Official Journal of the European Paediatric Neurology Society

Case study

Limited benefits of presymptomatic cord blood transplantation in neurovisceral acid sphingomyelinase deficiency (ASMD) intermediate type

Oriane Mercati [a,i], *Samia Pichard* [a,i], *Marie Ouachée* [b], *Roseline Froissart* [c], *Odile Fenneteau* [d], *Bastien Roche* [a], *Monique Elmaleh-Bergès* [e], *Yves Bertrand* [f], *Hélène Ogier de Baulny* [a], *Marie T. Vanier* [c,g,i], *Manuel Schiff* [a,h,*,i]

[a] *Reference Centre for Inborn Errors of Metabolism, Robert Debré University Hospital, APHP, Paris, France*
[b] *Department of Haematology, Robert Debré University Hospital, APHP, Paris, France*
[c] *Laboratory for Inborn Errors of Metabolism, CBPE, East Hospital, Hospices Civils de Lyon, Bron, France*
[d] *Department of Biological Haematology, Robert Debré University Hospital, APHP, Paris, France*
[e] *Department of Pediatric Imaging, Robert Debré University Hospital, APHP, Paris, France*
[f] *Department of Child Haematology and Oncology, IHOP University Hospital, HCL, Lyon, France*
[g] *INSERM U820, Lyon, France*
[h] *UMR1141, PROTECT, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France*

ARTICLE INFO

Article history:
Received 11 May 2017
Received in revised form
9 July 2017
Accepted 22 July 2017

Keywords:
Inborn errors of metabolism
Lysosomal storage disorders
Niemann-Pick disease type B
Sphingomyelinase deficiency intermediate type
HSCT, Hematopoietic stem cell transplantation

ABSTRACT

Acid sphingomyelinase (ASM) deficient Niemann-Pick disease is a lysosomal storage disorder resulting from mutations in the *SMPD1* gene. The clinical spectrum distinguishes a severe infantile neurological form (type A), a non-neurological visceral form (type B) and a rare intermediate neurovisceral form. We report the first case of presymptomatic cord blood transplantation in a child with the intermediate type of ASM deficiency due to a homozygous Tyr369Cys mutation, whose affected elder brother had developed neurodevelopmental delay from 19 months of age, and had died from severe visceral complications at the age of 3. In the transplanted propositus, neurological deterioration became evident by 4 years of age; the child was alive at age 8, although severely disabled. Whereas the transplant prevented visceral progression and early death, it could only delay neurocognitive deterioration.

* *Corresponding author*. Reference Centre for Inborn Errors of Metabolism, Robert Debré University Hospital, APHP, Paris, France.
E-mail address: manuel.schiff@aphp.fr (M. Schiff).
[i] These authors contributed equally to the manuscript.
http://dx.doi.org/10.1016/j.ejpn.2017.07.015

1. Introduction

Acid sphingomyelinase deficiency (ASMD) is a rare autosomal recessive lysosomal storage disorder (LSD) due to the enzyme defect of acid sphingomyelinase (ASM), caused by mutations in *SMPD1*. The resulting accumulation of sphingomyelin leads to a progressive multisystemic disease, historically known as Niemann-Pick disease of either type A or B (NPA or NPB, respectively), the incidence of which is estimated to 0.4–0.6/100,000 births. NPA is characterised by early-onset hepatosplenomegaly followed by rapidly progressive and severe and fatal neurodegenerative involvement. Conversely, NPB corresponds to the non-neurologic slowly progressive visceral form, associating hepatosplenomegaly and interstitial lung disease, with variable age of onset, from early childhood to adulthood. An increasing number of patients with features intermediate between types A and B,[1] namely visceral signs associated with neurological or cognitive signs ranging from minor to severe intellectual disability (ID) and neuromotor impairment is reported. The clinical features resulting from ASMD thus represent a continuum, rather than two distinct types. Some genotype–phenotype correlations have been described.[2] A study on 78 deceased ASM deficient patients (including the elder brother of the index case presented here) showed that the main causes of death in the combined NPB and intermediate phenotypes were respiratory failure and liver disease. In the intermediate type alone, survival was short and the main causes of death were neurodegeneration and respiratory failure.[1]

Although there is currently no therapy to cure the neurological impairment, some nonspecific options are available to improve the visceral signs: splenectomy, liver transplantation, whole-lung lavage. A clinical trial for enzyme replacement therapy (ERT) is underway for ASMD type B. Haematopoietic stem cell transplantation (HSCT) is another option. The latter has been increasingly used, with variable outcomes, in various LSDs. The rationale for HSCT in LSDs is that macrophages derived from donor HSCs have been shown to repopulate the recipient reticuloendothelial system, especially in the liver and lungs, where they provide normal levels of functional enzyme.[3] Most of the time, there is no improvement following HSCT in patients who already display neurological symptoms. This follows experience in mucopolysaccharidosis type 1 (MPS1) for which better long-term neurodevelopmental outcomes are obtained when HSCT is performed as early as possible.[4] Three cases of HSCT in NPB and intermediate type have been reported; all performed using as a donor source bone marrow from an unaffected sibling (with additional cord blood cells in one case). All three patients developed acute or chronic graft versus host disease (GVHD); the effects of transplant on visceral status have been disappointing[5–8] [for details, see Supplemental Table 1]. Six additional ASMD patients treated by HSCT were reported: 5 died from complications of the procedure.[1]

1.1. *Case report*

We report herein the first case of presymptomatic HSCT (using cord blood as a stem cell source) in a patient diagnosed as a neonate because of family history of intermediate ASMD. His elder brother (Pt1), was the first child of consanguineous parents originating from Senegal in whom investigations were performed at the age of 8 months, for hepatosplenomegaly associated with failure to thrive and interstitial bilateral pneumonia. Vacuolated lymphocytes on the blood smears and foamy histiocytes in the bone marrow aspirate (Fig. 1) were strongly suggestive of LSD. ASM activity measured in leukocytes was profoundly deficient; sequencing of *SMPD1* led to the identification of a homozygous (both parents studied) p.Tyr369Cys (c.1106A>G) mutation (reference sequence NM_000543.4). Further on, the patient developed interstitial pneumonia and exhibited several episodes of hypoxaemic failure. He then suffered from chronic respiratory failure. At the age of 19 months, he started exhibiting neurological signs, namely axial hypotonia with motor delay (no walking), ataxia and absence of deep tendon reflexes. Massive splenomegaly with subsequent hypersplenism led to partial splenectomy at the age of 2 years 9 months. Six months later, at the age of 3 years 3 months, he died from respiratory failure in a context of severe feeding problems due to massive hepatosplenomegaly (Fig. 2A).

The propositus (his younger brother, Pt2) was born at term with an uneventful neonatal period. Parents had refused prenatal diagnosis. Because of his brother's history, he was systematically tested for ASMD at 6 days of age and found affected (acid sphingomyelinase activity in leukocytes 2% of the normal mean value; homozygosity for the p.Tyr369Cys *SMPD1* mutation). Initial development was normal. At 4 months, a complete clinical pre-transplant evaluation was normal except for moderate hepatomegaly. Brain MRI showed no cerebellar atrophy and mild hyperintensities of posterior periventricular white matter (not shown). At the age of 5 months, he received a myeloablative-conditioning regimen with busulfan (15.5 mg/kg) fludarabine (125 mg/m^2) and antithymoglobulin. GVHD prophylaxis included cyclosporin and steroids. He received an unrelated cord blood 5/6 (B MM) with total nucleated cell dose of 6.5.10^7/kg. Haematological recovery occurred 21 days after transplantation. Engraftment was successful, with progressive increase in donor chimaerism (day 35 post-transplant: 66%; day 84: 88%). The most recent chimaerism (year 5 post transplant) was 93%. ASM activity in leukocytes was 162%, 135% and 66% of normal at 6 months, 13 months and 3.5 years post transplant, respectively. Visceral evolution showed moderate and stable hepatomegaly and no splenomegaly and no interstitial lung disease. Neurological examinations found mild peripheral hypertonia that resolved in a few weeks and persistent axial hypotonia. He started walking at the age of 17.5 months. When he was 3 years 10 months, neurological deterioration was suspected (Fig. 2A). Brain MRI showed moderate cerebellar atrophy (Fig. 2B). Three months later, degradation became obvious with ataxia, frequent falls and myoclonus. At 5 years 7 months, he underwent extensive evaluation of movement, which found active articular limitations, difficulty in maintaining contraction, ataxia, nearly impossible walking and generalised myoclonus. Posture could not be evaluated because of static ataxia. Brain MRI showed progression of cerebellar atrophy, consistent with the brain MRI findings of his brother