Clinical Evolution After Enzyme Replacement Therapy in Twins with the Severe Form of Maroteaux–Lamy Syndrome

M. Pineda • M. O’Callaghan • A. Fernandez Lopez •
M.J. Coll • R. Ullot • G. Garcia-Fructuoso

Received: 05 September 2015 / Revised: 27 November 2015 / Accepted: 10 December 2015 / Published online: 27 February 2016
© SSIEM and Springer-Verlag Berlin Heidelberg 2016

Abstract Mucopolysaccharidosis type VI (MPS VI) is a progressive, autosomal, recessive lysosomal disorder. This disorder, due to a deficiency in *N*-acetylgalactosamine-4-sulfatase (ASB), results in an accumulation of glycosaminoglycan (GAG), causing multiple organ failures. In this study, monozygotic diamniotic twins with the severe form of MPS VI underwent enzyme replacement therapy (ERT) with weekly infusions of recombinant human ASB (galsulfase) at 1 mg/kg. After 9 years of ERT, a comprehensive clinical examination was performed. Several types of biochemical, immunological, and genetic investigations were also conducted. Both twins showed the typical symptoms and signs of MPS VI at baseline, including short stature, progressive dysmorphic facial features, and dysostosis multiplex. Twin 2 presented stronger multi-systemic involvement, with marked musculoskeletal, neu-

rological, and odontological components. She also developed an ischemic spinal cord lesion after surgery, which is the first case described in the literature in Maroteaux–Lamy syndrome. However, the extent of disease was found to be equally stabilized in the two sisters, concretely the cardiac and respiratory functions and body length. The early diagnosis and treatment of MPS VI are critical for an optimal clinical outcome, and further evidence for the new treatment strategies is needed.

Introduction

Maroteaux–Lamy syndrome (also known as mucopolysaccharidosis type VI, MPS VI, or polydystrophic dwarfism) is a form of mucopolysaccharidosis that was first described by Pierre Maroteaux and his mentor, Maurice Emil Joseph Lamy, in 1963 (Maroteaux et al. 1963). Estimates of MPS VI incidence range from 1 in 238,095 to 1 in 1,300,000 in the Netherlands (Poorthuis et al. 1999); even higher rates have been reported in Portugal and Brazil (Valayannopoulos et al. 2010). This lysosomal disorder, caused by a deficiency in the enzyme *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B, ASB; EC 3.1.6.12), is a result of mutations in the arylsulfatase B gene (*ASB*) located on chromosome 5 (5q13–5q14) (Litjens et al. 1989). The pathogenic mutations of this gene reduce the activity of the ASB enzyme, leading to an accumulation of glycosaminoglycans (GAGs). In particular, there is a marked accumulation of dermatan sulfate in the lysosomes, producing irreversible cellular and tissue damage, with the consequent multiple organ system dysfunctions.

Patients with the most severe and rapidly progressing disease often show short stature, coarse facial features, and joint deformities. They also suffer from skeletal dysplasia,

Communicated by: Olaf Bodamer, MD PhD

Competing interests: None declared

M. Pineda (✉) • M. O’Callaghan
Fundación y Servicio de Neuropediatría, Hospital Universitario Sant Joan de Déu, CIBERER, Barcelona, Spain
e-mail: pineda@hsjdbcn.org

A. Fernandez Lopez
Servicio de pediatría, Hospital Sant Joan de Déu, Universidad de Barcelona, Spain

M.J. Coll
Sección Errors Congènits, Servei de Bioquímica i Genètica Molecular, Hospital Clinic, CIBERER, Barcelona, Spain

R. Ullot
Servicio de Traumatología y Ortopedia, Hospital Universitario Sant Joan de Déu, Barcelona, Spain

G. Garcia-Fructuoso
Servicio de Neurocirugía, Hospital Universitario Sant Joan de Déu, Barcelona, Spain

myelopathy, compromised cardiovascular function, corneal clouding, upper airway obstruction, and recurrent ear infections. Death usually occurs in the early teenage years due to respiratory and cardiac problems (Neufeld and Muenzer 2001; Valayannopoulos et al. 2010). Symptoms may appear later; in such cases, mortality is expected in the third to fifth decade of life (Thümler et al. 2012).

The international management guidelines for MPS VI have been drafted based on the evidence from randomized, controlled trials and recommend galsulfase (recombinant human ASB; rhASB; Naglazyme®) enzyme replacement therapy (ERT) as the first-line, long-term therapy for treating this disease (Giugliani et al. 2007). In this report, we describe the clinical evolution of Spanish monochorionic diamniotic twins with the severe form of MPS VI after galsulfase treatment.

Material and Methods

Patient Characteristics

The monochorionic diamniotic twins were born to non-consanguineous Spanish parents after 36 weeks of gestation. No family history of genetic disease was found, and the sister of the twins was healthy. At birth, both twins presented normal birth parameters (Twin 1: weight, 2,650 g; length, 49 cm; occipitofrontal circumference (OFC), 34.5 cm; Twin 2: weight, 2,265 g; length, 44 cm; cephalic perimeter, 28.0 cm). Both showed coarse facial features with hypertelorism and a cranial perimeter of 48.5 cm (percentile 70) at 11 months of age. They suffered from frequent otitis. The twins started walking at 16 months of age, both showing a slight lumbar kyphosis.

Twin 1

MPS VI was diagnosed at 18 months of age. The child had elevated urinary GAGs of 45.8 mg/mmol of creatinine (normal values: 0.9–5.5 mg/mmol of creatinine), and dermatan sulfate was identified. The activity of *N*-acetylgalactosamine-4-sulfatase was diminished in the leukocytes (79.6 $\mu\text{mol/g}$ of protein/min; normal value: 950.0 $\mu\text{mol/g}$ of protein/min) and in cultured fibroblasts (63.7 nmol/mg of protein/h, i.e., 15.8% of the parallel normal value of 403.2 nmol/mg of protein/h). The genetic analysis showed the mutations c.1142+2T>A and c238delG in the *ARSB* gene.

At the age of 3, the growth of Twin 1 decelerated. A year later, she underwent ventriculoperitoneal shunt implantation to treat her progressive hydrocephalus and papilledema. The implant was replaced with a programmable shunt after 3 months and required three later revisions. Inguinal hernia surgery was also required. Gingival hyperplasia, increased

lumbar lordosis with dragging of the forefoot, weakened right lower limb, increased osteotendinous reflexes, and clonus in the right Achilles tendon were observed. Surgical decompression of the foramen magnum, occipitocervical fixation with autologous bone grafts up to C2, and halo jacket were required at 4.5 years of age to treat the progressive cervical stenosis myelopathy.

Twin 2

MPS VI was diagnosed at 18 months of age with elevated urinary GAGs (39.6 mg/mmol of creatinine; normal values: 0.9–5.5 mg/mmol) and significantly increased levels of dermatan sulfate. We found diminished activity of *N*-acetylgalactosamine-4-sulfatase in leukocytes (38.7 $\mu\text{mol/g}$ of protein/min; normal value: 950.0 $\mu\text{mol/g}$ of protein/min) and in cultured fibroblasts (5.2 nmol/mg of protein/h, i.e., 1.7% of the parallel control normal value of 403.2 $\mu\text{mol/g}$ of protein/min). As expected, the genetic studies showed the same mutations, c.1142+2T>A and c238delG, in the *ARSB* gene.

At the age of 4, a ventriculoperitoneal shunt was placed to treat the progressive increase in cephalic perimeter caused by hydrocephalus, a decrease in visual acuity (0.6), and papilledema. The shunt required conversion to a programmable implant, as in the case of Twin 1, due to a bilateral subdural collection. The patient developed early progressive tetraparesis (4/5) and showed the signs of pyramidal tract dysfunction. Similarly to her twin sister, decompression of the foramen magnum was also required, with occipitocervical fixation with autologous bone grafts up to C2. A halo jacket was placed for the cervical stenosis myelopathy.

Biochemical and Molecular Determinations

GAGs were quantified in urine using a dimethylmethylene-blue spectrophotometric assay, as previously described (Panin et al. 1986). Qualitative analysis for the identification and characterization of dermatan sulfate was performed using thin-layer chromatography after cetylpyridinium chloride precipitation. The normal values for GAGs range from 0.9 to 5.5 mg/mmol of creatinine.

N-acetylgalactosamine-4-sulfatase activity in leukocytes and fibroblasts was determined in vitro by spectrophotometric quantification of the *p*-nitrocatechol produced by hydrolysis of the substrate, *p*-nitrocatechol sulfate (Baum et al. 1959). This assay was performed in three different samples to avoid inter-sample variation usually observed in patients.

The isolation of genomic DNA and mutation analysis of the *ARSB* gene were performed as described in a publication by Garrido et al. (2007).

The assay of galsulfase antibody levels for the evaluation of anti-rhASB antibodies was performed at Cambridge

Fig. 1 Growth charts showing weight (kg) and length (cm) from the age of 2 to 14 for dizygotic twins (Twin 1 and Twin 2) with the severe form of MPS VI. Growth was expressed as length-for-age and weight-

for-age using currently accepted cross-sectional chart for Spanish children and youth

Biomedical, Inc., Boston (www.cambridgebiomedical.com).

Results

The twins received recombinant human ASB galsulfase (Naglazyme®; BioMarin Pharmaceuticals Inc., Novato, CA) diluted with a physiological saline solution at 1 mg/kg/week, infused over a 4-h period. The ERT was started at 4 years and 9 months of age (Twin 1: length 90 cm, weight 17 kg; Twin 2: length 88 cm, weight 17 kg). By the time of writing, the twins have been treated for 9 years. No adverse events (including infusion-related events) were reported, and the ERT was well tolerated.

After the initiation of ERT, the baseline urinary GAG levels of the twins decreased rapidly, within a few months, to 8.2 mg/mmol of creatinine. The GAG levels remained between 6 and 10 mg/mmol of creatinine up to the time of writing, above the normal values of <4 mg/mmol of creatinine (Braunlin et al. 2013).

Growth charts for the twins showing weight (kg) and length (cm) from the age of 2 to 14 years are presented in Fig. 1. Weight graphs are similar for the two patients, with values within a normal range up to the year 4. The values remained near the lower percentiles until 9 years of age, after which they dropped below clinically normal levels. The decrease in growth rate was easier to see on the length graphs for both twins (Fig. 1); it became clear after the age of 3.

Clinical Manifestations

Twin 1

At the age of 7, Twin 1 was seen by a neurosurgeon due to a worsening of cervical myelopathy. The magnetic resonance imaging (MRI) findings showed a decompensation that produced restenosis in the foramen magnum and a longer cervical area. Therefore, a surgical decompression of the foramen, expansion of the cervical laminectomy, and posterior instrumented arthrodesis were performed. The patient recovered completely, with both upper and lower limbs remaining normal up to the time of writing. When the patient was 9 years old, an exodoncy was performed due to dental caries, ankylosis, and maxillary sinus retention cysts of teeth 73 and 83. The surgery was performed on the tooth 85.

Thickened mucosa in the retromolar pad blocked the eruption of the permanent teeth. At 9 years and 11 months of age, the patient underwent surgery for bilateral carpal tunnel syndrome. One month later, the audiometry examination showed a mild transmission hypoacusis, and ophthalmological tests demonstrated a slight symmetrical opacity of the cornea. An echocardiogram showed a minimal mitral insufficiency; however, the heart and pulmonary functions were normal. Control MRI showed mild stenosis at C5 and C6 without hydrocephalus. The 6-min walk test (6MWT) distance decreased from 460 m (at the age of 10, 6 years after the start of the ERT) to 400 m (age of 13, after 9 years of the ERT). The total antibody response to Naglazyme (galsulfase) showed >1,770,000 anti-rhASB antibodies and 0 neutralizing anti-rhASB antibodies.

Twin 2

Twin 2 was admitted for umbilical hernia surgery at the age of 5; at the same time, a bilateral tenotomy of the Achilles tendon and plantar fasciotomy were performed. One year later, a Gore-Tex mesh was placed by umbilical herniorrhaphy. At 8 years of age, the patient underwent deep anterior lamellar keratoplasty in the right eye, and one month later, in the left eye. Several odontological disorders were observed at the age of 9, including retention of permanent teeth, ectopic teeth, dental cysts, and exodoncy. At the same time, the patient underwent the surgery for carpal tunnel syndrome. During the audiometric evaluation, she showed a hearing loss in both ears at 10 years of age, with mixed hypoacusis in the left ear and conductive hypoacusis in the right. Mitral, tricuspid, and aortic insufficiency were also observed, although the pulmonary function was normal.

At the age of 11, the 6MWT distance was 345 m (7 years under the ERT) and improved to 426 m 2 years later (9 years of the ERT). The severity of the disease was manifest in the musculoskeletal and connective tissue disorders, with sacral hyperlordosis and articular mobility reduced due to mild retractions in the feet, hands, and shoulders. A control MRI showed no symptoms of hydrocephaly. A marked narrowing of the foramen magnum and the cervical spine diameter (C3–C5) was also registered. The imaging examination also showed scoliosis, bilateral valgus knee, and a subtle cavus foot. A hyperreflexia in the left extremities was also observed, which, at 13 years of age, became a progressive spastic tetraparesis, predominantly in the lower extremities.

A surgical decompression of the foramen, expansion of the cervical laminectomy down to C5, and posterior instrumented arthrodesis became necessary. After the surgery, the patient presented with complete paraplegia at the thoracic spine level. The subsequent delayed MRI confirmed that the symptoms were compatible with spinal cord ischemic lesion at the level of the maximum thoracic kyphosis. The results from the coronal plane MRI (T2) before and after ischemic lesion are shown in Fig. 2a and b, respectively. One year later, the patient achieved a good recovery from the thoracic-level paraplegia in the arms.

The total antibody response to Naglazyme showed >2,430 anti-rhASB antibodies and 0 neutralizing anti-rhASB antibodies.

Discussion

Because lysosomal storage disorders such as MPS VI are rare, only limited data are available, and the existing studies cover relatively short periods of observation. The assessment of the cases of rapidly progressive MPS VI reported in this work provides an overview of the clinical evolution during 9 years of therapy with galsulfase. Even though the patients were monozygotic diamniotic twins with the same mutations in the *ASB* gene, their clinical manifestations of this enzymatic deficiency were slightly different. Twin 2 presented stronger multisystemic involvement (with marked musculoskeletal, neurological, and odontological components) than Twin 1.

We found that GAG levels were lower before the infusion than 2 days after the galsulfase infusion treatment. To the best of our knowledge, there are no studies using the levels of antibodies to galsulfase to evaluate the level of anti-rhASB antibodies. In our study, both twins showed negative results, despite higher levels of total antibodies in Twin 1, probably associated with the increased basal levels of the endogenous enzyme. In other lysosomal diseases, the

Fig. 2 Results from the coronal plane MRI (T2) before (Fig. 2a) and after (Fig. 2b) ischemic lesion in Twin 2. (a) Results from the coronal plane magnetic resonance imaging (T2) were compatible with pronounced scoliosis but showed normal spinal cord image at the

mid-dorsal level in Twin 2. (b) Results from the coronal plane MRI (T2) showed intramedullary hyperintensity at the D5–6 dorsal level compatible with spinal cord lesion in Twin 2

antibody levels in the blood can affect the efficacy of the ERT by inhibiting the uptake of the enzyme by the target tissues (Brands et al. 2013). Our results show no galsulfase antibodies in MPS VI patients, so the marked signs and symptoms might be only associated with the rapid, progressive form of the disease.

The mean length increase in our patients from the start of the treatment to the last follow-up was 3.3 cm/year. Overall, the length and weight increases remained slightly below

normal. Our results are in-line with the previous studies of MPS VI, in which the growth rates are greater in patients below 16 years of age (Decker et al. 2010; McGill et al. 2010; Furujo et al. 2011; Hendriksz et al. 2013). It has been suggested that the improvement in growth is associated with the beneficial effects of the treatment on the bone cells and endocrine gland function, leading to reduced inflammation and a reduction in joint contractures (Decker et al. 2010). However, there is little information on the growth of

MPS VI patients who have not received ERT. Such data are necessary for the understanding of the effect of galsulfase therapy on the disease. Twin 2 in our study displayed progressive musculoskeletal and joint disorders despite being under ERT, but her length evolution was similar to that of her twin sister. In contrast, Twin 1 showed stabilization in the results of the skeletal radiographs and imaging analysis after ERT. Similarly to other cases described in the literature, our patients presented with some of the most common neurosurgical complications, including hydrocephalus and stenosis of the foramen magnum with progressive myelopathy (Lampe et al. 2013). Paraplegia after surgery was described in Twin 2. We have found only three similar cases with thoracolumbar kyphosis reported in patients with MPS who suffered from post-operative spinal cord lesion (2 with Hurler syndrome and 1 with Morquio disease) (Pauchard et al. 2014). In their publication, Pauchard et al. concluded that the narrowing associated with spinal hypermobility may be involved in the origin of this spinal cord damage, but it is not the only determining factor. This view is supported by the two cases of extra-spinal surgery with previously identified kyphosis (Pauchard et al. 2014). Bone dysplasia and spinal involvement are the predominant types of neurological damage in MPS VI patients; the risk of perioperative spinal cord complications must be individually analyzed before any surgery.

Another common clinical manifestation in MPS VI is cardiac involvement, a major cause of mortality. In particular, the left ventricular hypertrophy and functional abnormalities of the mitral and aortic valves are progressive in individuals who are not treated (Braunlin et al. 2013). These abnormalities are stabilized by galsulfase treatment (Brands et al. 2013; Giugliani et al. 2014). We found mild mitral insufficiency in both twins, although mitral valve regurgitation is described in most MPS VI pediatric reports (Azevedo et al. 2004; Scarpa et al. 2009; Fesslova et al. 2009; Lael et al. 2010). However, Twin 2 also presented tricuspid and aortic involvement. Nevertheless, cardiac performance measures were slowed at the age of 13 years in both twins.

A recent pooled long-term data analysis from the clinical ERT trials and the survey study in MPS VI patients showed that the galsulfase therapy partially improved the pulmonary function. The affected parameters are the forced vital capacity, forced expiratory volume in 1 s (FEV1), and the maximum voluntary ventilation (Harmatz et al. 2010). The twins in our study had a stable pulmonary function; the values of the listed parameters were within the normal range during the study period. Some authors have attributed this to the underlying increase in the endurance and the

beneficial changes in pulmonary function (Harmatz et al. 2008). These results agreed with the results of 6MWT of Twin 2, which showed an improvement of 81 m (measured at 11 and 13 years of age).

Finally, we reported ophthalmological and audiological outcomes with no tendency to improve after 9 years of the ERT. Almost 80% of patients with MPS VI have reduced visual acuity and 60% have impaired hearing according to the literature. These data are in accord with our results showing that the ERT had no impact on vision or hearing (Hendriksz et al. 2013).

In conclusion, the monochorionic diamniotic twins studied in this work showed typical characteristics of the severe form of MPS VI at the baseline. Even though the younger twin (Twin II) presented stronger clinical symptoms, the progression of the disease was similar in the two sisters; stabilization in the cardiac and pulmonary measures was observed after 9 years of the ERT. There were clear improvements in growth as well as in clinical endurance. In contrast, Twin 2 showed neurological damage with marked perioperative spinal cord complications. Here, we present for the first time the results of the assay of neutralizing anti-rhASB antibodies, which were negative for both twins. The reported spine ischemic kyphosis, a result of surgery in Twin 2, demonstrates the risk of spinal cord damage in MPS VI patients. Overall, we found the ERT to be effective and safe in these two cases. However, improved regimens or schedules might be required to increase the clinical benefits of galsulfase ERT in patients with the rapidly progressing disease.

Acknowledgments Scientific editorial assistance was provided by Irantzu Izco-Basurko and Fernando Rico-Villademoros (Cociente S. L.). The authors thank the family for their collaboration.

Synopsis

Comprehensive description of clinical manifestations in monochorionic diamniotic twins with the severe form of mucopolysaccharidosis type VI under enzyme replacement therapy.

Contributorship

MP analyzed data and drafted the manuscript. MO, GGF, and AF treated and followed up the patients and revised the manuscript. MJC conducted metabolic and genetic studies and revised the manuscript. All authors read and approved the manuscript.

Guarantor

Mercedes Pineda Marfa.

Compliance with Ethics Guidelines

Conflict of Interest

The authors RU, AF, MJC, and LG have no affiliations or financial involvement with any organization or entity with an interest in or conflict with the subject matter discussed in the manuscript. MO has received consulting fees or honoraria from Actelion Pharmaceuticals Ltd for travel, accommodations, or meetings and payment for lectures from BioMarin, Genzyme, and Shire. MP has received consulting fees or honoraria and payment for lectures from Actelion Pharmaceuticals Ltd and BioMarin.

Informed Consent

Informed consent was obtained from the parents of the patients before retrieving the data for the study.

References

- Azevedo ACMM, Schwartz IV, Kalakun L, Brustolin S, Burin MG, Beheregaray APC, Leistner S, Giugliani C, Rosa M, Barrios P, Marinho D, Esteves P, Valadares E, Boy R, Horovitz D, Mabe P, de Silva LCA, de Souza ICN, Ribeiro M, Martins AM, Palhares D, Kim CA, Giugliani R (2004) Clinical and biochemical study of 28 patients with mucopolysaccharidosis type VI. *Clin Genet* 66:208–213
- Baum H, Dogson KS, Spencer B (1959) The assay of arylsulphatases A and B in human urine. *Clin Chim Acta* 4:453–455
- Brands MM, Hoogveen-Westerveld M, Kroos MA, Nobel W, Ruijter GJ, Özkan L, Plug I, Grinberg D, Vilageliu L, Halley DJ, van der Ploeg AT, Reuser AJ (2013) Mucopolysaccharidosis type VI phenotypes-genotypes and antibody response to galsulfase. *Orphanet J Rare Dis* 8:51
- Braunlin E, Rosenfeld H, Kampmann C, Johnson J, Beck M, Giugliani R, Guffon N, Ketteridge D, Sá Miranda CM, Scarpa M, Schwartz IV, Leão Teles E, Wraith JE, Barrios P, Dias da Silva E, Kurio G, Richardson M, Gildengorin G, Hopwood JJ, Imperiale M, Schatz A, Decker C, Harmatz P, MPS VI Study Group (2013) Enzyme replacement therapy for mucopolysaccharidosis VI: long-term cardiac effects of galsulfase (Naglazyme®) therapy. *J Inherit Metab Dis* 36(2):385–394
- Decker C, Yu ZF, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda MC, Wraith JE, Beck M, Arash L, Scarpa M, Ketteridge D, Hopwood JJ, Plecko B, Steiner R, Whitley CB, Kaplan P, Swiedler SJ, Conrad S, Harmatz P (2010) Enzyme replacement therapy for mucopolysaccharidosis VI: growth and pubertal development in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. *J Pediatr Rehabil Med* 3:89–100
- Fesslova V, Corti P, Sersale G, Rovelli A, Russo P, Mannarino S, Butera G, Parini R (2009) The natural course and the impact of therapies of cardiac involvement in the mucopolysaccharidoses. *Cardiol Young* 19:170–178
- Furujo M, Kubo T, Kosuga M, Okuyama T (2011) Enzyme replacement therapy attenuates disease progression in two Japanese siblings with mucopolysaccharidosis type VI. *Mol Genet Metab* 104:597–602
- Garrido E, Chabás A, Coll MJ, Blanco M, Domínguez C, Grinberg D, Vilageliu L, Cormand B (2007) Identification of the molecular defects in Spanish and Argentinian mucopolysaccharidosis VI (Maroteaux–Lamy syndrome) patients, including 9 novel mutations. *Mol Genet Metab* 92:122–130
- Giugliani R, Harmatz P, Wraith JE (2007) Management Guidelines for Mucopolysaccharidosis VI. *Pediatrics* 120:405–418
- Giugliani R, Lampe C, Guffon N, Ketteridge D, Leão-Teles E, Wraith JE, Jones SA, Piscia-Nichols C, Lin P, Quartel A, Harmatz P (2014) Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux–Lamy syndrome)—10-year follow-up of patients who previously participated in an MPS VI Survey Study. *Am J Med Genet A* 164(8):1953–1964
- Harmatz P, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda MC, Wraith JE, Beck M, Arash L, Scarpa M, Ketteridge D, Hopwood JJ, Plecko B, Steiner R, Whitley CB, Kaplan P, Yu ZF, Swiedler SJ, Decker C, MPS VI Study Group (2008) Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: final results of three clinical studies of recombinant human N-acetylgalactosamine 4-sulfatase. *Mol Genet Metab* 94(4):469–475
- Harmatz P, Yu ZF, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda MC, Wraith JE, Beck M, Arash L, Scarpa M, Ketteridge D, Hopwood JJ, Plecko B, Steiner R, Whitley CB, Kaplan P, Swiedler SJ, Hardy K, Berger KI, Decker C (2010) Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. *J Inherit Metab Dis* 33(1):51–60
- Hendriksz CJ, Giugliani R, Harmatz P, Lampe C, Martins AM, Pastores GM, Steiner RD, Leão Teles E, Valayannopoulos V; CSP Study Group (2013) Design, baseline characteristics, and early findings of the MPS VI (mucopolysaccharidosis VI) Clinical Surveillance Program (CSP). *J Inherit Metab Dis* 36(2):373–384
- Lael GN, de Paula AC, Leone C, Kim CA (2010) Echocardiographic study of paediatric patients with mucopolysaccharidosis. *Cardiol Young* 20:254–261
- Lampe C, Lampe C, Schwarz M, Müller-Forell W, Harmatz P, Mengel E (2013) Craniocervical decompression in patients with mucopolysaccharidosis VI: development of a scoring system to determine indication and outcome of surgery. *J Inherit Metab Dis* 36(6):1005–1013
- Litjens T, Baker EG, Beckmann KR, Morris CP, Hopwood JJ, Callen DF (1989) Chromosomal localization of ARSB, the gene for human N-acetylgalactosamine-4-sulphatase. *Hum Genet* 82:67–68
- Maroteaux P, Leveque B, Marie J, Lamy M (1963) A new dysostosis with urinary elimination of chondroitin sulfate B. *Presse Med* 71:1849–1852
- McGill JJ, Inwood AC, Coman DJ, Lipke ML, de Lore D, Swiedler SJ, Hopwood JJ (2010) Enzyme replacement therapy for mucopolysaccharidosis VI from 8 weeks of age—a sibling control study. *Clin Genet* 77:492–498
- Neufeld E, Muenzer J (2001) The mucopolysaccharidoses. In: Valle D, Beaudet A, Vogelstein B, Kinzler K, Antonarakis S, Ballabio A (eds) *Scriver's online metabolic and molecular bases of inherited disease*. McGraw-Hill Global Education Holdings, LLC, New York, pp 2465–2494
- Panin G, Naia S, Dall'Amico R, Chiandetti L, Zachello F, Catassi C, Felici L, Coppa GV (1986) Simple spectrophotometric quantifi-

- cation of urinary excretion of glycosaminoglycan sulfates. *Clin Chem* 32(11):2073–2076
- Pauchard N, Garin C, Jouve JL, Lascombes P, Journeau P (2014) Perioperative medullary complications in spinal and extra-spinal surgery in mucopolysaccharidosis: a case series of three patients. *JIMD Rep* 16:95–99
- Poorthuis B, Wevers R, Kleijer W, Groener JE, de Jong JG, van Weely S, Niezen-Koning KE, van Diggelen OP (1999) The frequency of lysosomal storage disease in the Netherlands. *Hum Genet* 105: 151–156
- Scarpa M, Barone R, Fiumara A, Astarita L, Parenti G, Rampazzo A, Sala S, Sorge G, Parini R (2009) Mucopolysaccharidosis VI: the Italian experience. *Eur J Pediatr* 168:1203–1206
- Thümler A, Miebach E, Lampe C, Pitz S, Kamin W, Kampmann C, Link B, Mengel E (2012) Clinical characteristics of adults with slowly progressing mucopolysaccharidosis VI: a case series. *J Inherit Metab Dis* 35:1071–1079
- Valayannopoulos V, Nicely H, Harmatz P, Turbeville S (2010) Mucopolysaccharidosis VI. *Orphanet J Rare Dis* 5:5