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 (MPSs) 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 multi-system 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
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 Perinatología 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 28 days as a result of respiratory distress syndrome (transient tachypnea of the newborn), pneumonia and gastroesophageal reflux disease (GERD); echocardiogram analysis showed mild-to-moderate tricuspid failure. At the 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 Perinatología 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 28 days as a result of respiratory distress syndrome (transient tachypnea of the newborn), pneumonia and gastroesophageal reflux disease (GERD); echocardiogram analysis showed mild-to-moderate tricuspid failure.

Five months of age the twins were reassessed at the Instituto Nacional de Pediatría 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 thorax and abdomen, kyphoscoliosis, a palpable liver 2 cm below the rib cage border, and a right inguinal hernia apparently with hydrocele. The thorax and abdomen, kyphoscoliosis, a palpable liver 2 cm below the rib cage border, and a right inguinal hernia apparently with hydrocele.

The boys were referred to a Lysosomal Diseases Clinic for assessment and treatment. 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 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.

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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 compatibility in 6/6 alleles (HLA-A, -B and -DR without HLA-C), and the cell inoculum was 6.2 × 10⁸/Kg total nuclear cells for one twin and 4.8 × 10⁸/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 prescribed as prophylaxis for graft rejection. Twin-1 had fever and broad-spectrum antibacterial (meropenem) was prescribed as prophylaxis for graft rejection. Twin-1 had fever and broad-spectrum antibacterial (meropenem) was prescribed as prophylaxis for graft rejection.

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 Mongoloid spots on the trunk and limbs.

Twin 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) (Różdzyńska-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 tonsill 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 bilaterial high-tone hypoaucousis media.

Regarding cardiac and pulmonary function the echocardiogram and ventilatory tests are normal for both twins. With respect to joint stiffness,
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 Roździńska-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 (Keulmans 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

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 to 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 ventilricular 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; Johannson 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 1 Registry). ERT improves the efficacy of HSCT when they are combined, mainly ameliorating lung and orthopedic deterioration (Rakakis 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 who 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 valve 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 hypoausicus. 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, allogeneic 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 (Scrivier, 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 (Scrivier, 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).
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References

Aldenhoven, M., Boeijens, J.J., de Koning, T.J. 2008. The clinical outcome of Hurler syndrome after stem cell transplantation. Biol. Blood Marrow Transplant. 14, 485–498.

Boeijens, J.J. 2006. Trends in hematopoietic cell transplantation for inborn errors of metabolism. J. Inherit. Metab. Dis. 29, 415–420.

Boeijens, J.J., Wynn, R.F., O’Meara, A., Veyes, P., Bertrand, Y., Souillet, G., Wraith, J.E., Fischer, A., Cavazzana-Calvo, M., Sykora, K.W., et al., 2007. Outcomes of hematopoietic stem cell transplantation for Hurler’s syndrome in Europe: a risk factor analysis for graft failure. Bone Marrow Transplant. 40, 225–233.

Boeijens, J.J., Rocha, V., Aldenhoven, M., Wynn, R., O’Meara, A., Michel, G., Jonescu, I., Parikh, S., Prasad, V.K., Szabolcs, P., et al. Eurocord. Inborn error Working Party of Ebtnt and Duke University, 2009. Risk factor analysis of outcomes after unrelated cord blood transplantation in patients with Hurler syndrome. Biol. Blood Marrow Transplant. 15, 618–625.

Boeijens, J.J., Prasad, V.K., Tolar, J., Wynn, R.F., Peters, C. 2010. Current international perspectives on hematopoietic stem cell transplantation for inherited metabolic disorders. Pediatr. Clin. North Am. 57, 121–145.

Braunlin, E.A., Hunter, D.W., Krivit, W., Burke, B.A., Hesselin, P.S., Porter, P.T., Whitley, C.R. 1992. Evaluation of coronary artery disease in the Hurler syndrome by angiography. Am. J. Cardiol. 69, 1487–1489.

Clarke, L.A., Wraith, J.E., Beck, M., Kolodyn, E.H., Pastores, G.M., Muenzer, J., Rapport, D.M., Berger, K.L., Sidman, M., Kakisis, E.D., Cox, G.F., 2009. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics 123, 229–240.

Cox-Brinkman, J., Boeijens, J.J., Wraith, J.E., O’Meara, A., Veyes, P., Wijburg, F.A., Wulfnaart, N., Wynn, R.F., 2006. Haematoepoietic stem cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. Bone Marrow Transplant. 38, 17–21.

D’Aco, K., Underhill, L., Rangachari, L., Arn, P., Cox, G.F., Giugliani, R., Okuyama, T., Wijburg, F., Kaplan, P., 2012. Diagnosis and treatment trends in mucopolysaccharidoses I: findings from the MPS I Registry. Eur. J. Pediatr. 171, 911–915.

de Ru, M.H., Boeijens, J.J., Daas, A.M., Jones, S.A., van der Lee, J.H., Mahalouin, N., Ablel, O., Offringa, M., O’Meara, A., Parini, R., et al., 2011. Enzyme replacement therapy and/or hematopoietic stem cell transplantation at diagnosis in patients with mucopolysaccharidosis type I: results of a European consensus process. Orphanet J. Rare Dis. 6, 55.

du Cret, R.P., Weinberg, E.J., Jackson, C.A., Braunlin, E.A., Boudreau, R.J., Kuni, C.C., Carpenter, B.M., Hunter, D.W., Krivit, W., Bodeau, G., 1994. Resting Tl-201 scintigraphy in the evaluation of coronary artery disease in children with Hurler syndrome. Clin. Nucl. Med. 19, 975–978.

Erickson, R.P., et al., 1975. Lack of relationship bet the authorsen blood and urine levels of glycosaminoglycans and lysosomal enzymes. Biochem. Med. 12, 331–339.

Escolar, M.L., Poe, M.D., Provenzale, J.M., Richards, K.C., Allison, J., Wood, S., Wenger, D.A., Pietryga, D., Wall, D., Champagne, M., et al., 2005. Transplantation of bone marrow transplantation. Lancet 2, 709–718.

Fujimura, H., et al., 2019. Biomarkers in patients with mucopolysaccharidosis type II and IV. Mol. Genet. Metab. Rep. 19, 100455.

Gabrielli, O., Clarke, L.A., Bruni, S., Coppa, G.V., 2010. Enzyme replacement therapy in a 5-month-old boy with attenuated preosymptomatic MPS I: 5-year follow-up. Pediatrics 125, e183–187.

Gassas, A., Raiman, J., White, L., Scheckter, T., Clarke, J., Doyle, J., 2011. Long-term adaptive functioning outcomes of children with inherited metabolic and genetic diseases treated with hematopoietic stem cell transplantation in a single large pediatric center: parents’ perspective. J. Pediatr. Hematol. Oncol. 33, 216–220.

Gonzalez, A., Meneses, A., Ramirez, B., Rodriguez, J., 2010. Protocolo de actuacion en las mucopolisacaridosis. Protoc. Diagn. Ter Pediatr. 1, 24–36.

Greweal, S.S., Wynn, R., Abdenur, J.E., et al., 2005. Safety an ef

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