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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 4

Personalized precision medicine of strategic health action in Niemann-Pick type A/B disease: Case report

Juan Manuel Sanchez-Vargas[1,3]*; Lina Johanna Moreno-Giraldo[2,3,4]

[1]Resident of Specialization in Pediatrics, Universidad Libre sectional Cali, Colombia.

[2]Pediatrics, MSc and PhD. Medical Genetics. Attached to the Universidad Libre sectional Cali, Colombia.

[3]Pediatric Research Group (GRINPED), Universidad Libre sectional Cali, Colombia.

[4]Neurogenetics and Metabolic Diseases Research Line (NEUROMET), Colombia.

***Corresponding Author: Sanchez-Vargas JM**

Resident of specialization in Pediatrics; Universidad Libre sectional Cali; Colombia. Pediatric Research Group (GRINPED), Universidad Libre sectional Cali, Colombia.

Email: juanmasanchezv@gmail.com

Received: Feb 06, 2022

Accepted: Apr 03, 2023

Published: Apr 10, 2023

Archived: www.jcimcr.org

DOI: www.doi.org/10.52768/2766-7820/2363

Abstract

Niemann-Pick Diseases (NPD) is lysosomal storage diseases caused by Acid Sphingo Myelinase (ASM) deficiency, which catalyzes the hydrolysis of Sphingo Myelin (SM) to ceramide and phosphocholine. As a result, the SM and its precursor lipids accumulate in the lysosomes of the cells of the reticuloendothelial system, which produces an abnormal functioning, leading to the inability to degrade macromolecules, forming intracellular inclusions that are deposited in different organs such as the liver, spleen, lungs and brain. There are 5 subtypes, NPD-A and NPD-B are caused by variants in the Sphingo Myelin Phosphor Diesterase 1 (SMPD1) gene, which lead to abnormal or defective protein formation, which prevents the movement of lipids out of cells. It has been described that NPD worldwide affects 1 in 120,000-150,000 people and is characterized by autosomal recessive inheritance. We present the case of a 20 month old lactating female patient, with a diagnosis of global developmental delay associated with chronic protein-calorie malnutrition, dysmorphic fasciae, and hepatosplenic syndrome. In the initial approach, infectious and lymphoproliferative diseases were ruled out. Given the clinical complexity of the patient, a targeted clinical exome was requested, finding two variants, one of clinical pathogenic significance and the other probably pathogenic in the SMPD1 gene (compound heterozygous). The enzymatic activity of lysosomal enzymes was requested, pathologically increased biomarker lyso-SM-509 was found, and pathologically decreased ASM activity. Results with which a phenotype-genotype correlation is made with the NPD-A/B. With a defined and precise diagnosis, it is possible to guide health actions, follow-up guidelines, heritability risk assessment through an index case in order to find other possible carriers, carry out complete genetic counseling, implement and start targeted treatments that reduce the morbidity and mortality associated with this pathology, given that there are currently several studies in different phases of research on molecules that may intervene in the natural history of the disease.

Keywords: Lysosomal storage disease; Niemann-Pick diseases; Sphingomyelin phosphodiesterase; Exome; Early diagnosis; Specific treatment; Molecular targeted therapy; Genetic counseling; Precision medicine; Prognosis.

Introduction

Niemann-Pick Diseases (NPD) makes a part of the group of lysosomal storage diseases. They are characterized by hereditary deficiencies of one or more lysosomal enzymes involved in the degradation of lipids and their products (Bajwa & Azhar, 2022). It is caused by Acid Sphingo Myelinase (ASM) deficiency, which catalyzes the hydrolysis of Sphingomyelin (SM) to ceramide and phosphocholine. As a result, the SM and its precursor lipids begin to accumulate in lysosomes. Lysosomes are cell organelles whose function is the catabolism of substances. The most abundant lysosomal enzymes are acid hydrolases. If there is a genetic defect in any of the structures that make up the lysosome, abnormal functioning will occur, leading to the inability to degrade macromolecules, resulting in their accumulation, forming intracellular inclusions [1]. The cells that mainly accumulate in 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, leading to hepatosplenomegaly, cytopenias, lung disease, and neurological symptoms [2].

These diseases are characterized by autosomal recessive inheritance. NPD-A and NPD-B are caused by missense variants in the sphingomyelin phosphodiesterase 1 (SMPD1) gene, in subband 1 or 4, band 5, region 1 of the short arm of chromosome 11. (11p15.4), which encodes ASM [3]. In the SMPD1 gene, more than 180 variants have been identified, which lead to abnormal or defective protein formation, which prevents the movement of lipids out of cells and ultimately leads to their accumulation within them [4].

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 three years of age. 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 a cherry red spot [5,6]. Type B (NPD-B) (MIM # 607616), known as the non-neuropathic form, presents in childhood, is described as less severe 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 spot and neurological symptoms [1]. Type C (NPD-C) (MIM # 257220), also known as the chronic neuropathic form, is caused by an intracellular failure in cholesterol transport. It can present at any age, has a heterogeneous clinical presentation, and manifests as infantile jaundice, hepatosplenomegaly, or isolated splenomegaly, symptoms that precede neurological 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 the Nova Scotia variant is phenotypically like type C. Finally, type E (NPD-E) is described, which is a non-neuropathic adult form. It is a less common variant of HPN in which the most common neurological manifestations include delayed cognitive or motor development, vertical supranuclear gaze palsy, ataxia, dysarthria, dysphagia, and dystonia [5,6].

Around the world, it has been described that HPN in general affects 1 in 120,000-150,000 people [2]. NPD-A and NPD-B types affect 1 in 250,000 births. The prevalence is high in Ashkenazi Jewish descent, where it affects 1 in 40,000 people [8]. In Colombia, there is still no consolidated population burden. NPD is part of the recognized orphan diseases and its reporting is being promoted [9]. In a 2021 national epidemiological bulletin on orphan diseases, it is described that 467 cases of endocrine, nutritional and metabolic diseases were reported, 9.4% of the total, however, without discrimination of these [10].

As the gold-standard to confirm or rule out NPD-A or NPD-B, ASM activity in leukocytes is measured. It has been shown that ASM activity in NPD-A is less than 5% of normal, so 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, performing sequencing of the SMPD1 gene [12]. The variant detected in the SMPD1 gene has previously been described in homozygosis as associated with HPN. Once the diagnosis is confirmed, liver enzyme measurements, spirometry, lung Computed Tomography (CT) to rule out interstitial lung disease, platelet count, high-density lipoprotein (HDL) cholesterol, and High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL), bone marrow aspirate, should be performedamong others, to confirm affectations in the target organ due to the accumulation of macrophages in lipid-loaded lysosomes. Similarly, a complete neurological examination should be performed, including a fundoscopy to look for the cherry-red spot in the macula [13,14].

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 enzyme deficient in Gaucher disease is glucocerebrosidase, which leads to the accumulation of glucocerebroside within cells instead of sphingomyelin. Tay-Sachs disease, although it does not present 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 can manifest as ataxia or other neurological symptoms [15].

Symptomatic and supportive management for NPD is the mainstay of treatment. It seeks to treat dyslipidemia, liver failure, thrombocytopenia, bleeding episodes, and complications of interstitial lung disease. On some occasions, patients may develop complications such as fulminant hepatic failure, respiratory failure, dementia, seizures, schizophrenia-like psychosis, severe thrombocytopenia, heart disease, and bone involvement [16].

The finding that there is a close link between neurodegenerative disorders and lysosomal storage disorders offers the opportunity for new therapeutic strategies. Drugs capable of efficiently enhancing protein clearance and slowing the progression of proteinopathies can be expected to be developed in the future, thus providing benefit for patients with lysosomal

storage disorder [17]. Enzyme replacement therapies and gene therapies are undergoing trials and may become the mainstay of treatment in the future [18]. Enzyme therapy aims to reduce the accumulated substrate by exogenous enzyme supply, an alternative approach is to decrease the produced substrate 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 the use of competitive inhibitors of the enzyme to enhance lysosomal activity. Since glucosylceramide is the first step in the synthesis of gluco-based glycosphingolipids, including glucosylceramide and gangliosides, synthase inhibitors would decrease the amounts presented to the lysosome for degradation [18]. Miglustat, an imino sugar, glucose analogue, and glucosylceramide synthase inhibitor, has been reported 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 [19].

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 ASM deficiency who are exposed to long-term treatment with this drug, started in December 2013 and ends in February 2024 [20]. Similarly, a prospective observational clinical trial is being carried out with 55 patients in France, which seeks to describe the outcomes in the lung, liver, and kidney after the use of olipudase alfa. It began in June 2022 and has an expiration date. Completion in January 2025 [21].

The needs of patients have driven efforts to improve diagnosis, access to therapies, and the development of basic and clinical research in lysosomal storage 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 US Food And Drug Administration (FDA)-designated products. In 2015, 243 diseases have at least one orphan drug approved, a small increase compared to the 200 diseases reported in 2010 [22]. In 2022, the FDA approved the first targeted therapy with xenpozyme (olipudase alfa-rpcp) infusion to treat the non-central nervous system manifestations of ASM deficiency in NPD A, B, and A/B [23]. Additionally, new technologies such as nanomedicine are being worked on to deliver drugs to the nervous system. Strategies are being developed to cross the blood-brain barrier and thus more efficiently ensure the transport of large molecules, such as enzymes and other proteins. Nanocarriers, nanomedicine tools that can be loaded with a variety of drugs, shielded from the environment, and delivered safely into the brain, are being studied. Effective design of nanocarriers targeted at brain therapies may guide future therapeutic interventions for the treatment of NPD-A, other lysosomal storage diseases, and could easily be extended to the treatment of Alzheimer's and Parkinson's diseases [24]. Precision medicine is key to continue carrying out studies and interventions and impacting the morbidity and mortality of patients with this type of pathology.

Case report

A 20-month-old lactating female patient, first pregnancy of an 18-year-old mother, pregnancy with irregular prenatal checkups, threatened abortion and repeated urinary tract infections. Product of non-consanguineous parents, with no history of genetic or metabolic diseases or familial congenital malformations. She was born at term with adequate weight, height, and neonatal adaptation. Subsequently, with global developmental delay associated with chronic protein-calorie malnutrition, low-volume anemia, dysmorphic fasciae, and hepatosplenic syndrome. Within the syndromatic approach, hematological, oncological, immunological and infectious causes of the condition 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, various clinical manifestations, possible differential diagnoses, inconclusive initial diagnostic tests, and suspicion of a rare genetic disease, a targeted clinical exome was requested, diagnostic aid which analyzes exons of a set of known coding genes of the genome that could justify the present symptoms and confirm a specific pathology.

Results

Two variants were found in the exome, one of clinical pathogenic significance and the other probably pathogenic 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 frameshift in exon 6, which causes the loss of the Thr residue at position 594, a variant that has previously been described in homozygous associated with NPD. 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 previously been described as homozygous and compound heterozygous in patients with HPN. 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 storage disease, among which it was evidenced that the activity of the lyso-SM-509 biomarker was 6.4 ng/ml (normal value 0.03–0.06 ng/mL [26]. and low ASM by liquid chromatography <0.4 µmol/l/h (normal value ≥2 µmol/l/h [25]. The concentration of the biomarker lyso-SM-509 was found to be pathologically increased and the activity of ASM was found to be pathologically decreased. Results with which a phenotype-genotype correlation was made with the NPD-A/B.

Discussion

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

Patient who presented symptoms and paraclinical results like those described in the literature. One of the main types of this pathology described, NPD-A, clinically characterized by its onset in the neonatal period or early childhood with developmental delay, hepatosplenomegaly, and rapidly progressing neurodegenerative disorders [5,6]. NPD-B also occurs in childhood and is characterized by the appearance of hepatospleno-

megaly, growth retardation, and lung disorders [1]. Both types have very low ASM activity [5,6].

Results of the clinical exome showed pathogenic variants in the SMPD1 gene, which encodes ASM [3]. In the SMPD1 gene, more than 180 variants have been identified, which lead to abnormal or defective protein formation, which prevents the movement of lipids out of cells and ultimately leads to their accumulation within them [4]. Nonsense variants, which are associated with NPD-A/B disease.

Once pathogenic variants causing NPD have been identified in an affected family member, carrier testing for relatives at risk of heritability and prenatal testing for a higher-risk pregnancy are possible. Also, it is possible to talk about prognosis, carry out a complete genetic counseling, implement and start targeted treatments that reduce the morbidity and mortality associated with this pathology, because with current studies the natural history of the disease can be changed, and it can be intervened.

Conclusion

NPD is characterized by hereditary deficiencies of one or more lysosomal enzymes involved in the breakdown of lipids and their products, leading to their accumulation and deposition in different organs such as the liver, spleen, lungs, and brain [5,2]. It is an orphan disease that according to global statistics, both NPD-A and NPD-B affect 1 in 250,000 births [8]. In Colombia, there is still no consolidated population burden; however, it is part of the recognized orphan diseases and its report is being promoted [9].

These diseases are characterized by autosomal inheritance. NPD-A and NPD-B are caused by missense variants in the SMPD1 gene, which lead to abnormal or defective protein formation, preventing the movement of lipids out of cells, ultimately leading to their accumulation within them [4]. They affect the child population, depending on the severity of this, individuals who suffer from this disease present with progressive hepatosplenomegaly, failure to thrive and neurological deterioration.

Symptomatic and supportive management for HPN is the mainstay of treatment. Enzyme replacement therapies and gene therapies are undergoing trials and may become the mainstay of treatment in the future, since it aims to reduce the substrate accumulated by exogenous enzyme supply, an alternative approach is to decrease the substrate produced inhibiting its synthesis or giving substrate reduction therapy [18]. In 2022, the FDA approved the first targeted therapy with xenpozyme (olipudase alfa-rpcp) infusion to treat the non-central nervous system manifestations of ASM deficiency in NPD A, B, and A/B [23]. 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 [20,21].

Given the advances in diagnostic aids, confirmatory methods and new pharmacological therapies, it is necessary to carry out more studies to better address this disease, increase screening, describe the population burden, and carry out an awareness of the union of health personnel to consider this pathology as a differential diagnosis to carry out a good genetic counseling. An early identification of this disease is a priority through a complete clinical history and physical examination, knowing family genetic risks, the importance of screening the population and phenotype-genotype correlation in order to talk about perspective, prognosis, follow-up and genetic counselling. 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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