Scientific Research Publishing

Open Journal of Pediatrics, 2023, 13, 907-913
https://www.scirp.org/journal/ojped
ISSN Online: 2160-8776
ISSN Print: 2160-8741

Niemann-Pick A/B Disease in a 13-Year-Old Child and Review of the Literature

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How to cite this paper: Taha, I., Tadmori, I. and Hida, M. (2023) Niemann-Pick A/B Disease in a 13-Year-Old Child and Review of the Literature. *Open Journal of Pediatrics*, **13**, 907-913.
https://doi.org/10.4236/ojped.2023.136099

Received: October 21, 2023
Accepted: November 13, 2023
Published: November 16, 2023

Abstract

Niemann-Pick disease (NPD) refers to a group of patients who have varying degrees of lipid storage and foam cell infiltration in tissues, as well as overlapping clinical features, including hepatosplenomegaly, insufficiency pulmonary and/or central nervous system (CNS). Thanks to the pioneering work of Roscoe Brady and colleagues, we now know that there are two distinct metabolic abnormalities that explain NPD. The first is due to the deficient activity of the acid sphingomyelinase enzyme (ASM; NPD "types A and B"), and the second is due to defective functioning in the transport of cholesterol (NPD "type C"). We report the case of a 13-year-old adolescent diagnosed with Niemann-Pick A/B disease.

Keywords

Nieman Pick, Splenomegaly, Hepatomegaly, Enzymatic Test

1. Introduction

Niemann-Pick disease (NP) is a rare metabolic disease characterized by lysosomal overload. It is a lipidosis linked to the accumulation of sphingomyelin and cholesterol, it is transmitted in an autosomal recessive manner [1]. To date, three main forms of the disease have been identified: types A, B and C. These forms are distinguished from each other by their age of onset, neurological manifestations and substances accumulated in the body. Forms A and B of NP disease are relatively rare, with an incidence of approximately 1 case per 250,000 people, while the prevalence of form C is more difficult to estimate (most likely underdiagnosed) and is estimated to be approximately 1 case per 130,000 people [2] [3]. The clinical presentation of NP disease is heterogeneous and varies de-

pending on the type. Typically, symptoms of the disease appear in childhood. Type B is characterized by a later onset, with symptoms that may appear from childhood to adulthood, and it has a favorable prognosis in the absence of neurological disorders [4] [5] [6] [7].

We report the case of a 13-year-old adolescent diagnosed with Niemann-Pick disease, discovered incidentally during a systematic examination.

2. Clinical Case

A 13-year-old male adolescent with no notable pathological history, notably no notion of consanguinity, recurrent infections, neonatal cholestasis or hemorrhagic syndrome, presented good psychomotor development. The child presented with a fever, for which the diagnosis of tonsillitis was made. The systematic clinical examination carried out by the attending physician revealed splenomegaly. The child was referred to the University Hospital Center (CHU) for additional care.

On admission to the department, the child had a blood pressure of 11/7 mmHg, a heart rate of 80 beats per minute, a respiratory rate of 24 cycles per minute, with a correct saturation of 97%. The child was conscious with a Glasgow Coma Score (GCS) of 15, afebrile, and without dysmorphia. The general examination revealed a stature delay with a height of 135 cm (−2.5 standard deviations), a weight of 30 kg (−1.5 standard deviations), and a head circumference of 51 cm (+1 standard deviation). No jaundice observed.

Abdominal examination showed a supple abdomen with hepatomegaly (hepatic arrow of 10 cm) and splenomegaly of 5 cm in relation to the costal margin. No abdominal pain or ascites was noted. Neurological examination revealed no ataxic syndrome, seizures, pathological rapid eye movements (RPM), or cranial nerve involvement. Ocular examination showed no nystagmus or strabismus, and cardiovascular examination revealed no signs of heart failure. The rest of the examination, in particular, showed neither lymphadenopathy nor hemorrhagic syndrome, including the absence of digestive bleeding (hemorrhage, rectal bleeding), nor bone pain.

The child underwent a biological evaluation, the results of which were as follows: The blood count (CBC) was normal, with hemoglobin (Hb) at 13.30 g/dl, mean blood cell volume (MCV) at 78, 1 Fl, a mean corpuscular hemoglobin concentration (MCHC) of 35.5 g/dl, a white blood cell count (WBC) of 9940 uL, 4510 polymorphonuclear neutrophils (PNN), 3660 lymphocytes, and 159,000 platelets per mm^3. The reticulocyte count was 80,000/mcL, and there were no blasts. The sedimentation rate (ESR) was 10 mm at the 1st hour and 20 mm at the 2nd hour. Serology for Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), and hepatitis A revealed normal results. Liver assessment was also within normal limits, with values for Aspartate Aminotransferase (AST) at 51 IU/L, Alanine Aminotransferase (ALT) at 52 IU/L, Total Bilirubin (BT) at 42 mg/L, direct Bilirubin (BD) at 7 IU/L, and indirect Bilirubin (BI) at 35 IU/L. The lipid profile

was normal, with total cholesterol at 2.21 g/L, HDL (High-Density Lipoprotein) at 0.18 g/L, LDL (Low-Density Lipoprotein) at 1.57 g/L, and triglycerides (TG) at 2.33 g/L. PT/TCA was normal.

A radiological assessment was requested, including an abdominal ultrasound. Ultrasound results revealed homogeneous hepatosplenomegaly, as well as the presence of some small pre-aortic lymphadenopathy. The spleen measured 16 cm, while the liver measured 15 cm. As previous assessments were normal, a metabolic disease was suspected. However, an enzyme test confirmed the diagnosis of Niemann-Pick disease type A/B (ASMD), thus excluding Gaucher disease. The acid sphingomyelinase dosage was 0.2 umol/L/h (cut-off value > 1.2), Lyso SPM was 316.4 ng/ml (cut-off value 0.0 - 70.0 ng/ml). The genetic study revealed the presence of the following mutations in the heterozygous state: c.739G > A (p.(Gly247Ser)) and c.1829_1831del (p.(Arg610del)).

Investigations were carried out to detect other possible damage, including heart, lung, bone and eye problems. Chest x-ray revealed alveolar-interstitial syndrome, which was confirmed by chest CT showing diffuse interstitial lung disease. The child's bone age was estimated at 11 years. The fundus was normal. Cardiac echocardiography showed no abnormalities, and pulmonary function tests were within normal range. In addition, a fibroscopy revealed no abnormality.

The patient was treated because of his symptoms and is awaiting replacement treatment with olipudase alfa, which has been prescribed. Additionally, genetic counseling was discussed with the parents.

3. Discussion

Niemann-Pick disease was discovered by the German pediatrician Albert Niemann in 1914, during the observation of an infant [8]. In 1927 Ludwig Pick, identified and defined this disease as distinct from Gaucher disease, which is now commonly referred to as NPD [9] [10].

In 1934, biochemist Klenk identified sphingomyelin as the lipid accumulated in NPD, suggesting that it resulted from the absence of an enzyme responsible for the breakdown of sphingomyelin [11]. In 1966, Brady and his team characterized a sphingomyelin-cleaving hepatic enzyme, and soon after, they discovered a deficiency of this enzyme (ASM) in the tissues of six patients with infantile-type NPD [12] [13] [14].

The prevalence of consanguinity within families is high, which confirms the genetic component of the disease [7]. For example, Willvonseder *et al.* reported the case of a patient with NP who had three brothers also affected [15]. However, it is important to note that in the literature there are cases of NP types A, B and C that are not associated with consanguinity [5] [16] [17] [18].

Patients with Niemann-Pick type B usually do not show signs of central nervous system involvement. However, they may present with severe hepatosplenomegaly, accompanied by symptoms of liver failure [19] [20]. The lungs are

frequently affected, which can lead to problems with lung function. A distinctive feature is the presence of a reddish-brown halo around the macula in the eyes of these patients, and in some cases a distinct cherry red spot can be identified. There are also cases of patients with characteristics intermediate between types A and B of NPD. Their HDL cholesterol levels are usually low, while their serum triglycerides and LDL cholesterol levels are often high [21].

The diagnosis of NPD types A and B is based on the analysis of the activity of the ASM enzyme, which is reduced in these types of the disease. This analysis is performed on samples of cells such as peripheral blood leukocytes or cultured skin fibroblasts, and is the standard confirmation procedure [22] [23]. SMPD1 gene sequencing can also be used to confirm the diagnosis. The presence of vacuolated cells in peripheral blood smears or bone marrow is suggestive of the disease, but it requires enzymatic and/or genetic confirmation for accurate diagnosis [24]. The differential diagnosis between NPD types A and B should include Gaucher disease and Niemann-Pick type C, and biochemical and/or genetic laboratory testing can accurately distinguish these conditions.

The main lipid that accumulates in patients with Niemann-Pick types A and B is sphingomyelin [25] [26]. In addition to sphingomyelin, elevated levels of bis (monoacylglycero) phosphate (BMP) and lysosphingomyelin (sphingosine phosphocholine) are observed [27] [28]. Cholesterol, glucocerebroside, lactosylceramide, and gangliosides, particularly ganglioside GM3, are also present at high levels, although less than in Niemann-Pick type C.

The ASM enzyme is encoded by a single gene, SMPD1, located in chromosomal region 11p15.4 [29] [30]. This region of chromosome 11 is known to be associated with genomic imprinting, and studies have shown that the SMPD1 gene is primarily expressed from the maternal chromosome, that is, it is paternally imprinted [31]. Niemann-Pick types A and B are inherited in a recessive manner, and disease severity largely depends on the type of SMPD1 mutations inherited [32].

Currently, the management of NP disease mainly relies on the treatment of symptoms and requires a multidisciplinary team. It includes supportive measures and the use of symptomatic medications, which, although useful, have variable effects. These approaches aim to improve the quality of life of patients, relieve symptoms and alleviate disabilities [4]. Early diagnosis is essential to allow adequate therapeutic management of the patient and to offer genetic counseling to family members. In the case of children, treatment often involves child psychiatry consultations and physiotherapy sessions, including gait and limb rehabilitation to prevent contractures [6] [33] [34] [35].

Olipudase alfa is an enzyme replacement therapy based on recombinant human ASM, also known as rhASM [36]. This therapy has shown clinical improvements and improvement in patients' quality of life, although it has no impact on neurological disease progression. To date, olipudase alpha is primarily used to treat non-neurological symptoms of NP type B. It is the first and only

enzyme replacement therapy in late-stage development to treat this disease. No treatment has yet been approved to treat acid sphingomyelinase deficiency [37].

4. Conclusion

Niemann-Pick disease is an extremely debilitating condition for individuals who suffer from it. Despite the current lack of curative treatment, research and the commitment of the scientific community offer prospects of hope for the future. It is imperative to continue efforts in awareness, research and support to improve the lives of patients affected by this disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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