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Case Report

Unexplained splenomegaly as a diagnostic marker for a rare but severe disease with an innovative and highly effective new treatment option: A case report

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ABSTRACT

Acid Sphingomyelinase Deficiency (ASMD) is a lysosomal storage disorder that can lead to severe complications if not promptly treated. This case aims to highlight the critical importance of early awareness of ASMD and to introduce, for the first time in the literature, a new and highly effective treatment option for children.

1. Introduction

ASMD type B (NPD-B, OMIM 607616), is an acid sphingomyelinase deficiency and one of the most common Lysosomal storage diseases (LSD) [1]. The estimated incidence at birth of this rather rare, progressive and often fatal LSD is between 0.4 and 0.6 on 100.000 [2]. The origin of this disorder lies in a defect in the degradation cascade of the sphingolipidoses.

A mutation in the gene sphingomyeline-phosphodiesterase 1 (SMPD1, location 11p15.4) results in a reduction or absence in activity of the enzyme acid-sphingomyelinase [3,4]. Due to a defect in the enzyme acid-sphingomyelinase, Sphingomyelin cannot be broken down into ceramide, causing a progressive accumulation of this compound [3,4].

This accumulation occurs within several tissues abundant in reticuloendothelial cells, as for example in the spleen, liver, bone marrow, lungs and lymph nodes. The abnormal accumulation creates anatomical and functional abnormalities in each of these locations in the body. The range of possible clinical symptoms is very diverse although splenomegaly is nearly almost present [3,4]. Other possible clinical manifestations include hepatomegaly, liver disease, bone marrow failure with associated blood disorders such as anaemia, thrombocytopenia and coagulopathy (typically seen as epistaxis which even might be lethal), pulmonary involvement with consequences such as pulmonary hypertension interstitial lung disease/lung fibrosis, growth retardation, osteoporosis and failure to thrive The abnormal accumulation creates a wide range of possible symptoms that require a lot of alertness [3,4].

The clinical presentation of ASMD type B is very similar to that of Gaucher disease (GD) [5,6]. As a result, the differential diagnostic distinction between the two cannot be made based on a clinical base [7].

The diagnostics of ASMD are in many cases delayed. This is mainly due to the possibility of very diverse presentations, its rarity and because it might be overlooked in a differential diagnostic workup where there are more urgent haemato-oncological conditions in the foreground [8]. When suspected, specific clinical results such as diffusion capacity measured by spirometry, spleen volume, platelet count, low-density lipoprotein cholesterol and liver fibroses measured with a fibroscan are hallmarks for the disease [9]. The definitive diagnosis is established

Abbreviations: ASMD, Acid Sphingomyelinase deficiency; CMV, Cytomegalovirus; EEG, electroencephalogram; ERT, enzyme replacement therapy; FEV1, forced expiratory volume in 1 s; FVC, Forced vital capacity; GD, Gaucher Disease; HLH, Hemophagocytic LymphoHistiocytosis; IV, intravenous; MRI, Magnetic resonance imaging; NPD-B, ASMD type B or Acid Sphingomyelinase deficiency type B; SMPD1, sphingomyeline-phosphodiesterase 1.

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through laboratory assessment, specifically by measuring the elevated levels of the biomarker, Lyso-Sphingomyelin, and the deficient enzyme activity [10,11]. The confirmation is made by detection of pathogenic mutations by DNA analysis [12].

Once the diagnosis is made, appropriate supportive treatment can be initiated. This mainly consists of the close monitoring and control of possible coagulopathy and terminal liver disease, treatment of hyperlipidemia and osteoporosis or osteopenia and possible supplementation of oxygen in case of symptomatic lung disease [12]. Besides the supportive treatment, there is recently enzyme replacement therapy (ERT) available with recombinant human acid sphingomyelinase (Olipudase alfa, Sanofi) [13,14]. This recombinant human acid sphingomyelinase enzyme replacement therapy is initiated at a starting dose of 0.03 mg/kg in children and is administered biweekly. There is an individualised dose escalation over a minimum period of 16 weeks to achieve the target maintenance dose of 3 mg/kg. Potential side effects are generally mild to moderate, with the most common being urticaria, pyrexia, vomiting and headache [15]. ERT is essential in preventing complications and preserving the quality of life in patients [15]. This novel therapy raises critical questions regarding the optimal timing for initiation versus delay treatment and therapeutic monitoring. Given the clinical similarities, comparison with the therapeutic goals for Gaucher disease could be made as well [16]. While recent studies propose preliminary criteria, further research is necessary to provide definitive guidance [17,18]. With proper treatment, patients can lead a comfortable life significantly longer, even within the expected ranges of the healthy population. However, without appropriate treatment, there is a progressive worsening of the disease during childhood or sometimes (early) adulthood. The most common cause of death is the progressive decline in lung capacity and respiratory complications [3,4].

Proper and timely treatment initiation is therefore essential is patients with ASMD type A/B and B [13,14].

2. Case presentation

We describe a boy who presented at the age of 1 year and 10 months with febrile convulsions, accompanied by stomatitis and tonsillitis. His previous medical history includes a term birth without complications following a normal pregnancy, and a circumcision at 2 months due to phimosis, which was uneventful. He experienced four consecutive viral respiratory infections, including RSV bronchiolitis at 7 months, which required hospitalization. Other viral respiratory infections were well tolerated and managed with inhaled medication. He also had a single episode of viral gastroenteritis caused by rotavirus. Upon presentation to the emergency department, in addition to significant stomatitis and tonsillitis, a palpably enlarged but non-tender spleen was diagnosed.

The boy was admitted for hydration while his own intake was virtually absent. During admission, the boy developed severe acute respiratory failure due to a developing pneumonia with need of oxygen suppletion. Elective intubation and mechanical ventilation were even necessary because of atelectasis and necrotizing bilateral pneumonia. Respiratory cultures were only positive for adenovirus, but broad spectrum antibiotics were continued during the entire hospital stay.

During admission, the boy additionally developed an abnormal blood count with pancytopenia, elevated serum LDH, triglycerides and ferritin, and increased hepatosplenomegaly. In addition, a cytomegalic virus was detected in nasopharyngeal aspirate. A picture strongly suggestive of a secondary hemophagocytic syndrome was suspected, but not enough criteria were met at this time to formally make this diagnosis [19].

In intensive care, the boy recovered under antibiotic therapy and respiratory support could be gradually reduced until discontinuation. Eventually spontaneous intake resumed, and the boy could leave the hospital again. However, a substantial splenomegaly up to the umbilicus and hepatomegaly with persistent thrombocytopenia after an active CMV infection with a possible secondary hemophagocytic syndrome were persistently retained.

At the age of 1 year and 11 months, he was readmitted to the hospital because of febrile convulsions associated with a pneumonia. Nasopharyngeal aspirate showed positive cultures for *Haemophilus influenzae* and *Streptococcus pyogenes*. Antibiotic treatment was quickly started during admission and the boy recovered without the need for additional support (such as oxygen or tube feeding). Over the following months, the boy was followed up with blood tests and ultrasound evaluation of the spleen and liver. Persistent anaemia, elevated platelets and elevated liver values were found. These hematologic and biochemical abnormalities increased during infections.

Given the persistent disease without a very clear explanation, a hemophagocytic syndrome secondary to an active CMV infection was considered a valid explanation, but the diagnostic criteria were not fulfilled to officially confirm this diagnosis[13]. In addition, a bone marrow puncture was performed at the age of 2 years and 10 months. This showed a cell-rich to hypercellular preparation with multiple macrophages that had an increased phagocytosis of red blood cells and platelets.

Given the lack of diagnosis with permanent haematological abnormalities and enlargement of the spleen and liver, the boy consulted various specialists. A series of additional tests followed, echo of the heart, EEG, brain MRI, blood tests for genetics and glycosaminoglycans in urine. However, without clear confirmation of an underlying diagnosis. In the meantime, regularly episodes of heavy epistaxis occurred that were not always easy to control.

At the age of 3 years, given the continuously increasing volume of the spleen, a splenectomy was advised. Vaccinations in preparation for this were administered. Parents wanted a second opinion before accepting this procedure. They consulted the pediatric gastroenterology department, and an additional genetic blood sample was performed to exclude any other possible causes, looking broader than the initial genetic screening. In the meantime, lab results of lysosomal enzyme activities showed a normal beta-glucosidase and an acid-sphingomyelinase of 0.584 μmol/Lh (reference value $\geq$ 1.48 μmol/Lh). Additionally, the genetic results confirmed a homozygous deletion of c1829_1831, p. Arg610del in the SMPD1 gene, most commonly described in patients with non-neuronopathic ASMD. These results indicate the presence of sphingomyelinase deficiency giving rise to ASMD type B disease, which could explain all clinical manifestations.

After making the diagnosis, more information and education about the disease could be given to the boy, his parents and the caregivers involved. As soon as possible Olipudase alfa enzyme replacement therapy intravenously was initiated at a starting dose of 0.03 mg/kg at the age of 4 years and 7 months in a medical need program provided by Sanofi (FAMPH, Federal Agency for Medicines and Health Products, Belgium). The therapy was administered biweekly with an individualised dose escalation over a minimum period of 16 weeks to achieve the target maintenance dose of 3 mg/kg. No side effects were observed during the intravenous administration of the therapy or in the intervals between doses. From the start of this treatment clear clinical improvement was observed. Blood counts recovered to near normal, hepatomegaly resolved, and spleen volume returned to near normal. The boy went through a few infections afterwards, but always without any need for hospitalization.

To date, the boy in this case is 7 years of age, is doing well on two weekly IV enzyme replacement therapy with Olipudase alfa, is developing normally and has no additional haematological complications. The last imaging showed a mild splenomegaly on abdominal ultrasound with a maximum diameter of 11.6 cm (upper limit in men between 6 and 8 years is 10.5 cm) and a normal aspect of the liver. The skeletal age at the age of 7 years and 9 months was 8 years according to the standard atlas of Greulich and Pyle, indicating that growth retardation had completely recovered. Finally, a chest X-ray showed no special abnormalities of the heart and lungs. Lung function demonstrated FEV1 of 82 %, FVC of 83 % and a Tiffeneau of 86 %. After administration of 400 μg

Salbutamol, a small improvement to FEV1 of 90 %, a FVC of 85 % and a Tiffeneau of 93 % was observed. Showing that despite the complicated history of lung problems the boy has a stable respiratory state under treatment. Since start of treatment there were no episodes of excessive epistaxis anymore.

3. Conclusion

In conclusion, we presented a case where the diagnosis was significantly delayed due to the initial focus on the infection-related issues. We recommend that in patients presenting with (hepato-)splenomegaly and cytopenia, the early-stage diagnostic workup should include analysis of enzyme activity and associated biomarkers for ASMD and Gaucher disease, due to the overlapping clinical features. Even in cases with active infections, with or without febrile convulsions, the underlying cause might not be directly related to the immune system, whereby HLH can be a good and logical possible differential diagnosis due to the potentially very similar clinical presentation. A combination method on DBS cards to optimize diagnostics was recently published for this purpose [11].

With this case we represent for the first time in literature a report of the beneficial results in a child after the initiation of Olipudase alfa, a new therapy for non-central-nervous-system manifestations of ASMD. The therapy was highly effective, reversing almost all complications and preventing further, possibly very serious, complications of the condition. This underscores not only the importance of timely diagnosis and treatment but also highlights the potential of this innovative therapy in managing children with ASMD, emphasizing the critical role of selecting the appropriate treatment approach.

Consent

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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CRediT authorship contribution statement

Amber Van Baelen: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Conceptualization. **Stijn Verhulst:** Writing – review & editing, Visualization, Supervision. **François Eyskens:** Writing – review & editing, Supervision, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used no AI-assisted technology.

Declaration of competing interest

The authors declare the following personal relationships which may be considered as potential competing interests.

François Eyskens reports a relationship with the European Reference Network of hereditary Metabolic Disorders that includes: board membership. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data supporting the current study are available from the corresponding author upon request.

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