *Evaluations*

Patients with MPS VI should receive cardiac evaluation every 1 to 2 years. This evaluation should include obtaining a blood pressure reading and performing electrocardiography and echocardiography to assess abnormal cardiac rhythm or changes in heart structure or function. Additional cardiology consultation should be considered before major surgical procedures.

Echocardiography and blood cultures may be required to evaluate fever or suspected endocarditis in patients.

#### *Interventions*

In consultation with a cardiologist, treatment may include antibiotic subacute bacterial endocarditis prophylaxis for dental and other indicated surgical procedures, afterload reducing agents, and supplemental oxygen and/or positive-pressure support for patients with cor pulmonale. Additional cardiac medications may be prescribed if the patient develops congestive heart failure.

Successful replacement of aortic and mitral valves singly or in combination has been reported in patients with MPS VI despite small annuli and difficulty inserting large adult prostheses.<sup>71</sup>

Physicians who prescribe ERT for patients with artificial cardiac valves will certainly be challenged by the

need to place permanent central venous access devices. They will have to weigh the benefit of ERT administration versus the risk of infection in the artificial valve. Efforts to continue delivery by intravenous infusion rather than via a central venous access device should be considered.

### Skeletal Symptoms

#### Overview

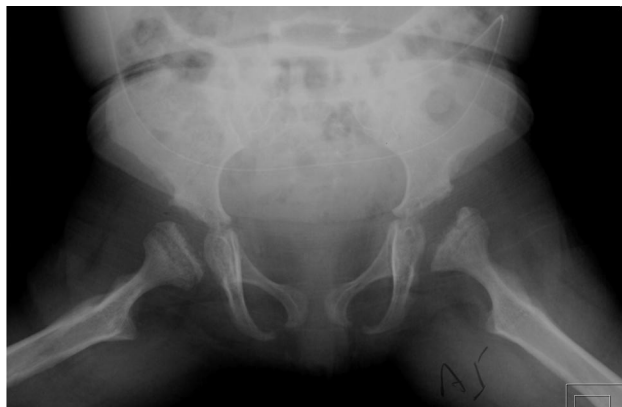
The term “dystosis multiplex” is used to describe the radiologic skeletal deformities seen in patients with MPS VI. Radiographic signs may include point-shaped metacarpal bones, dysplastic femoral head, defective development of the vertebral bodies with anterior beaking, widening of the ribs, and short, irregular clavicles (Figs 3–5). Clinically, skeletal involvement may be obvious from birth when a gibbus deformity or dorsolumbar kyphosis is present as a result of anterior hypoplasia of vertebral bodies at the thoracolumbar junction. Complications that result from skeletal disease are described below.

#### Spinal Cord or Nerve Root Injury

Cord injury caused by atlantoaxial instability from odontoid dysplasia is an important complication to be avoided. In addition, abnormally shaped vertebral bodies (flattening, beaking) may produce spinal nerve entrapment or acute spinal cord injury related to spondylolysis. Kyphosis, scoliosis, increased lumbar lordosis, and severe back pain are common (Fig 3).



**FIGURE 3**  
Lateral radiograph of thoracolumbar spine showing anterior, inferior beaking L2 vertebral body with upper lumbar kyphosis.



**FIGURE 4**  
Anteroposterior radiograph of pelvis showing irregularity and underdevelopment of acetabular roofs and wide, flat, irregular femoral heads. Ossification of the capital femoral epiphyses is incomplete. A ventriculoperitoneal shunt is present in the lower abdomen.



**FIGURE 5**  
Anterior posterior radiograph of hand showing short, broad metacarpals and phalanges, with pointed base of second metacarpal. Broad metaphyses were noted for distal radius and ulna.

#### Joint Abnormalities

Patients with a combination of a poorly formed pelvis, dysplasia of the femoral heads, and coxa valga are at risk of developing progressive and debilitating hip disease (Fig 4). Progressive flexion contractures of the fingers and claw-hand deformity lead to a decline in hand dexterity and fine motor skills (Figs 5 and 6). Symmetrical stiffness, pain, and flexion contractures of the elbows, shoulders, hips, and knees lead to decreased range of motion and gait abnormality. Walking ability typically decreases and “toe-walking” can be observed. Ultimately, patients may become wheelchair bound as a result of hip or spine disease.



FIGURE 6  
Photograph of hands with claw-hand deformity.

### *Growth Impairment*

In rapidly advancing disease, height prognosis is very poor, and patients often obtain an adult height of only 95 to 100 cm. In more slowly advancing disease, height can approach the low-to-normal range of 140 to 150 cm. An abnormal thoracic cage is frequently seen across the spectrum of disease, as well, and may compromise respiratory function.

### *Evaluation*

Clinical examination may be used to follow the progression of bony deformities. Joint range of motion should be evaluated by goniometry. A radiographic skeletal survey including hip films may be performed at baseline and at regular intervals to monitor the progression of skeletal deformities.

### *Interventions*

Physical therapy and antiinflammatory medications may provide benefit for some patients. Orthopedic surgical procedures may significantly improve mobility.

## **Ophthalmologic Symptoms**

### *Overview*

Vision should be carefully monitored and treated aggressively to prevent blindness. Ashworth et al<sup>72</sup> provided a description of eye and vision findings in 16 patients with MPS VI.

### *Blindness and Decreased Visual Acuity*

Visual impairment is common and occurs in ~40% of patients with MPS VI, with 15% having only light perception. Most patients are hypermetropic (farsighted).

### *Corneal Opacification*

Corneal opacification seems to be particularly prevalent in patients with MPS VI (95%, of which 38% are classified as severe) (Fig 7). The severe corneal clouding associated with thickening of the cornea can make as-

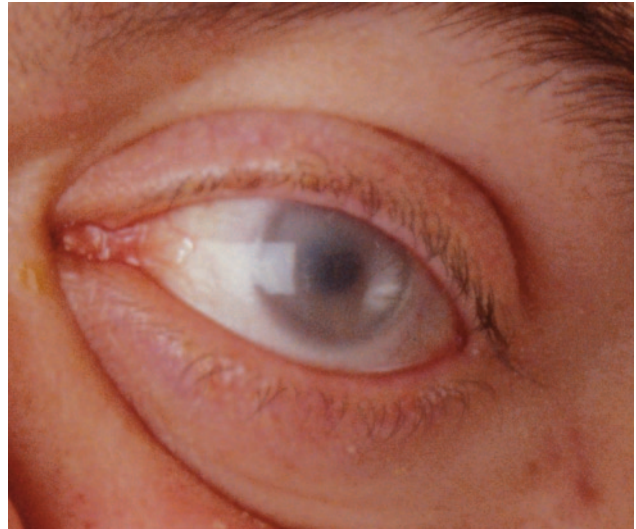


FIGURE 7  
Photograph of eye with corneal clouding.

essment of intraocular pressure (IOP) and visualization of the retina and optic nerve impossible.

### *Retinopathy*

Retinopathy seems to be rare in MPS VI compared with MPS I or II but has been reported.<sup>73–75</sup> Night blindness or dimness may be reported.

### *Optic Nerve Abnormalities*

An abnormal optic disk is a frequent finding, with mild-to-moderate swelling noted in 50% of patients with MPS VI, optic nerve atrophy in 15%, and optic disk cupping associated with increased IOP. Optic nerve swelling may be associated with increased intracranial pressure (ICP), glycosaminoglycan storage in optic nerve ganglion cells, or compression of the optic nerve by thickened dura along the optic nerve track.

### *Ocular Hypertension and Glaucoma*

Increased IOP is a common finding (50%) in patients with MPS VI, although thickening of the cornea may contribute to false elevation of IOP measurements. Increased IOP may be related to narrowing of the anterior chamber angle by iridociliary cysts<sup>76</sup> (closed-angle glaucoma) or glycosaminoglycan deposition in trabecular cells blocking reabsorption (open-angle glaucoma). Some patients with previously documented high IOP demonstrate normal IOP after corneal transplantation.

### *Evaluation*

Regular age-appropriate evaluations by an ophthalmologist are recommended. Recent vision changes including blurring, dimness, loss of night vision, or loss of visual acuity should be evaluated promptly. At yearly examinations, patients should generally be assessed for strabismus, visual acuity, refraction, and IOP by tonometry, if possible. Although difficult to obtain, visual fields



should be assessed when there are changes in optic nerve appearance or increased IOP is noted. A fundoscopic examination should be performed after dilation to evaluate the retina and optic nerve, with photographs taken when possible.

Visual evoked-potential examinations may be used to evaluate the visual system's response to light when severe corneal clouding prevents fundoscopic examination of the optic disk.

### Interventions

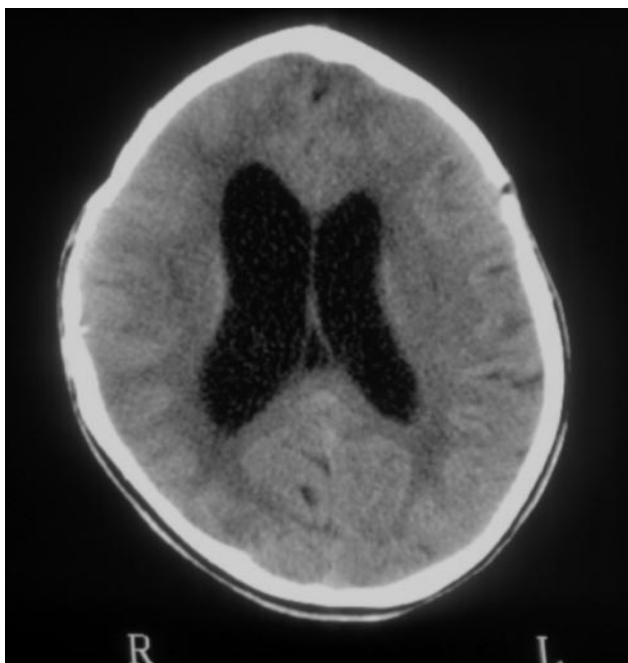
Interventions may include corrective lenses, medications, and/or surgery to control increased IOP, patching for amblyopia, or surgery to correct strabismus when relevant. In addition, corneal transplantation (penetrating keratoplasty) may be performed to correct severe corneal clouding with vision loss.

If increased ICP is documented, a ventriculoperitoneal shunt may prevent optic atrophy and vision loss in some patients. Decompression of the optic nerve by neurosurgery may also be considered, although it is conceivable that ERT may be found to be effective for these patients.

## Central and Peripheral Nervous System–Related Symptoms

### Overview

Hydrocephalus, spinal cord disorders, and compressive neuropathies are the most frequent nervous system disorders in MPS VI (Fig 8). In a patient diagnosed with



**FIGURE 8**  
Head computed tomography axial image of moderate ventriculomegaly, showing asymmetric hydrocephalus with moderate distension of lateral ventricles (right is greater than left).

MPS VI, the presentation of mental retardation should raise the consideration of multiple sulfatase disease, a distinct LSD.<sup>31,62,77</sup>

Although the frequencies of the more common neurologic abnormalities such as carpal tunnel syndrome (CTS) and hydrocephalus have been documented,<sup>62</sup> the frequencies of less-common abnormalities such as cervical myelopathy with atlantoaxial instability or spinal cord compression are unknown. It is possible that patients with these rare abnormalities are being underdiagnosed, thus delaying and hindering their treatment.

### Carpal Tunnel Syndrome

CTS<sup>78–80</sup> is caused by compression of the median nerve that results from the accumulation of glycosaminoglycan in the retinaculum of the flexor muscles and is aggravated by the bone alterations in the region of the carpus (Fig 5). In patients with MPS VI, spontaneous reporting of typical complaints of pain and paresthesias is rare; however, many patients do claim symptomatology when directly questioned. When investigated by means of electrophysiological studies, most patients with MPS VI have evidence of bilateral CTS, which is usually severe and progressive.

### Communicating Hydrocephalus

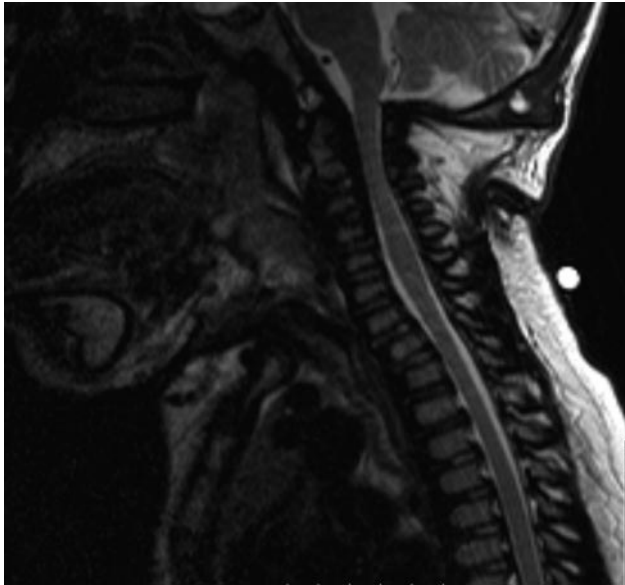
In MPS VI, raised ICP<sup>78,79,81</sup> is thought to be caused by dural thickening and dysfunction of the arachnoid villi. The diagnosis of this complication by computed tomography or MRI studies is not always an easy task, because the ventricular dilation may be related to cortical atrophy, and direct measurement of central nervous system pressure may be required. Typical signs of obstructive hydrocephalus such as early-morning headache, vomiting, and papilledema are often absent, although some patients may present with rapid visual deterioration.

### Compressive Myelopathy

In MPS VI, progressive compressive myelopathy<sup>78,79,82,83</sup> may involve multiple spinal cord levels, although it occurs most frequently in the cervical region (Fig 9). Its etiology is multifactorial and may involve progressive accumulation of glycosaminoglycan in the dura and supporting ligaments, kyphoscoliosis, and bony stenosis. It may initially become evident on clinical examination with long-tract signs but progresses to lower-extremity weakness and then to spastic paraplegia or quadriplegia.

### Evaluation

Regular clinical neurologic and ophthalmologic examinations conducted at a minimum of yearly intervals are essential for identifying early abnormalities. Baseline brain and spine MRI, radiographic views of the cervical spine in flexion and extension, and electrophysiologic examinations to evaluate carpal tunnel disease should be obtained. Repeat MRI examinations should be obtained



**FIGURE 9** Sagittal T2 MRI of cervical spine, showing narrowing of the upper cervical canal and effacement of the cerebrospinal fluid space. Odontoid hypoplasia with ligamentous hypertrophy can be seen at the C2 level with no evidence of spinal cord signal abnormality.

depending on disease severity and development of symptoms, although a frequency of every 2 to 3 years should be considered standard for rapidly progressing disease. Cervical spine flexion/extension examinations and electrophysiologic examinations for CTS should be obtained on a regular basis to identify pathology before symptoms appear.<sup>78–83</sup>

### Interventions

Surgical decompression of CTS, especially when performed in the early stages, reduces signs and symptoms of compressive myelopathy and improves the chance of preserving hand function. When MRI of the brain shows dilated ventricles, shunting should be considered if increased ICP can be documented.<sup>78–83</sup>

### Anesthetic Considerations

#### Symptoms

Children with mucopolysaccharidosis represent a major challenge to the anesthesiologist. A survey of airway complications in this group of patients at the Royal Manchester Children’s Hospital (Manchester, United Kingdom) showed an overall incidence of difficult intubation of 25% of all subgroups and a failed intubation rate of 8%.<sup>84</sup> Besides the features previously described related to airway obstruction, patients also have craniofacial abnormalities, a short neck, stiffening of the temporomandibular joints, an anteriorly positioned larynx, and, in some patients, an unstable atlantoaxial joint, requiring avoidance of hyperextension of the neck, all of which may complicate laryngoscopy and intubation. Cardiac abnormalities such as coronary artery narrowing

**TABLE 1 Recommended Schedule of Assessments**

	Initial Assessments	Every 3 mo	Every 12 mo	As Clinically Indicated <sup>a</sup>
Confirmation of MPS VI	X			
Medical history <sup>b</sup>	X		X	
Physical examination	X		X	
Neurologic examination	X		X	
Height, weight	X		X	
Head circumference	X		X <sup>c</sup>	
Tanner stage	X		X <sup>d</sup>	
Photographs	X			X
Endurance <sup>e</sup>				
12MWT	X		X	
3MSC	X		X	
Ophthalmology				
Visual acuity	X		X	
Corneal examination	X		X	
Fundoscopic examination	X		X	
IOP	X		X	
Refraction	X		X	
Audiometry	X		X	
Cardiology				
Echocardiogram	X		X	
Electrocardiogram	X		X	
Blood pressure	X		X	
Electrophysiology				
Nerve conduction <sup>f</sup>	X			X
Pulmonary function				
Forced vital capacity, forced expiratory volume in 1 second, maximum voluntary ventilation <sup>g</sup>	X		X	
Sleep study	X			X
Imaging studies				
Hip films <sup>h</sup>	X			X
Skeletal survey	X			X
Flex/ext radiograph of cervical spine	X			X
MRI of brain and spine <sup>i</sup>	X			X
Laboratory assessments				
Urinary glycosaminoglycan level	X		X	
Supplemental assessments for patients on ERT <sup>j</sup>				
Total anti-ASB antibody <sup>k</sup>	X	X	Yearly after 24 mo	

<sup>a</sup> “As clinically indicated” generally means every 2 to 3 years depending on the rate of disease progression and clinical symptoms.

<sup>b</sup> For infants, more frequent examinations are necessary.

<sup>c</sup> Monitored until head growth has stopped

<sup>d</sup> Continue assessments until pubertal maturation is completed.

<sup>e</sup> Endurance-testing paradigm before and after ERT: distance walked in 12 minutes (or 6-minute walk test per American Thoracic Society guidelines<sup>85</sup> but preferably same minute length as completed in previous test); number of stairs climbed in 3 minutes.

<sup>f</sup> Median nerve conduction measured to evaluate CTS.

<sup>g</sup> Pulmonary-function tests are to include forced vital capacity, forced expiratory volume in 1 second, and maximum voluntary ventilation.

<sup>h</sup> Anteroposterior and “frog-leg” lateral views of pelvis

<sup>i</sup> MRI of brain and spinal cord may require sedation or general anesthesia depending on patient age and cooperation. General anesthesia carries substantial risk for patients with MPS VI.

<sup>j</sup> For patients on ERT, results should be obtained at baseline, then at months 3, 6, 12, 18, and 24 and then yearly.

<sup>k</sup> Anti-ASB antibody testing is only available for US patients enrolled in the CSP.

(reported to date only in MPS I) or pulmonary hypertension may be present, and pulmonary edema may complicate efforts to extubate in the postoperative period.

### Evaluation

Cardiologic, respiratory, and upper-airway statuses should be fully evaluated before any procedure that requires sedation or anesthesia.

### Interventions

Consider referral to a center with anesthesia experience in caring for these patients. Because intubation is often challenging as a result of upper-airway abnormalities, it is helpful to involve an otolaryngologist in airway evaluation and management. Spontaneous breathing induction with a volatile agent, use of a laryngeal mask airway, and fiber-optic bronchoscopy to guide intubation are also procedures that are recommended by Walker et al.<sup>84</sup>

### INITIATION OF ERT WITH NAGLAZYME

The recommended dose of Naglazyme is 1 mg/kg body weight administered once weekly as an intravenous infusion over a minimum of 4 hours.<sup>49</sup> Details of reconstitution may be found in the package insert. Naglazyme does not contain preservatives and should be used immediately. It must not be infused with other products in the infusion tubing. After dilution with saline in the infusion bags, any unused product or waste material should be discarded. For additional information, consult the package insert.<sup>49</sup>

Before infusion, the patient's airway and respiratory status should be evaluated. We suggest that physicians consider delaying Naglazyme infusions in patients who present with an acute febrile or respiratory illness.

Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes before the start of the infusion to reduce the incidence of infusion-associated reactions. Because sleep apnea is common in patients with MPS VI and somnolence-inducing antihistamine pretreatment may increase the risk of apneic episodes, we recommend that physicians consider using an antihistamine that is nonsedating. Patients who use supplemental oxygen or CPAP during sleep should have these treatments readily available during infusion.

Despite routine pretreatment with antihistamines, infusion-associated reactions occurred in 30 of 55 patients who were treated with Naglazyme during clinical trials. Symptoms typically abated with slowing or temporary interruption of the infusion and administration of additional antihistamines, antipyretics, and, occasionally, corticosteroids. Subsequent infusions were managed with a slower rate of Naglazyme administration accompanied by concomitant treatment with additional prophylactic antihistamines. In the case of a more severe reaction, treatment with prophylactic corticosteroids may be required during the 12- to 18-hour period before an infusion.

### BIOMARIN CLINICAL SURVEILLANCE PROGRAM

A registry that tracks affected individuals (MPS VI Clinical Surveillance Program [CSP]) was first established by BioMarin Pharmaceutical Inc in the United States in 2005 and was introduced in Europe during 2006. The objective of this program is to learn more about the natural history of the disease and gather additional information about MPS VI treatments. The program will also monitor the effect of Naglazyme on pregnant women and their offspring. All patients should be advised that their participation in the CSP is voluntary, requires a standard institutional review board informed consent process, and may involve long-term follow-up. For more information, patients or physicians may contact BioMarin patient and physician support at 866-906-6100 (option 1) if in the United States. Patients and physicians in the European Union may contact CSP at BioMarin Europe Ltd: +44(0)207-534-9357. Patients and physicians outside the United States and European Union may contact BioMarin Medical Information at +1-415-506-6345 or by e-mail at [medinfo@bmrn.com](mailto:medinfo@bmrn.com). A description of the CSP may be found at [www.naglazyme.com/HCP/CSP.aspx](http://www.naglazyme.com/HCP/CSP.aspx).

### RECOMMENDED ASSESSMENTS

Recommended assessments are shown in Table 1. These may need to be repeated more frequently if clinically indicated.

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The consensus panel consisted of Michael Beck, MD\* (Children's Hospital, University of Mainz, Mainz, Germany), Nathalie Guffon, MD\*† (Hôpital Edouard Herriot Pavillon S, Maladies Métaboliques, Lyon, France), John J. Hopwood, PhD (Lysosomal Diseases Research Unit, Department of Genetic Medicine, Children Youth and Women's Health Service, North Adelaide, Australia), David Ketteridge, MBBS† (Department of Genetic Medicine, Children Youth and Women's Health Service), Joseph Muenzer, MD, PhD (Department of Pediatrics, University of North Carolina, Chapel Hill), Gregory M. Pastores, MD, PhD\* (Division of Neurogenetics, Department of Neurology, New York University School of Medicine, New York, NY), Clara Sá Miranda, PhD\*† (Unidade de Biologia do Lisossoma e Peroxisoma, Instituto de Biologia Molecular e Celular, Porto, Portugal), Maurizio Scarpa, MD, PhD\* (Department of Pediatrics, University of Padova, Padova, Italy), Ida Schwartz, MD, PhD\*† (Medical Genetics Service, Hospital de Clinicas de Porto Alegre, Genetics Departmente, Universidade Federal do Rio Grande Do Sul, Porto Alegre, Brazil), Robert

\*Participated in the BioMarin-sponsored clinical trial (phase 3).

†Participated in the BioMarin-sponsored clinical trial (phase 2).

‡Participated in the BioMarin-sponsored clinical trial (phase 1/2).

D. Steiner, MD\*† (Division of Metabolism, Oregon Health and Science University, Portland, OR), and Elisa Leão Teles, MD\*† (Unidade de Doenças Metabólicas, Departamento de Pediatria, Hospital de São João, Porto, Portugal). The expert consultants were Simone Chaves Fagundes, MD, PhD (Department of Pulmonary Medicine, Hospital de Clinicas de Porto Alegre, RS, Brazil), Selim T. Koseoglu, MD (Division of Ophthalmology, Children's Hospital and Research Center Oakland, Oakland, CA), Howard Rosenfeld, MD (Division of Cardiology, Children's Hospital and Research Center Oakland), and Ronald Cohen, MD (Department of Radiology, Children's Hospital and Research Center Oakland).

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**APPENDIX Physician Resources and Patient Support Organizations for Mucopolysaccharidoses and LSDs (Listed Globally by Country and Arranged in Alphabetical Order)**

Resource	Web-Site Address
Global	
Global Organisation for Lysosomal Diseases	<a href="http://www.goldinfo.org">www.goldinfo.org</a>
A Living Resource	<a href="http://www.mpsvi.com">www.mpsvi.com</a>
Naglazyme	<a href="http://www.naglazyme.com">www.naglazyme.com</a>
Australia	
Lysosomal Diseases Australia	<a href="http://www.lida.org.au">www.lida.org.au</a>
Mucopolysaccharide and Related Diseases Society Australia Ltd	<a href="http://mpssociety.org.au">http://mpssociety.org.au</a>
Austria	
Gesellschaft für Mukopolysaccharidosen und Ähnliche Erkrankungen	<a href="http://www.mps-austria.at">www.mps-austria.at</a>
Brazil	
Sociedade Brasileira Mucopolissacaridoses	<a href="http://www.mpsbrasil.cjb.net">www.mpsbrasil.cjb.net</a>
Rede MPS Brasil	<a href="http://www.ufrgs.br/redempbrasil">www.ufrgs.br/redempbrasil</a>
MPS Brasil Webpage	<a href="http://www.mpsbrasil.org.br">www.mpsbrasil.org.br</a>
Canada	
Canadian Society for Mucopolysaccharide Diseases and Related Diseases Inc	<a href="http://mpssociety.ca">http://mpssociety.ca</a>
France	
Vaincre les Maladies Lysosomales	<a href="http://www.vml-asso.org">www.vml-asso.org</a>
Germany	
Gesellschaft für Mukopolysaccharidosen e.V.	<a href="http://www.mps-ev.de/index.php">www.mps-ev.de/index.php</a>
Italy	
Associazione Italiana Mucopolisaccaridosi	<a href="http://www.mucopolisaccaridosi.it">www.mucopolisaccaridosi.it</a>
New Zealand	
Lysosomal Diseases New Zealand	<a href="http://www.ldnz.org.nz">www.ldnz.org.nz</a>
Portugal	
Portugal-Associação Portuguesa das Doenças do Lisosoma	<a href="http://aplisosoma.org">http://aplisosoma.org</a>
United Kingdom	
Society for Mucopolysaccharide Diseases	<a href="http://www.mpsociety.co.uk">www.mpsociety.co.uk</a>
United States	
National MPS Society	<a href="http://mpssociety.org">http://mpssociety.org</a>