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Hematopoietic stem cell transplantation in mucopolysaccharidosis type IIIA: A case description and comparison with a genotype-matched control group

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ABSTRACT

Background: Mucopolysaccharidosis type IIIA (MPS IIIA, Sanfilippo A syndrome) is a chronic progressive neurodegenerative storage disorder caused by a deficiency of lysosomal sulfamidase. The clinical hallmarks are sleep disturbances, behavioral abnormalities and loss of cognitive, speech and motor abilities. Affected children show developmental slowing from the second year of life, dementia occurs by the age of 5 years followed by death in the second decade of life. Only a few studies concerning HSCT in MPS IIIA have been published and do not document a clear benefit of treatment.

Methods: The present study summarizes the clinical outcome of a girl with MPS IIIA who received HSCT at the age of 2.5 years. Her clinical course was compared with the natural history of six untreated MPS IIIA patients carrying the same mutations (p.R74C and p. R245H) in the *SGSH*-gene.

Results: Eight years after successful HSCT, the patient showed a global developmental delay. However, cognitive abilities continued to develop, albeit very slowly. There was no sign of regression. She could talk in short sentences, had good motor abilities and performed basic daily living activities by herself. She did not present with sleeping problems, but behavioral abnormalities were profound. In contrast, the six untreated patients with identical mutations in the *SGSH*-gene showed the typical progressive course of disease with early and continuous loss of abilities.

Conclusions: The present data suggest a beneficial effect of HSCT performed at an early stage of MPS IIIA on cognitive skills, motor function and quality of life.

1. Introduction

Mucopolysaccharidosis type IIIA (MPS IIIA, Sanfilippo A syndrome, OMIM #252900) is a neurodegenerative glycosaminoglycan storage disorder caused by a deficiency of lysosomal sulfamidase (EC 3.10.1.1). The incidence has been estimated as approximately 1.1 cases in 100,000 newborns in Germany [1].

The disease is primarily characterized by behavioral and sleep disturbances as well as loss of cognitive, speech and motor abilities. Affected children with the classical severe form of the disease show a developmental delay, beginning in the second year of life and commonly reach a maximum developmental age of approximately 20–30 months at a chronological age of 42–48 months [2]. Dementia usually occurs by 5 years of age followed by death in the second decade of life. Several studies on the natural history of MPS IIIA have been published [2–8].

More than 100 mutations in the *SGSH*-gene (NCBI Gene ID 6448) have been reported [2,4,9]. Most of them are associated with the classical severe form of the disease. The mutation p.R245H is the most common mutation in MPS IIIA patients in Germany and the Netherlands, whereas p.R74C is the second common mutation in Germany and most frequent in Poland [10]. Patients carrying these mutations present

Abbreviations: AEq, age-equivalent score; ATG, antithymocyte globulin; Avg., Average; DQ, developmental quotient; FPSS, four point scoring system; GAG, Glykosaminoglycans; HSCT, hematopoietic stem cell transplantation; ICLD, International Center for Lysosomal Disorders; MPS IH, mucopolysaccharidosis type I (Hurler syndrome); MPS IIIA, mucopolysaccharidosis type IIIA; MPS IIIB, mucopolysaccharidosis type IIIB; SGSH, N-sulfoglucosamine sulfohydrolase; TDS, total disability score; UCBT, umbilical cord blood-derived hematopoietic stem cell transplantation; VABS-II, Vineland Adaptive Behavior Scales; y, years

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with a classical severe phenotype [9–12].

Located at the c-terminus, the mutation p.R245H induces early degradation of the protein and therefore a significant decrease in sulfamidase protein levels. The substitution of the arginine residue by cysteine at position 74 of the amino acid sequence in the mutation p.R74C affects the active site of the enzyme also leading to a severe phenotype [10,13].

To date, no approved treatment is available for MPS IIIA. A clinical trial on intrathecal enzyme replacement therapy (NCT02060526) was stopped in 2016 due to a lack of efficacy. An intracerebral gene therapy study in four MPS IIIA patients showed amelioration of cognitive function only in the youngest one [14]. Other clinical trials testing a new intravenous enzyme replacement therapy (NCT03423186), intravenous gene therapy (NCT02716246), as well as intracerebral (NCT03612869) and intracerebroventricular gene therapy (EudraCT 2015-000359-26) are ongoing. Furthermore, a study using hematopoietic stem cells transduced *ex vivo* with lentiviral vector encoding for *SGSH* is under investigation (NCT04201405).

Hematopoietic stem cell transplantation (HSCT) has been performed to treat patients with various lysosomal diseases [15,16]. In MPS IH (Hurler syndrome) patients younger than 2.5 years of age, HSCT is the treatment of choice and halts progressive neurodegeneration due to metabolic correction [17].

Few studies on the clinical outcome of MPS III patients treated with HSCT have been published indicating no clear benefit on neuropsychological function. Moreover, some authors reported a deterioration of cognitive function despite successful HSCT [15,18–20]. Others observed stabilization or even improvement of the course of the disease compared to untreated siblings [21–24]. However, data on HSCT in children with MPS IIIA are still scarce.

The aims of the present study were to summarize and to compare the clinical outcome of an 11-year-old girl with MPS IIIA, who received HSCT at the age of 2.5 years, with the natural history of six untreated MPS IIIA patients carrying the same mutations (p.R74C and p.R245H) in the *SGSH*-gene.

2. Methods

2.1. Study population

This case-control study was conducted at the International Center for Lysosomal Disorders (ICLD) of the University Medical Center Hamburg-Eppendorf, Germany. All patients included in the study were compound heterozygous for the mutations p.R74C and p.R245H in the *SGSH*-gene. Hence, all study patients had MPS IIIA. The 11-year old girl, who received HSCT at the age of 2.5 years, was defined as patient A, the six untreated patients carrying the same mutations in the *SGSH*-gene as patient A were defined as cohort B (patients B1-B6).

For identifying patients of cohort B, genotype reports of all MPS IIIA patients from the ICLD were screened. A retrospective chart analysis of data acquired during routine visits was conducted in all patients.

2.2. Hematopoietic stem cell transplantation (HSCT)

HSCT of patient A was performed following comprehensive informed consent at the transplant unit of the children's hospital, Hannover Medical School according to an established transplant protocol for MPS patients [25]. Conditioning regimen was a fully myeloablative regimen consisting of Fludarabin (day -10 until day -5, 6 × 30 mg, cumulative dose 180 mg/m^2), intravenous Busulfan (Busilvex, day -8 until day -5, 8× weight-adjusted dosage), Melphalan (day -4, 1 × 140 mg/m^2), and antithymocyte globulin (ATG; day -3 until day -1, 3×10mg/kg, cumulative dose 30 mg/m^2). The number of transfused CD34-positive cells was 18.74 × 10^6/kg. Graft *versus* host prophylaxis was not performed as the graft was T-cell depleted, and CD34-selected stem cells were given. Donor specification was unrelated donor, peripheral blood stem cells, 1 HLA-A mismatch, and AB0 incompatibility.

Table 1
Four point scoring system (FPSS) for mucopolysaccharidosis (MPS) type III [3].

Function	Performance	Score
Motor function	Normal walking	3
	Clumsy walking	2
	Aided walking	1
	Wheel chair/ immobile	0
Speech abilities	Normal speech	3
	Impairment of speech	2
	Speech difficult to understand	1
	Loss of speech	0
Cognitive function	Normal cognitive function	3
	Deterioration of cognitive function	2
	Loss of interest in environment	1
	Unresponsiveness	0

2.3. Four point scoring system (FPSS)

Progression of the disease was visualized using the FPSS implemented by Meyer et al. in 2007 [3]. Hereby, each of the 3 domains: motor function, speech abilities and cognitive function was scored with 0–3 points (Table 1). A total disability score (TDS) was calculated by an average of the scores assessed in the 3 function domains.

2.4. Testing of adaptive behavior

Testing of adaptive behavior was performed by parent interviews during routine visits using the 2nd Edition of the Vineland Adaptive Behavior Scales (VABS-II) [26]. Age-equivalent scores (AEqs) and developmental quotients (DQ) were calculated as described previously [2].

2.5. Ethical considerations

Written informed consent was obtained from the parents of patient A. Data of cohort B was anonymized before analysis.

3. Results

3.1. Study population

In total, seven patients compound heterozygous for the mutations p.R74C and p.R245H in the *SGSH*-gene were included in the study. Patient A received HSCT at the age of 2.5 years. At the time of data collection, she was 11.5 years of age. Patients B1-B6 (cohort B) were untreated and had a mean age of 10 years (range 4–15 years). Among them, sex equaled up with 3 male and 3 female patients. The patient characteristics are summarized in Table 2.

3.2. Course of the disease of patient A

The girl was born spontaneously at a gestational age of 38 weeks after an uneventful pregnancy. Her parents were not consanguineous and of Polish origin. Early childhood development was normal (ability to sit at the age of 7 months, walking independently at 13 and first words at 12 months of age). At the age of 1.5 years, she was admitted to hospital due to gastroenteritis and pneumonia. During this hospital stay, coarse facial features, macrocephaly and hepatomegaly were noticed. Further examination revealed elevated urinary glycosaminoglycan (GAG) levels (77 mg/mmol creatinine; normal range 7.8–14.4). Diagnosis of MPS IIIA was made by enzymatic testing at the age of 1.75 years, showing absent sulfamidase activity in leucocytes, and by molecular genetic analysis.

Table 2
Characteristics of the study population.

Patients	Age at data collection	Gender	Mutation	Age at diagnosis	HSCT
A	11.5 y	f	p.R74C, p.R245H	1.75 y	yes[a]
B1	10.0 y (†)	f	p.R74C, p.R245H	4.5 y	no
B2	14.25 y (†)	m	p.R74C, p.R245H	3.25 y	no
B3	5.75 y	f	p.R74C, p.R245H	2.5 y	no
B4	4.5 y	f	p.R74C, p.R245H	3 y	no
B5	13.25 y	m	p.R74C, p.R245H	4.5 y	no
B6	15.5 y	m	p.R74C, p.R245H	4.75 y	no

Abbreviations: †, dead; f, female; m = male; HSCT, hematopoietic stem cell transplantation, y, years.
[a] At 2.5 years of age.

The decision to perform HSCT was made against the backdrop of the parents' strong desire to treat their daughter considering that no other treatment options existed at that time. On the grounds of the young age at the time of diagnosis, HSCT was contemplated.

HSCT was performed at the age of 2.5 years. The procedure was well-tolerated, no serious HSCT-associated complications such as graft *versus* host disease were observed. Engraftment occurred on day +18. Sulfamidase activity and urinary GAG levels normalized after HSCT. Eight years later, chimerism analysis revealed 97% of donor alleles, indicating stable engraftment.

Before HSCT, a delay in speech development (no regression) and signs of restless behavior were observed. At the time of HSCT, the girl's development stagnated. Thereafter, she continued to make slow developmental progress. Shortly following HSCT, she developed sleep disturbances: she regularly woke up several times in the night and stayed awake for hours. At 5 years of age, the sleeping problems disappeared.

Eight years after HSCT (at 11 years of age) the girl presented with a global developmental delay – however, she showed no signs of regression. She was still progressing in development, albeit very slowly. She was able to talk in short sentences (2–4 words). She could run, climb, jump with both feet and stand on one leg for a few seconds. To perform activities of daily living (eating, drinking, getting dressed, going to the toilet), she only required little support. She learned to swim independently and managed 60-piece jigsaw puzzles. No sleep problems were reported at that time, but severe behavioral abnormalities (lack of risk awareness, hyperactivity, aggressiveness, temper tantrums, inadequate laughing, compulsive behavior, stereotypes) were present and had worsened at the age of 7.5 years. Behavior improved under aripriprazole and guanfacine (atypical antipsychotic drugs) treatment.

3.3. Treatment of cohort B

No patient in cohort B received HSCT. Patient B3 received high dose synthetic genistein aglycone from 3.8 years of age. Patients B4 and B5 were treated with low dose natural genistein for a period of 6 months and 2 years, respectively.

3.4. Comparison of the courses of disease of patient A with cohort B

3.4.1. FPSS

The course of the disease was evaluated using the FPSS in all patients (Fig. 1). Patient A showed a decrease in the speech ability score (from normal speech to impaired speech) at 2 years of age when a delay in language development became obvious. She did not show signs of regression in motor or cognitive abilities. In contrast, all patients in the control cohort B showed a continuous decrease of cognitive, motor, and speech abilities.

In cohort B, a decrease of the TDS was noted at a mean of 2.3 years of age, mainly due to ceasing speech abilities. At the time of data collection, all patients of cohort B, except the youngest (B4, 4.5 years), had lost their ability to speak. A speech score of 0 was reached at a mean age of 8.2 years (range 4–11.75 years). While the two younger patients (B3 and B4) were still walking at the time of data collection, the other four patients were wheel-chair bound at a mean age of 11.4 years (range 8–13.25 years). The five older patients had reached a cognitive score of 1 (loss of interest in environment) at a mean age of 8.8 years (range 4.0–13.0 years). The youngest patient (B4) still showed a cognitive score of 3 at the time of data collection.

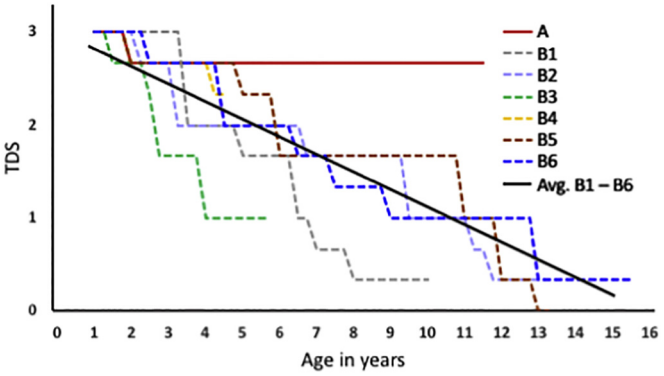

Fig. 1. Total disability scores (TDS) of all patients.
Regression of abilities as assessed by the FPSS (0–3). The total disability score of patient A (transplanted MPS IIIA patient) was compared to the TDS of cohort B (control group; patient B1-B6).

3.4.2. Neurocognitive development

Neurocognitive development was assessed using the VABS-II in patient A and in four out of six patients of cohort B (Table 3). Patient A showed the highest AEq score (51 months) of all patients. AEqs of cohort B patients were between 8 and 29 months of age. The DQ score of the youngest patient (B4, 4.5 years of age) was 51 and therefore higher than the DQ score of patient A (11.5 years), who scored 39. However, in contrast to patient A, patient B4 already started to lose skills. All other patients from cohort B showed lower DQ scores.

3.4.3. Behavior

To analyse behavior, twelve different behavioral patterns were assessed (Table 4). Patient A exhibited seven out of twelve MPS III-typical

Table 3
Neurocognitive Development.

Patients	Chronological age [months]	AEq (VABS-II) [months]	DQ
A	134	51	39
B1	–	n/a	–
B2	–	n/a	–
B3	62	8	13
B4	56	29	51
B5	162	12	7
B6	193	12	6

n/a, not available, DQ, developmental score, AEq, age equivalent score.

Table 4
Behavioral patterns of study patients.

	A	B1	B2	B3	B4	B5	B6
Lack of risk awareness	+	+	+	+	−	+	+
Hyperactivity	+	+	+	+	+	+	+
Aggressiveness	+	+	+	+	+	−	−
Temper tantrums	+	+	+	+	+	−	+
Inadequate laughing	+	unknown	+	+	−	+	+
Compulsive behavior	+	unknown	−	−	+	−	+
Anxious behavior	−	+	−	−	+	−	+
Whining	−	+	+	+	+	−	+
Chewing	−	+	+	+	+	+	+
Lack of distance	−	+	+	+	−	+	+
Stereotypies	+	+	+	+	+	+	+
Staring	−	+	+	+	+	+	−

+, present; −, absent.

behavioral patterns, patients of cohort B an average of 9.3 (range 7–10). The most frequent behavioral disturbances in all patients were: hyperactivity and stereotypes. The second most frequent behavioral abnormalities were: lack of risk awareness, temper tantrums and chewing (six out of seven patients).

Patient A neither displayed chewing, that was present in all patients of cohort B, nor whining, that was found in five out of six patients of cohort B.

3.4.4. Sleep pattern

Patient A presented with sleep disturbances lasting from 2.5 to 5 years of age. From 5 years of age onwards, she slept throughout the night. In contrast, five out of six patients of cohort B showed severe sleep abnormalities with recurrent awakenings and waking hours during the night.

3.4.5. Neurological findings

Patient A did not show any signs of seizures, whereas four out of six patients of cohort B developed an epilepsy at a mean age of 10.25 years (range 8.5–12.0 years). Additionally, she did not present any swallowing problems, whereas swallowing difficulties were present in all but in the youngest patient of cohort B.

3.4.6. Gastrointestinal findings

Patient A showed frequent diarrhea in infancy that stopped after successful HSCT. All other patients (B1-B6) showed a variable frequency of diarrhea.

4. Discussion and conclusion

The present study summarizes the clinical course of the disease in an 11 year old girl (patient A) with MPS IIIA, who received HSCT from an HLA-matched unrelated donor at 2.5 years of age. The outcome was compared to the clinical course of six genotype-matched untreated control patients (cohort B). In contrast to the control cohort, who showed continuous decrease of cognitive, motor, and speech abilities, the girl preserved motor function and maintained cognitive and speech skills on a pre-school level, with no signs of developmental regression.

To the best of our knowledge, this is the first case of an MPS IIIA patient showing a preservation of cognitive function in the long-term follow-up after HSCT.

Among others, Shapiro et al. reported on nine children with MPS III, in whom HSCT failed to alter the expected downward course of the disease [18]. Therefore, our findings are in contrast to cases reported so far.

It seems likely, that the course of disease cannot be altered when children already present with a regression of development prior to HSCT [22] or once they show a significant cognitive impairment [15]. Our patient presented with speech impairment, but she had not lost any skills at the time of HSCT. Hence, the time point of HSCT might be an important factor affecting the outcome of HSCT in MPS III patients. HSCT at an early stage of the disease might influence the course of disease positively.

Another explanation for the heterogenous results after HSCT might be the stem cell source. Sivakumur and Wraith reported on a child with MPS IIIA, who underwent haploidentical HSCT at the age of 10 months before the onset of any neurological symptoms. The neurocognitive outcome was poor, including immobility and swallowing dysfunction 7 years after HSCT. The course of disease of the transplanted patient was comparable to that of his untreated older sibling [20]. Vellodi et al. described twin sisters with MPS IIIB, who also underwent haploidentical HSCT at the age of 2 years. By the time of transplantation, their cognitive abilities reached a low average. When followed-up after HSCT, they presented with better cognitive function than their two untreated older brothers with MPS IIIB. Nine years after HSCT, both girls showed a significant cognitive delay and decreasing Griffith Scale General Scores. Furthermore, one twin showed profound behavioral abnormalities and hyperactivity [21,22]. It remains unclear, whether developmental regression caused the decreasing Griffith Scale General Scores or whether slow progress still occurred (while the chronological age increased). Lack of effectivity of haploidentical HSCT might be explained by lower enzyme activity in donor cells from a heterozygous carrier. Therefore, the use of unrelated donors or umbilical cord blood-derived hematopoietic stem cells (UCBT) was recommended for MPS I patients [27] and might also be the superior method of HSCT in MPS III as well.

Prasad et al. reported on 19 MPS III patients who received UCBT between August 1995 and April 2007. Only 12 of these patients survived. The authors reported on disease stabilization with less impact on cognitive function in nine out of 12 MPS III patients following UCBT and a positive impact on behavioral problems and sleeping patterns. Only two of these patients were transplanted before two years of age and showed modest gains in cognitive skills as well as a global developmental delay three to five years after transplantation [24]. Attention should be paid to the low survival rate of the MPS III patients in this publication. Whereas the 1-year survival was 78.9%, and therefore similar to Hurler patients after UCBT (77.8%), the 5-year survival was only 56.2% (74.5% in Hurler patients), indicating a potential specific risk for MPS III patients. Unfortunately, it was not stated why the individual MPS III patients died, but it has to be taken into account that death was reported to occur from school age in the natural history of severe MPS IIIA (from 7.9 years of age: Lin et al. 2018 [28], 10.4 years of age: Malm et al. 2010 [5], 11.5 years Delgadillo et al. 2013 [7]).

More recently, Welling et al. reported on two patients, who underwent UCBT at the age of 25 and 30 months. Despite full engraftment and a normalization of urinary GAG excretion, heparan sulfate concentration in the cerebrospinal fluid still remained high two years after UCBT. Both children showed decreasing DQ scores within the 7 year follow-up period. However, the age equivalent scores remained stable at a low level in the first patient (classical phenotype) and were still increasing in the second patient (attenuated phenotype) [29].

In our transplanted patient the cognitive age equivalent (AEq) assessed with the VABS-II was 51 months at a chronological age of 134 months. This score is considerably higher than expected from the natural course in rapidly progressing MPS IIIA disease [2]. Nevertheless, taking the DQ score of 39 into account, the patient is severely retarded. In addition to the cognitive impairment, our patient displays profound behavioral abnormalities. However, the patient does not show sleep disturbances, epilepsy, swallowing difficulties or diarrhea.

The time-point of transplantation and pre-transplantation stage of disease are likely to have a major impact on the outcome. Nevertheless, we do not know whether cognitive decline can be permanently prevented or if the start of cognitive decline is only delayed. Reliable analyses might require longer follow-up periods. Another limiting factor is that formal cognitive testing could not be performed in the

transplanted patient due to a lack of compliance.

Langford-Smith et al. [30] reported on HSCT mediated improvements in many pathological markers (reduction of heparan sulfate, normalization of GM2 gangliosides and neuroinflammation) in the brain of MPS IIIA mice. Nevertheless, there was no significant effect on enzyme brain levels or behavior. In contrast, HSCT using lentiviral vectors for SGSH expression in murine wild type cells was able to significantly improve all pathological markers and brain enzyme levels to 10% of normal as well as fully correct behavior of MPS IIIA mice. These findings might explain that HSCT has shifted the phenotype of our patient from severe and rapid progressive to a more attenuated form of the disease, but failed to correct behavior and cognitive function entirely. Current studies using hematopoietic stem cells transduced *ex vivo* with lentiviral vector encoding for *SGSH* might therefore be a promising therapeutic option for patients with MPS IIIA.

In conclusion, our transplanted patient presented with maintained cognitive skills, preserved motor function and improved quality of life suggesting a positive impact of HSCT on the natural course of the disease. Nevertheless, we cannot exclude that other genetic factors might have contributed to the relatively mild phenotype. So, even though we cannot draw any universally applicable treatment recommendations from this case, HSCT performed at an early stage of the disease could be considered in patients where other treatment options or participation in clinical trials are not available.

Informed consent

Informed consent was obtained from the legal guardians of patient A. They agreed on the use of clinical data for scientific research and publication. Data of cohort B was anonymized before analysis.

Declaration of Competing Interest

Anja F. Köhn has received honoraria from Genzyme and Shire as well as travel grants from Amicus. Nicole M. Muschol is a consultant for BioMarin, Sanofi Genzyme, Lysogene, Shire, and SOBI, has received grants/research support from Amicus, BioMarin, Sanofi Genzyme, and Shire, and has received honoraria and/or travel grants from Actelion, Amicus, BioMarin, Chiesi Farmaceutici S.p.A., Sanofi Genzyme, and Shire. All other authors declare that they have no competing interests

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