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Case report

Long-term evolution of mucopolysaccharidosis type I in twins treated with enzyme replacement therapy plus hematopoietic stem cells transplantation

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ABSTRACT

Mucopolysaccharidoses (MPSs) are a heterogeneous group of diseases that have in common the accumulation of glycosaminoglycans (mucopolysaccharides) within the lysosome. The diseases are caused by a deficiency of the enzyme α-L-iduronidase which is responsible for the degradation of glycosaminoglycans (GAGs or mucopolysaccharides). More than 100 mutations in the gene have been reported, resulting in marked clinical/response variability. MPSs usually present as multisystem and progressive clinical disorders which affect psychomotor and cardiovascular development, the cornea and the musculoskeletal system. Seven phenotypically distinct diseases have been described, and MPS type I (MPS-I) is divided into three clinical forms: severe (Hurler syndrome), intermediate (Hurler-Scheie syndrome) or mild (Scheie syndrome).

For the treatment of MPS-I, Enzyme Replacement Therapy (ERT) with α-L-iduronidase and Hematopoietic Stem Cells Transplantation (HSCT), separately or in combination, have produced clinical improvement, especially with regards cardiovascular symptoms and psychomotor development. This article presents the long-term (more than seven years) follow-up of monochorionic, diamniotic twins who were diagnosed with MPS-I at an early stage, and treated with ERT (from age 10 months) plus HSCT (from age 18 months). Overall, the treatment has facilitated stable development with an overall good response and better control of symptoms associated with MPS-I.

1. Introduction

The mucopolysaccharidoses (MPS) are a heterogenous group of different inherited lysosomal storage diseases (LSDs). In common, they are associated with the accumulation of glycosaminoglycans (GAGs), also called mucopolysaccharides, in the lysosome. The MPS are divided into seven subtypes (I, II, III, IV, VI, VII, and IX) according to which lysosomal enzyme is deficient. The net result is an accumulation of different GAGs, and increased urinary elimination of these GAGs, leading to a multisystem and progressive clinical condition that in severe cases causes the death of compromised individuals (Wraith, 2005). The clinical phenotype and the involvement of target organs vary in the different subtypes of MPS. For example, if the enzymatic capacity to degrade heparan sulfate is decreased the clinical phenotype will be more associated with mental impairment; whereas, if the enzymatic deficit relates to dermatan sulfate, keratan sulfate and chondroitin sulfate, mesenchymal disruptions are mainly observed (Wraith, 2005).

In severe forms of the disease, there can be substantial damage to the central nervous system (CNS), and clinical deterioration occurs in the first six months to two years of life. The most important clinical symptoms include coarse facial features, prominent eyebrows, corneal opacity, macroglossia, hepatosplenomegaly, stunting, multiple skeletal abnormalities, and dysostosis multiplex demonstrated by X-rays. Intermediate forms of the disease have less CNS involvement and are generally diagnosed between the ages of 3 and 8 years. On average, such patients usually die during the second decade of life. Mild forms of the disease are detected much later (10–20 years of age), and the patient's mental ability and physical size are generally normal, and life expectancy is not adversely affected (Muenzer, 2004; Muenzer et al., 2009; Vijay and Wraith, 2005; Pastores et al., 2007; White, 2011).

The treatment of LSDs has changed in the last 25 years. During the 1980s, hematopoietic stem cells transplantation (HSCT) offered the possibility of treatment for some forms of the disease; however, it was associated with high morbidity and mortality. During the 1990s, enzyme

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replacement therapy (ERT) was introduced as a new treatment option (Gutiérrez, 2006). Worldwide there are few reports regarding the long-term evolution of the MPS-I subtype in twins treated with HSCT and ERT.

In the current case report, the clinical evolution of monochorionic, diamniotic twins with MPS-I treated with HSCT and ERT since an early age, and followed for more than seven years is presented and discussed.

2. Clinical presentation

The informed consent of the parents of the twins was obtained for the publication of the clinical data and photographs contained in this report, as well as the absolute adherence to the safeguarding of their confidential data in accordance with national and international laws and agreements.

We describe male monochorionic, diamniotic twins born on January 20th 2009, both Mexican, racially mixed, with neither a consanguinity background between their parents, nor endogamy. The infants were the result of a first pregnancy which was delivered by C-section. During pregnancy, the mother had three threatened miscarriages on separate occasions, but sought no medical attention. From the sixth month of pregnancy the mother started prenatal care at the Instituto Nacional de Perinatologia in Mexico City. At birth, the first twin (twin-1) weighed 2.60 kg and was 40.5 cm in length and the following were recorded: Apgar 8/9, Silvermann-Anderson 2, and the Capurro-estimated gestational age was 36.3 weeks. He remained in the neonatal intensive care unit for seven days, where he presented a continuous positive airway pressure (CPAP). The echocardiogram analysis showed persistence of a ductus arteriosus. Twin-2 weighed 2.56 kg and was 42 cm long, and the following were recorded: Apgar: 8/9, Silvermann-Anderson: 2 and the Capurro-estimated gestational age were 36.3 weeks. He remained in the neonatal intensive care unit for 28 days as a result of respiratory distress (transient tachypnea of the newborn), pneumonia and gastroesophageal reflux disease (GERD); echocardiogram analysis showed mild-to- moderate tricuspid failure.

At five months of age the twins were reassessed at the Instituto Nacional de Pediatria in Mexico City. The following data were recorded for twin-1: weight 6.49 kg; length 45 cm without cephalic support; brachycephalic, hypertonic, coarse facial features (Figure 1), hypertrichosis of the forehead, a broad depressed nasal bridge, wide and bulbous nose base, marked philtrum, and mouth corners pointing downwards. During physical examination the following were noted: bilateral corneal opacity, "Mongolian" blue spots distributed on the thorax and abdomen, kyphoscoliosis, a palpable liver 2 cm below the rib cage border, and a right inguinal hernia apparently with hydrocele. The following data were recorded for twin-2: weight 7.68 kg; length 46 cm with cephalic support; "Mongolian" blue spots distributed on the thorax

Figure 2. Twin-2 (left and right): Extensive Mongolian spots on the trunk and knees.

and abdomen (Figures 1 and 2); similar clinical data to twin-1, except two inguinal hernias, a transverse fold in both hands, and bilateral clinodactyly of the fifth finger. Orthopedic assessment showed the presence of mild dysostosis. Metabolic screening of the two twins was normal, while enzymatic determination established an α-iduronidase deficiency (Table 1). On March 2011, at 6 months of age, a diagnosis of MPS-I was confirmed through the determination of alpha-l-iduronidase enzymatic activity, with report of enzymatic activity below the reference range. No glycosaminoglycans determination was done because the cellular and enzymatic tests confirmed the diagnosis. MRI was not indicated either because in our hospital is not commonly practiced in children under 10 years of age because of the use of contrast material. Besides, in this type of patients with MPS-I, MRI is contraindicated because of their bone dysplasia as well as their infiltration in the upper respiratory area. They do have high anesthetic risk, which probably could cause the need of intubating them and develop a respiratory disorder (Rodríguez-Herrera R de León-Bojorge B 2008). On May 2016, the molecular analysis was performed with the report of abnormal *IDUA* gene sequencing analysis with two mutations reported as heterozygous, one located in the exon 6/IVS 6 and another in the exon 8 of *IDUA* gene (Table 2). The c.767_793-15dup112 alteration is expected to be pathogenic, as it creates frameshift, and therefore an aberrant protein. The c.1186_1188delCTG alteration results in the in-frame deletion of a single amino acid (p.L396del) and its clinical significance is less clear. However, a missense change at the same codon (p.L396P) is reported in HGMD as a pathogenic change. In the context of the patient's low alpha-iduronidase activity, the presence of these two changes (if in *trans*) is most likely consistent with a diagnosis of Mucopolysaccharidosis type I.

The boys were referred to a Lysosomal Diseases Clinic for assessment and follow-up. ERT (laronidase; Aldurazyme®) was proposed, with the possibility of carrying out HSCT. When the twins were 10-months-old ERT with laronidase enzyme was started at a dose of 0.58 mg/kg every 8 days and they continue to receive this regimen.

The boys were assessed at the institute Bone Marrow Transplantation Unit to determine their suitability for HSCT. Histocompatibility studies

Figure 1. Left: Twin-1. Mild coarse face features are observed. Right: Twin-2: Coarse face features and extensive Mongolian spots on the trunk.

Table 1. Enzymatic determination in DBS of α-L-iduronidase at six months of age in twins with MPS-I.

	Value	Normal range
Twin-1		
α-L-iduronidase (nmol/ml)	0.01	0.04 to 0.4 nmol/spot*21 h
Twin-2		
α-L-iduronidase (nmol/ml)	0.01	0.04 to 0.4 nmol/spot*21 h

University Clinic Hamburg-Eppendorf, Clinic for Children and Adolescents and Institute of Clinical Chemistry, Metabolic Diseases Laboratory.

Table 2. Abnormal IDUA sequencing analysis in both twins.

Exon/Intron	Nucleotide change	Aminoacid change	Zygosity	Type	Database #
Exon6/IVS 6	c.767_793-15dup112		Heterozygous	Previously unreported; expected to be pathogenic	N/A
Exon 8	c.1186_1188delCTG	p.L396del	Heterozygous	Previously unreported; pathogenicity unknown	N/A

Greenwood Genetic Center. Molecular Diagnostic Laboratory.

were carried out and it was decided to use umbilical cord cells as a source of stem cells, since no donor siblings with 100% compatibility were identified. Prior to transplantation, both twins exhibited signs of mild psychomotor retardation during clinical evaluation, but this was not a contraindication to proceed with HSCT. The conditioning regime comprised busulfan 1 mg/kg four times a day for 4 days (16 mg/kg/total dose), cyclophosphamide 120 mg/kg (total dose over 2 days), and antithymocyte globulin 1.5 mg/kg/day for 3 days with one rest day (Table 3).

Infusion of umbilical cord cells was successfully performed on June 4th, 2010 when the twins were 18-months-old. The umbilical cord had

Table 3. Treatment received by twins with MPS-I as conditioning regimen prior to the bone marrow transplantation.

Drug	Dose	Days
Busulfan	1 mg/kg/dose, 4 doses	-10, -9, -8, -7
Cyclophosphamide	60 mg/kg/day	-6, -5
ATG	1.5 mg/kg/day	-4, -3, -2
Rest		-1
Infusion		0

MSP-I: Mucopolysaccharidosis type I. ATG: Anti-thymocyte globulin.

compatibility in 6/6 alleles (HLA-A, - B and -DR without HLA-C), and the cell inoculum was 6.2×10^8/Kg total nuclear cells for one twin and 4.8×10^8/Kg total nuclear cell for the other. Cyclosporine 3 mg/kg/day was prescribed as prophylaxis for graft *versus* host disease, and fluconazole, acyclovir and ciprofloxacin were administered to provide antimicrobial cover. Blood cultures were negative and viral load analyses were negative for Epstein-Barr virus and cytomegalovirus. During hospitalization, twin-1 had fever and a broad-spectrum antibacterial (meropenem) was started. Twenty-four days after the HSCT, recovery of neutrophils was observed, confirming an adequate myeloid graft.

When the graft was completed and during follow-up at 3, 6, 9 and 12 months, 100% chimerism of the donor's cells was demonstrated (Table 4). At five years follow-up, the chimerism of twins dropped due to the type of source "umbilical cord blood". However, this did not affect the functionality of the chimerism for the type of disease in the twins. For this reason, they did not need a new intervention such as donor lymphocyte infusion (DLI). At 12 months, the immunological profile with CD56, CD4, CD8, as well as the relation CD4/CD8, CD19 and the immunoglobulins profile demonstrated complete reconstitution, which made it possible to restart the vaccination scheme. Neurodevelopmental

assessments at three years of age showed the following: both twins were able to repeat all words, recognize all their body parts, draw circles, walk, run, ascend and descend stairs, and were in the process of toilet training. Using the WISC-R test, we evaluated the IQ (intelligence quotient) and the EI (executive intelligence) in both twins at the age of 12. Executive intelligence measures the executive brain functions, this means, the ability to take decisions, the skills to change and curb impulses, and reflect on what we feel and what we think. The verbal coefficient in the twin 1 was 59% and the executive coefficient was 65%, with an overall IQ of 59%, this translates into a mild mental deficiency. In the twin 2 his verbal coefficient was 45% and the executive coefficient was 45%, with an overall IQ of 40% which translates into a moderate mental deficiency. With regards symptoms they presented with: corneal opacity, mild macroglossia, hypoplasia of central incisors and cavities, grade II hypertrophic oropharynx, short neck, dorsal hump, and extensive Mongolian spots on the trunk and limbs.

Twins growth has been followed for more than 10 years. At the beginning (by the age of four years), the twins development in terms of body stature (body height percentile) exceeded the maximum described in the literature for patients with MPS-I. (Figure 3) (Róźdżyńska-Świątkowska et al., 2014) and, at this stage, they had achieved bladder and anal control, they ate by themselves and dressed partially by themselves. At five years of age, they started pre-school education (kindergarten) and maintained sphincter control. Twin-2 had corneal opacity of the right eye, with a 3 mm inactive ulcer and xerosis. At six years of age, twin 2 still had macroglossia and tonsil hypertrophy, cleft hands, as well as corneal opacity and corneal leucoma. At seven years of age, the twins attend the second year of kindergarten. They dress by themselves, pronounce 50 words, interact adequately with their family, play video games, and have a language deficit of about 25%. Enzymatic analysis demonstrated low levels of α-iduronidase. Last GAG determination was done on August 2020, at eleven years and eight months of age, with negative results for both twins (Table 5). It is worth noting that in Mexico GAGs (HS, DS, KS) are not reported separately, reports only mention if GAG in urine is positive or negative. GAGs are not correlated with clinical improvement but they are useful for initial diagnosis (Erickson RP et al., 1975; Saville JT et al., 2018; Fujitsuka H et al., 2019; Khan SA et al., 2018; Shimada T et al., 2015).

At the last appointment, with ERT administered, both twins had cataracts, but this did not materially affect their visual skills, and they had normal visual and somatosensory potential responses. Regarding auditory potential responses, both twins presented bilateral high-tone hypoacusis media.

Regarding cardiac and pulmonary function the echocardiogram and ventilatory tests are normal for both twins. With respect to joint stiffness,
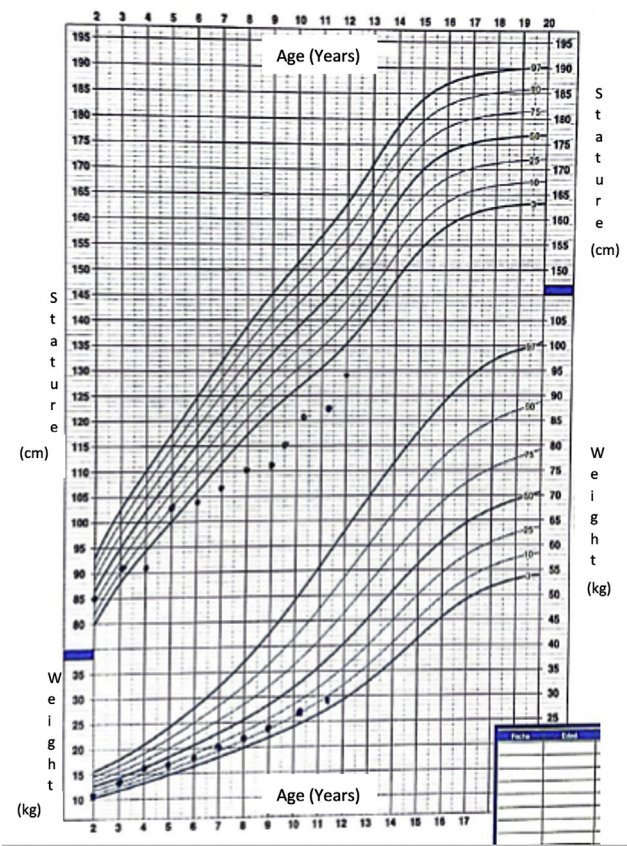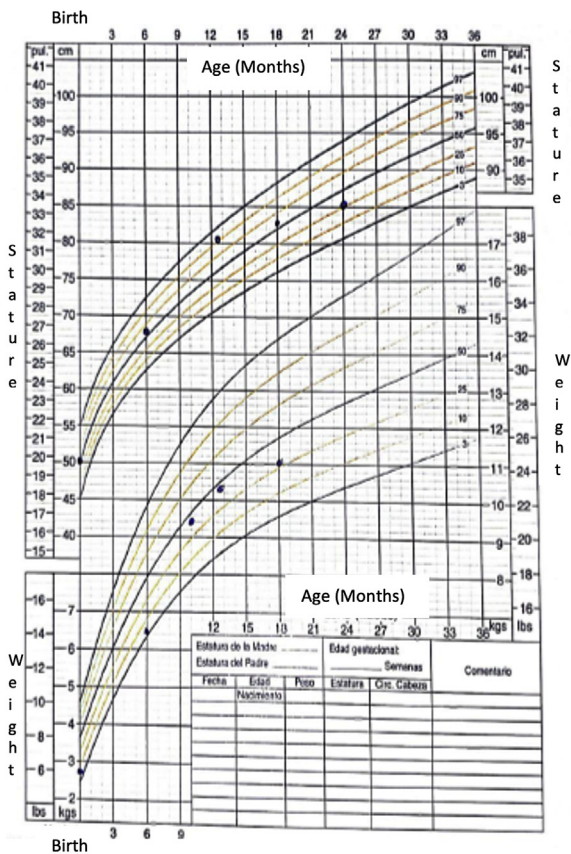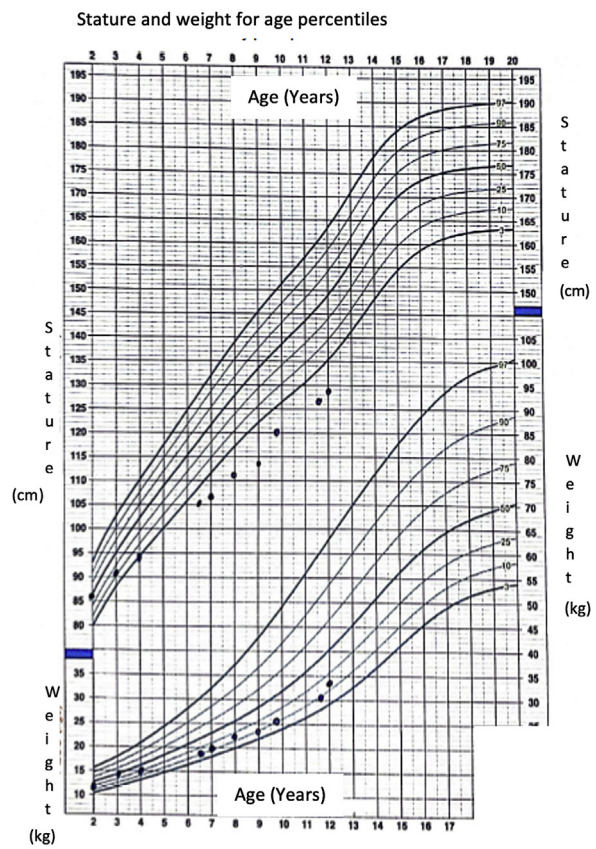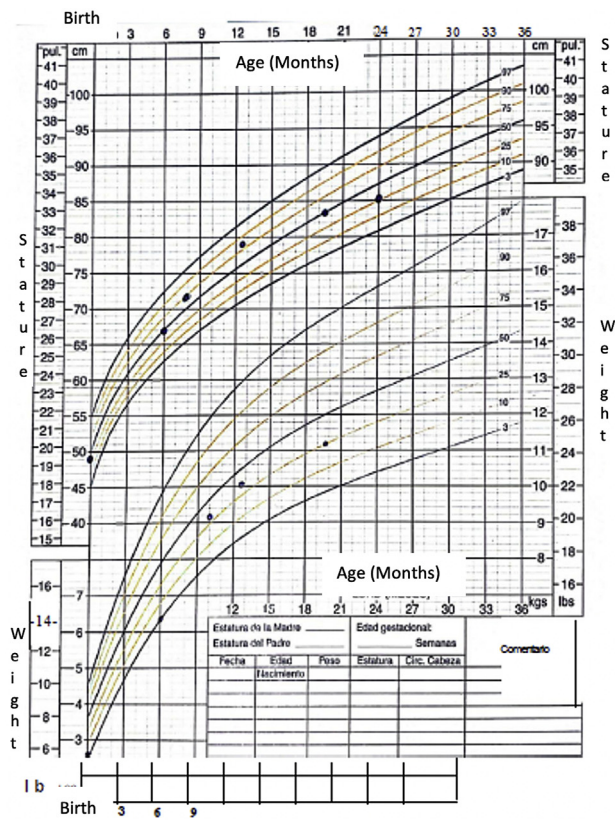
Table 4. Chimerism and immunological reconstitution post-HSCT in twins with MPS-I during the follow-up.

Time after TMO	Chimerism		Immunological reconstitution	
	Twin-1	Twin-2	Twin-1	Twin-2
30 days	100%	100%	NK	NK
90 days	100%	100%	NK/CD8	NK/CD8
180 days	100%	100%	NK/CD8	NK/CD8
360 days	100%	100%	NK/CD8/CD4/	NK/CD8/CD4/
5 years	80%	70%	Complete	Complete

MSP-I: Mucopolysaccharidosis type I. HSCT: Hematopoietic stem cells transplantation.

Figure 3. CDC Growth Charts: United States. Body Height Growth Twin-1 and Twin 2. Mean value of body height in patients with MPS-I from Różdżyńska-Świątkowska et al., (2014).

they have mild joint stiffness in hands since they cannot close them completely, but they do up to an 80%. The skeletal age taken in 2020 shows discrete dysrhythmia in both twins. They assist to the hospital twice a month for follow up, and perform physiotherapeutic exercises at home.

3. Discussion

Six patients with MPS-I have been referred for HSCT in our institution, but only the twins in this report have received HSCT concomitant with ERT. We have described long-term evolution of the disease after receiving ERT and HSCT, according to age, clinical indications at baseline, and to HLA compatibility. Both twins achieved a stable response following ERT and HSCT. The tricuspid failure observed in twin-2 resolved and a corneal ulcer is currently inactive. These findings match previous reports of patients with MPS-I who underwent HSCT (Malone et al., 1988; Scriver, 1995; Braunlin et al., 1992; du Cret et al., 1994). As the last assessment enzyme activity remained below normal levels, and ERT treatment has been maintained as previously described (D'Aco et al., 2012). Repeated ERT treatment facilitates disease stabilization and will be continued indefinitely until normal enzyme levels are achieved (González et al., 2010).

Overall, patients with MPS have coarse facial findings, corneal opacity in some cases, blockage of the upper airway, abdominal enlargement (notably the liver), dysostosis multiplex and occasionally, reduced psychomotor performance (Muenzer et al., 2009). MPSs are recessive autosomal disorders, with the exception of MPS-II which is linked to chromosome X (Escolar et al., 2005; Cox-Brinkman et al., 2006). The overall prevalence of MPS is 3.5–4.5 per 100,000 inhabitants and the most common subtype is MPS-III, followed by subtypes I and II (Keulemans et al., 2002; Martin et al., 2008). According to the clinical type, MPS-I is divided in three clinical forms: severe or Hurler syndrome, intermediate or Hurler-Scheie syndrome and mild or Scheie syndrome. At the Instituto Nacional de Pediatria in Mexico, between January 1998 and December 2011, hereditary metabolic diseases accounted 4.1% of cases requiring bone marrow transplantation (BMT).

MPS-I in its severe form (Hurler syndrome) is a progressive disease involving multiple organs and tissues, and causes premature death in children aged 10 years and younger. Mongolian spots have now been shown that coexist with inborn errors of metabolism, most commonly gangliosidosis type 1 (GM 1) and MPS-I, followed by MPS-II, mucolipidosis, Niemann-Pick disease and mannosidosis (Gupta and Mohan Thappa 2013). During lactation these children often seem normal, but from 6 to 24 months of age they develop signs and symptoms such as hepatosplenomegaly, skeletal deformation, coarse face features, corneal opacity, macroglossia, prominent forehead, articular stiffness and small size, and in some cases, cardiomyopathy. Most children with Hurler syndrome have very limited linguistic capabilities due to developmental defects including chronic hypoacusis and tongue enlargement. Hypoacusis is caused by a combination of nerve conduction disorders and neurosensory disturbances. Many patients develop recurrent infections of the upper airways and ears, with associated loud breathing, and abundant and persistent nasal discharge. A progressive ventricular dilatation may also occur, along with intracranial hypertension caused by communicating hydrocephalus. Corneal opacity, glaucoma, and retinal degeneration are usual. In the later stages of the disease, obstructive airways disease affects many patients and there is an increased possibility of a tracheostomy being required. Common causes of death in children reaching this stage of the disease include: airways obstruction, respiratory infections and heart disease complications (Escolar et al., 2005; Martin et al., 2008; Cox-Brinkman et al., 2006; Johansson et al., 2007).

MPS-I is caused by lysosomal enzyme α-L-iduronidase deficiency, whose gene is located on the short arm of chromosome 4 (4p 16.3). It is approximately 19 kb in length with 14 exons, and more than 100 mutations have been reported, including nonsense, missense, splicing, deletion and insertion mutations (Scott et al., 1995). Of these mutations, two main alleles are outstanding: W402X and Q70X, and a secondary one: P533R. These represent more than half of the affected alleles in MPS-I in the white population, and many other patients are heterozygous for less common alleles. None of these alleles are able to produce functional enzyme, and in the composite homozygote they give rise to Hurler syndrome. It has been suggested that mutation analysis might be beneficial to establish a genotype-phenotype correlation in Hurler syndrome, but for most mutations the clinical phenotype cannot be predicted. Enzymatic deficiency in MPS-I results in a deficit in the degradation of the GAGs heparan sulfate and dermatan sulfate which contribute to the production of connective tissue and extracellular matrix. GAG accumulation causes damage to various tissues and organs as well as altered cellular function. The gold standard for diagnosing MPS is determination of α-L-iduronidase levels in fibroblasts, serum leucocytes or in blood, as was performed in the two reported cases.

Table 5. Enzymatic determination in DBS of α-L-iduronidase in twins with MPS-I at 7 and 11 years of age.

	Value	Normal range
7 years		
Twin-1		
α-L-iduronidase (nmol/ml)	1.01	3.18 to 22.8
Glycosaminoglycans in urine (mg/mmol)*	5.44	0.00 to 10.30
IgG antibodies against laronidase	Negative	
Dermatan sulfate (DS) and heparan sulfate (HS)	Not measured	
Twin-2		
α-L-iduronidase (nmol/ml)	1.09	3.18 to 22.8
Glycosaminoglycans in urine (mg/mmol)*	6.81	0.00 to 10.30
IgG antibodies against laronidase	Negative	
Dermatan sulfate (DS) and heparan sulfate (HS)	Not measured	
11 years		
Twin 1		
Glycosaminoglycans in urine (mg/mmol)*	4.00	0.00 to 10.30
IgG antibodies against laronidase	Negative	
Twin 2		
Glycosaminoglycans in urine (mg/mmol)*	4.00	0.00 to 10.30
IgG antibodies against laronidase	Negative	

* GAG levels were referenced to creatinine levels.

Nowadays ERT is available in the form of the substitute enzyme laronidase (Aldurazyme®) which is synthesized using recombinant DNA technology and administered every 1–2 weeks. Its absorption into the cell is via a mannose-6-phosphate receptor (Wraith, 2001). In patients with MPS-I, this treatment has been shown to ameliorate motion restrictions (Kakkis et al., 2001), increase the ability to take long walks (Wraith et al., 2007) and improve disability and activities of daily living (Clarke et al., 2009); as well as reducing abdominal enlargement, and improving obstructive sleep apnea and forced vital capacity (Clarke et al., 2009). It has been estimated that small increases in intracellular enzyme activity can have an impact on disease pathology and be beneficial for patients (Parenti, 2009). ERT for MPS-I has been used in the United States and Europe since 2003, with a usage registry in more than 600 patients according to the international registry of MPS (The MPS I Registry). ERT improves the efficacy of HSCT when they are combined, mainly ameliorating lung and orthopedic deterioration (Kakkis et al., 2001; Valayannopoulos et al., 2010; Wynn et al., 2009; Stoop et al., 2013; Aldenhoven et al., 2008; Gassas et al., 2011).

ERT does not cross the blood-brain barrier (because of its large molecular size), or reverse skeletal changes, heart anomalies or corneal opacity (Sifuentes et al., 2007), which are probably induced by inflammation and fibrosis secondary to the continuous storage of GAGs and increased cytokine activity (Laraway et al., 2013; Wraith et al., 2004; Gabrielli et al., 2010). It has been observed that a high proportion of patients (12–50%) develop IgG antibodies against ERT proteins without diminishing its efficacy, this tends to decrease with repeated infusions (immunotolerance) (Kakavanos et al., 2003). ERT is recommended for children with severe MPS-I and for patients that have not previously received HSCT, either for health reasons, age, or even because of a lack of funding. Treatment onset time with ERT and BMT is an important factor for achieving a good clinical outcome [D'Aco et al. (2012); Gabrielli et al. (2010); Peters et al. (1998).

Significant residual disease burden may persist after HSCT including non-progressive mental retardation, orthopedic manifestations, and damage to various organs such as mitral and aortic value deformities, decreased visual acuity and chronic ear infections (Aldenhoven et al., 2008). Consequently, ERT treatment has been performed in an attempt to counteract the somatic disease manifestations experienced by most patients after successful HSCT, in some cases several years beyond the peri-transplant period.

HSCT embraces all types of BMT, peripheral blood or umbilical cord, and it is also an efficient treatment for severe MPS-I, especially if it is applied during the first stages of the disease and prior to the onset of deterioration (Whitley et al., 1993; Vellodi et al., 1997). Correction of enzymatic defects in fibroblast cultures of patients with Hurler and Hunter syndromes was demonstrated in the early 1980s and the use of HSCT in patients with Hurler syndrome was suggested (Hobbs et al., 1981). HSCT produces clinical improvement in MPS-I disease and increases the long-term survival of patients; it is recommended in children aged less than 24 months without significant neurological disease at the time of transplantation. HSCT improves hepatosplenomegaly, joint stiffness, face appearance, obstructive sleep apnea, and cardiomyopathy, as well as communicating hydrocephalus and hypoacusis. According to the European Society for Blood and Marrow Transplantation (EBMT) guidelines, all patients with MPS-type metabolism errors, especially with Hurler syndrome, are candidates for HSCT (Boelens et al., 2007). Intravenous laronidase improves somatic load; however it is unknown how this load enhances the therapy after bone marrow transplantation (Polgreen et al., 2019; Tolar et al., 2007). For both procedures, the European Consensus recommends evaluating the patients adequately before two and a half years of age for Hurler form. Regarding the safety and efficacy of this combination, it is well tolerated and with a good safety margin when using it (Grewal et al., 2005).

Our patients have a good immunological reconstitution with mixed donor chimerism and 30% of normal enzyme activity and this has helped avoid disease progression. Wang et al. (2016) reported 34 cases with MPS I, of which 31 (91.2%) had a full donor chimerism and of these only 80.6% had normal enzyme level and 3.2% had low enzyme levels; for those cases with mixed chimerism, the percentage of patients with normal enzyme levels was reported to be 50%.

The only published case report describes a male patient who underwent a successful HSCT procedure at 2.5 years of age and who presented with progressive respiratory failure at the age of 14 years, despite good donor chimerism and 50% of normal IDUA activity, matching that of his donor sibling. The patient was treated with weekly laronidase accompanied by non-invasive ventilation for 24 months. Within the therapy period his respiratory function significantly improved, as did his quality of life (Valayannopoulos et al., 2010).

In one case report, allogenic HSCT administered to a 1-year-old child resulted in near to normal cognitive development in the years following treatment (Hobbs et al., 1981). Furthermore, in patients with the milder Scheie form of MPS-I, HSCT helped to preserve cognitive development (Malone et al., 1988) and, in some patients, corneal opacity was stabilized or it even recovered slowly (Peters et al., 1998). It has also been reported that HSCT may improve hearing capacity, joint mobility, respiratory and heart function, and communicating hydrocephalus (if it existed) with increased intellectual capacity and without modification of the CNS disruption (Scriver, 1995). Improvement of cardiac abnormalities have been observed one year after HSCT onset, with longer term benefit reported for myocardial function and arterial permeability up to 14 years after transplantation (Braunlin et al., 1992; du Cret et al., 1994). However, no amelioration of valvular malformations was observed (Peters et al., 1998).

In order to perform HSCT in MPS-I, is necessary to identify the donors, to categorize them and to match the histocompatibility antigens, as well as to assess enzyme levels. To improve the success of HSCT, the transplantation must be sufficiently immunosuppressant and myeloablative (Peters et al., 1998). It should be noted that if complete grafting cannot be achieved, morbidity and mortality will increase; reaching 10–20% with compatible-HLA donors and exceeding 40% when they are not compatible (Scriver, 1995). These rates are lower if T-lymphocyte reducing agents are used (Peters et al., 1998). Since the first HSCT for MPS-I in its severe form was carried out in 1981, up to a 90% improvement of survival has been achieved (Boelens et al., 2010). The use of busulfan and early diagnosis have been the most important factors associated with this successful improvement in treatment (Boelens et al., 2009, 2010., Boelens et al., 2009; de Ru et al., 2011). Other factors linked to the improvement in clinical outcome include: the child's age at the time of transplantation, clinical signs and symptoms, type of donor, and achieving a stable graft without developing graft *versus* host disease (de Ru et al., 2011). Very little is known about the effect of HSCT in the intermediate forms of MPS-I.

Initial studies reported a high incidence of transplantation failure (15–75%), as well as elevated mortality related to the lack of availability of unrelated donors and rapid disease progression (Escolar et al., 2005; Peters et al., 2003; Boelens, 2006). Nonetheless, identifying graft rejection risk factors as well as improving HSCT techniques, including rapid availability of umbilical cords, has resulted in less graft rejection and less mortality after transplantation. It should be noted that if there is irreversible damage to the CNS, starting HSCT is contraindicated (Boelens et al., 2007). Studies have shown that patients in advanced stages of the disease have a worse progress after transplantation. It has also been demonstrated that patients presenting with lung complications such as alveolar hemorrhage, had worse outcomes compared to patients who received transplantation at the same age, but without pulmonary complications (Orchard et al., 2010).

Before 2000, reported mortality rates associated with HSCT for MPS were as high as 27%. The major causes of death in patients with MPS-I within the first-year post-transplantation include viral infection, pulmonary hemorrhage, and GVHD. Factors contributing to a high mortality rate include advanced disease stage at the time of HSCT and use of a mismatched donor (Taylor et al., 2019).

Rodgers et al. reported a persistent steady mortality rate in adolescents and young adults at >1 year post-transplantation, and higher incidences of infection, and pulmonary and cardiac complications compared with healthy counterparts even at 10-years post-transplantation (Rodgers et al., 2017). Although patients with untreated MPS-I usually die from cardiac and pulmonary causes, those who undergo HSCT can also die from pulmonary complications and infection during the first-year post-transplantation.

In 2012, 891 cases of MPS-I registered in the MPS International Registry database were reviewed (D'Aco et al., 2012). Age, onset of symptoms, time until diagnosis, and initiation of treatment with ERT, HSCT, both, or neither for the three phenotypes (MPS type I severe/-Hurler syndrome; MPS type I moderate/Hurler-Scheie syndrome; and MPS type I mild/Scheie syndrome) were assessed. It was found that the interval between diagnosis and treatment with ERT had decreased between 2006 and 2009 following the introduction of laronidase in 2003 and was 0.2 years for severe MPS, 0.5 years for moderate MPS and 1.4 years for mild MPS. According to these findings, the treatment tends to be more limited in the last two (attenuated) forms of the disease. The age at diagnosis had not decreased for any MPS phenotype and the interval between symptom onset and treatment was substantial for intermediate (2.42 years) and mild (6.71 years) forms of the disease. Moreover, there is no agreement related to the optimal timing for the ERT and HSCT, although the advantages of early treatment have been advocated. ERT is considered to be a lifelong therapy and is administered as a weekly intravenous infusion (D'Aco et al., 2012). Unfortunately, not all patients can receive ERT or HSCT, either because of their high cost or due to the lack of specialized care centers. Despite all of this, umbilical cord cells are nowadays the best option as a source of cells for HSCT in this disease.

In the current report, the twins had the advantage of receiving both ERT and HSCT using international recommendations, and they have a good quality life (adequate psychomotor development with only a mild retardation on language skills). Other cases of reporting a positive impact of ERT administered several years after successful HSCT have been reported at specialist meetings and MPS I Advisory Boards, where some of the authors have participated in the recent years.

At that moment, the twins have a good quality of life. In August 2020 a neurological assessment was carried out. We found that both have a normal development according to their chronological age, having only a deficit of 15% in the hability to speak. Currently they are in the elementary school, just one year below than they should. They lost one school year because of all the medical treatments they underwent.

Declarations

Author contribution statement

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Data will be made available on request.

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Additional information

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