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CASE REPORT

Precision Personalized Medicine of Strategic Health Action in Niemann-Pick Disease type A/B

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Abstract

Introduction: Niemann-Pick A and B diseases (NPD), are part of the group of lysosomal storage diseases caused by acid sphingomyelinase (ASM) deficiency, which catalyzes the hydrolysis of sphingomyelin (SM) to ceramide and phosphocholine. As a result, SM and its precursor lipids accumulate in lysosomes in cells of the reticuloendothelial system, leading to loss of the ability to degrade macromolecules, forming intracellular inclusions that are deposited in organs. NPD-A/B are caused by deleterious variants in the sphingomyelin phosphodiesterase 1 (SMPD1) gene, leading to defective formation of this enzyme and preventing the movement of lipids out of the cells.Case report: 20-month-old infant with neurodevelopmental delay, malnutrition, dysmorphic facies and hepatosplenomegaly. The initial approach ruled out infectious and lymphoproliferative diseases. A targeted clinical exome was performed which showed two variants of the SMPD1 gene (compound heterozygous), one of pathogenic clinical significance and the other probably pathogenic. In the enzymatic activity, it was found increased biomarker lyso-SM-509 and decreased ASM activity, with which phenotype-genotype correlation with NPD-A/B is performed.Discussion and Conclusion: With a defined and precise diagnosis it is possible to guide health actions, follow-up guidelines, risk assessment of the inheritance model through an index case in order to find possible carriers, perform a complete genetic counseling, implement and initiate targeted treatments to reduce morbidity and mortality associated with this pathology.

INTRODUCCION

Niemann-Pick A and B diseases (NPD), are part of the group of lysosomal storage diseases. Lysosomal storage diseases are characterized by inherited deficiencies of one or more lysosomal enzymes involved in the degradation of lipids and their products [1]. Niemann-Pick diseases type A and B (NPD-A and NPD-B, respectively) are caused by deficiency of acid sphingomyelinase (ASM), which catalyzes the hydrolysis of sphingomyelin (SM) to ceramide and phosphocholine. As a result, SM and its precursor lipids begin to accumulate in lysosomes. If there is a genetic defect in any of the structures that form the lysosome, abnormal functioning and inability to degrade macromolecules will occur, resulting in their accumulation, forming intracellular inclusions [2].

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The cells that mainly accumulate in the lysosomes are lipid-laden macrophages, the most abundant being SM and cholesterol, and are deposited in different organs such as the liver, spleen, lungs and brain, presenting hepatosplenomegaly, cytopenias, pulmonary disease and neurological symptoms [3].

These diseases are characterized by autosomal recessive inheritance. NPD-A and NPD-B are caused by loss-of-function variants in the sphingomyelin phosphodiesterase 1 (SMPD1) gene in sub-band 1 or 4 of band 5 of region 1 of the short arm of chromosome 11 (11p15.4), which encodes ASM [4]. In the SMPD1 gene, more than 180 variants have been identified, which lead to abnormal or defective protein formation, preventing the movement of lipids out of the cells and ultimately leading to their accumulation inside the cells [5].

NPD is divided into 5 subtypes: NPD A-E. Type A (NPD-A) (MIM # 257200), also called the classic infantile form or infantile neurovisceral form with very low ASM activity, presents at the age of 6-12 months and is usually fatal before the age of three years. Individuals with this disease present with progressive hepatosplenomegaly, failure to thrive and neurological deterioration. By the age of one year, neurological symptoms appear as psychomotor retardation and regression of developmental milestones. All individuals with this type have a classic ocular finding called cherry red spot [1,6]. Type B (NPD-B) (MIM # 607616), known as the non-neuropathic form, presents in childhood, is described as being of lesser severity than NPD-A and is characterized by the appearance of hepatosplenomegaly, thrombocytopenia and interstitial lung disease. About one-third of patients with NPD-B have cherry-red spotting and neurological symptoms [2]. Type C (NPD-C) (MIM # 257220), also known as the chronic neuropathic form, is caused by an intracellular failure of cholesterol transport. It can present at any age, has a heterogeneous clinical presentation, and manifests as infantile jaundice, hepatosplenomegaly or isolated splenomegaly, symptoms preceding neurologic involvement such as ataxia, dystonia, supranuclear gaze palsy, dysphonia, and dysphagia. NPD-C is divided into severe infantile, late infantile, juvenile, and neonatal hepatitis forms [7]. Type D (NPD-D), or Nova Scotia variant, is phenotypically similar to type C. Finally, type E (NPD-E) is described, which is an adult non-neuropathic form. It is a less common variant of NPD in which the most common neurological manifestations include delayed cognitive or motor development, vertical supranuclear gaze palsy, ataxia, dysarthria, dysphagia, and dystonia [1,6].

Worldwide, NPD in general has been described to affect 1 in 120,000-150,000 people [3]. NPD-A and NPD-B types affect 1 in 250,000 births. The prevalence is high in Ashkenazi Jewish ancestry, where it affects 1 in 40,000 people [8]. Although NPD is part of the recognized orphan diseases and its reporting is being promoted [9,10], in Colombia there is still no consolidated population burden and other relevant indicators.As a gold-standard to confirm or rule out NPD-A or NPD-B, ASM activity is measured in leukocytes. It has been shown that ASM activity in NPD-A is less than 5% of normal, so that SM levels are very high. In contrast, in NPD-B, ASM activity is higher, constituting 2-10% of its normal activity [11].

In the case of low enzyme activity, additional genetic testing can better assess the disease by performing sequencing of the SMPD1 gene [12].

As differential diagnoses, other lysosomal storage diseases should be considered, especially Gaucher disease, Tay-Sachs disease and metachromatic leukodystrophy. Gaucher disease also presents with hepatosplenomegaly and cytopenias, but bone pain and lesions are more prominent. The deficient enzyme in Gaucher disease is glucocerebrosidase, which leads to the accumulation of glucocerebroside within cells instead of sphingomyelin. Tay-Sachs disease, although not presenting with hepatosplenomegaly, neurodegeneration, developmental delay and cherry-red spots in the macula are prominent features. The deficient enzyme in this disease is hexosaminidase A, which causes an accumulation of GM2 gangliosides. Metachromatic leukodystrophy causes central and peripheral demyelination and may manifest as ataxia or other neurological symptoms [13].

Symptomatic and supportive management for NPD is the mainstay of treatment. It seeks to treat dyslipidemia, liver failure, thrombocytopenia, bleeding episodes and complications of NPD. Occasionally, patients may develop complications such as fulminant hepatic failure, respiratory failure, dementia, seizures, schizophrenia-like psychosis, severe thrombocytopenia, heart disease, and bone involvement [14].

The finding that there is a close link between neurodegenerative disorders and lysosomal storage disorders offers the opportunity for new therapeutic strategies. It can be expected that in the future drugs will be developed that are able to efficiently enhance protein clearance and slow the progression of proteinopathies, thus providing a benefit for patients with a lysosomal storage disorder [15]. Enzyme replacement therapies and gene therapies are undergoing trials and may become the mainstay of treatment in the future [16].Enzyme therapy aims to reduce the accumulated substrate by exogenous enzyme supply, an alternative approach is to decrease the substrate produced by inhibiting its synthesis or by giving substrate reduction therapy. One approach has been to modify the endogenous variant enzyme with agents that interact with the dysfunctional enzymes. Another has been to use competitive inhibitors of the enzyme to enhance lysosomal activity.

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Since glucosylceramide is the first step in the synthesis of glycosphingolipid-based glycosphingolipids, including glucosylceramide and gangliosides, synthase inhibitors would decrease the amounts presented to the lysosome for degradation [16]. Miglustat, an imino sugar, glucose analog and glucosylceramide synthase inhibitor, has been described to help in NPD and Gaucher disease by decreasing glucocerebroside production. It is approved in Europe, Canada, and Japan, but is not yet approved in the United States or Latin America [17].

Regarding recent clinical trials, a study is underway in the United States and Argentina, which aims to obtain data on the safety of olipudase alfa in patients with MSA deficiency who are exposed to long-term treatment with this drug, started in December 2013 and ends in February 2024 [18]. Similarly, a prospective observational clinical trial with 55 patients is underway in France to describe lung, liver and kidney outcomes following olipudase alfa, which started in June 2022 and is due to end in January 2025 [19].

Patient needs have driven efforts to improve diagnosis, access to therapies, and the development of basic and clinical research in lysosomal depot diseases by different research groups. Substantial opportunities and challenges remain in the current development of treatments for rare genetic diseases, as 92% of rare diseases lack U.S. Food and Drug Administration (FDA)-designated products. In 2015, 243 diseases have at least one approved orphan drug, a small increase from the 200 diseases reported in 2010 [20]. In 2022, the FDA approved the first targeted therapy with xenpozyme infusion (olipudase alfa-rpcp) to treat the non-central nervous system manifestations of ASM deficiency in NPD A, B, and A/B [21].

In addition, new technologies such as nanomedicine are being developed to deliver drugs to the nervous system. Strategies are being developed to cross the blood-brain barrier to more effectively ensure the transport of large molecules, such as enzymes and other proteins. The use of nanotransporters, nanomedical tools that can be loaded with a variety of drugs, protect them from the environment, and deliver them safely into the brain, are being explored. The effective design of nanotransporters targeting brain therapeutics may guide future therapeutic interventions for the treatment of NPD-A, other lysosomal depot diseases, and could easily be extended to the treatment of Alzheimer's and Parkinson's diseases [22]. Precision medicine is key to continue to conduct studies and interventions and make an impact on the morbidity and mortality of patients with these types of pathologies.

CASE REPORT

Older female infant, 20 months old, first pregnancy with an 18-year-old mother, irregular prenatal care due to threatened miscarriage and repeated urinary tract infections. At term with adequate neonatal adaptation, weight and height at birth. Parents were not consanguineous, with no history of genetic or metabolic diseases or family congenital malformations. Subsequently he presented global developmental delay, chronic protein-calorie malnutrition, low volume anemia, dysmorphic facies and hepatosplenomegaly. Within the syndromic approach, hematologic, oncologic, immunologic and infectious causes were ruled out. Paraclinical tests showed elevated transaminases and hypertriglyceridemia for her age. Given the clinical complexity of the patient, given her perinatal and family history, phenotypic heterogeneity, diverse clinical manifestations, possible differential diagnoses, inconclusive initial diagnostic tests and the suspicion of a rare genetic disease, a targeted clinical exome was requested.

Two variants, one of clinical pathogenic significance and the other probably pathogenic, were found in the SMPD1 gene (compound heterozygous) associated with NPD-A and NPD-B. The first, c.1780_1782del p.(Thr594del), is a 3-bp deletion with no change in reading frame in exon 6, which causes the loss of the Thr residue at position 594, a variant that has been previously described in homozygosis as NPD-associated. It is classified as probably pathogenic (class 2) according to the recommendations of the CENTOGENE Bio-Database and the American College of Genetics and Genomics (ACMG). The second variant, c.688C>T p.(Arg230Cys), causes an amino acid change from Arg to Cys at position 230. This variant has been previously described in homozygosis and compound heterozygosis in NPD patients. It is classified as pathogenic (class 1) according to the recommendations of the CENTOGENE Bio-Database and the American College of Genetics and Genomics (ACMG).

Studies were requested to confirm the type of lysosomal deposit disease, among which lyso-SM-509 biomarker activity

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was evidenced at 6.4 ng/mL (normal value 0.03-0.06 ng/mL [23]) and ASM low by liquid chromatography <0.4 umol/L/h (normal value ≥ 2 umol/L/h [24]). The concentration of the biomarker lyso-SM-509 was found pathologically increased and ASM activity was found pathologically decreased. Results with which phenotype-genotype correlation is performed with NPD-A/B.

DISCUSSION

In this article, we report the case of a patient who, given her clinical complexity, absence of perinatal and family history, phenotypic heterogeneity, diverse clinical manifestations, possible differential diagnoses, inconclusive initial diagnostic tests and the suspicion of a rare genetic disease, a targeted clinical exome was requested, finding two variants, one of pathogenic clinical significance and the other probably pathogenic in the SMPD1 gene (compound heterozygous). Specific tests were requested to confirm the type of lysosomal deposit disease, among which it was evidenced that the concentration of the biomarker lyso-SM-509 was pathologically increased and the ASM activity pathologically decreased.

One of the main described types of this pathology, NPD-A, clinically characterized by onset in the neonatal period or early infancy with developmental delay, hepatosplenomegaly and rapidly progressing neurodegenerative disorders [1,6]. NPD-B also presents in childhood and is characterized by the appearance of hepatosplenomegaly, growth retardation, and lung disorders [2]. Both types have very low ASM activity [1,6].

Clinical exome results showed pathogenic variants in the SMPD1 gene, which encodes ASM [4]. In the SMPD1 gene, more than 180 causative variants have been identified, which lead to abnormal or defective formation of sphingomyelin phosphodiesterase, preventing the movement of lipids out of cells and ultimately leading to their accumulation within cells [5].

Once the pathogenic variants causing NPD have been identified in an affected family member, carrier testing for relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible. Similarly, it is possible to talk about prognosis, perform a complete genetic counseling, implement and initiate targeted treatments that reduce the morbidity and mortality associated with this pathology, due to the fact that current studies have molecules that can change the natural history of the disease and intervene in it.

CONCLUSION

NPD is characterized by hereditary deficiencies of the ASMlysosomal enzyme involved in the degradation of lipids and their products, leading to their accumulation and deposition in different organs such as the liver, spleen, lungs and brain [1,3]. It is an orphan disease that according to global statistics, both A and B affect 1 in 250,000 births [8]. In Colombia, a detailed epidemiological and population burden assessment of this disease is still lacking; however, progress is being made with the promotion of the report as a recognized orphan disease [9].

These diseases are characterized by autosomal recessive inheritance. NPD-A and NPD-B are caused by deleterious variants in the SMPD1 gene, which lead to abnormal or defective protein formation, preventing the movement of lipids out of cells, which ultimately leads to their accumulation inside cells [5]. Depending on the severity of the disease, individuals with this disease present with progressive hepatosplenomegaly, failure to thrive and neurological impairment.

Symptomatic and supportive management for NPD is the mainstay of treatment. Enzyme replacement therapies and gene therapies are undergoing trials and may become the mainstay of treatment in the future, as it aims to reduce the accumulated substrate by exogenous enzyme supply, an alternative approach is to decrease the substrate produced by inhibiting its synthesis or giving substrate reduction therapy [16]. In 2022, the FDA approved the first targeted therapy with xenpozyme infusion (olipudase alfa-rpcp) to treat the non-central nervous system manifestations of ASM deficiency in NPD A, B and A/B [21]. Currently in Colombia, there are no drugs approved for the treatment of this disease. Clinical trials are ongoing worldwide to obtain data on the safety of olipudase alfa in patients with ASM deficiency [18,19].

Given the advances in diagnostic aids, confirmatory methods and new pharmacological therapies, it is necessary to conduct more studies to better address this disease, increase screening, describe the population burden, raise awareness of the guild of health personnel to consider this pathology as a differential diagnosis to perform a good genetic counseling. Early identification of this disease is a priority through a complete clinical history and physical examination, knowing the family genetic risks, the importance of population screening and phenotype-genotype correlation in order to be able to talk about perspective, prognosis, follow-up and genetic counseling. With a defined and precise diagnosis, it is also possible to implement and initiate targeted treatments that reduce the morbidity and mortality associated with this pathology, bringing us closer to precision, anticipatory, preventive, predictive and participatory medicine.

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Contributions

JMSV - information search, topic review, writing, editing, submission.

LJMG - writing, editing and final revision of the manuscript.

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