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Niemann-pick Disease: A Diagnostic Approach, Evolution Clinic and Review

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Abstract

Introduction: Niemann-Pick disease is a rare autosomal recessive enzymopathy, which causes a deficiency in the activity of the acid sphingomyelinase enzyme found in liposomal cells, resulting in a defect in the degradation of sphingomyelin into ceramide - the product that makes up the lipid bilayer of the cells. In this way, it generates accumulation and deposition of sphingomyelin mainly in the liver, spleen, brain, bone marrow and lungs, whichcan cause hepatosplenomegaly, pulmonary/neurological diseases and cytopenia.

Case presentation: Male patient, 16 years old, seeks care at a health center, accompanied by his mother, due to the drop in school performance in the last year. According to school assessment, the patient presentsgradual cognitive impairment, in addition to dysarthria.

Discussion: The disease in this report is rare and can occur in both sexes, with incidence and clinical presentation varyingaccording to each subtype of the pathology. Due to its multisystem involvement, its clinical presentation can be nonspecific and make its diagnosis difficult.

Conclusion: It should be noted that this work aims to spread knowledge about this rare pathology, showing the importance of recognizing it in childhood so that the diagnosis can be madeas early as possible, bringing better survival for those affected.

Keywords: niemann-pick disease; hepatosplenomegaly; sphingomyelin; enzymopathy

Introduction

Niemann-Pick disease is a rare and widespread condition with autosomal recessive inheritance. It is considered serious, considering that it causes deposits of concentrated fat in the lysosomes, altering cellular functions and affecting tissues of various organs such as: brain,lung, liver, spleen and also the bone marrow. Despite presenting clinically similar conditions, biological differences bring classifications and subtypes of the disease, with types A, B, C1 and C2 being the best known. Why notThere is a cure for this clinical condition, expertise on the part of health professionals is necessary to identify and treat early, giving the patient the best possible prognosis.

About this disorder, Frieger (2023) says: Disturbances of lipid homeostasis in cells cause human diseases. Elucidating the underlying mechanisms and developing efficient therapies represent formidable challenges for biomedical research. Exemplary cases are two rare, autosomal recessive, and ultimately fatal lysosomal diseases historicallynamed "Niemann-Pick" after the physicians whose pioneering observations led to their discovery. Acid sphingomyelinase deficiency (ASMD) and Niemann-Pick type C disease (NPCD) are caused by specific variants of the

sphingomyelin phosphodiesterase 1 (SMPD1) and NPC intracellular cholesterol transporter 1 (NPC1) or cholesterol transporter genes. intracellular NPC 2 (NPC2) that disrupt homeostasis of two key membrane components, sphingomyelin and cholesterol, respectively. Patients with severe forms of these diseases experience visceral and neurological symptoms and succumbto premature death.

In the present study, the clinical case of a patient with Niemann-Pick, aiming to discuss epidemiology, diagnostic methods, classification and evolution. Related complications will also be addressed, as they affectdirectly on the patient's medical management and prognosis.

Case Presentation

Female patient, 22 years old, attends a university health centre, accompanied by her father, complainingof difficulties in daily and professional activities over the last six months. According to her father's report, the patient has suffered from cognitive loss and difficulty speaking. In Addition, Furthermore, the patient mentions atypical auditory and visual experiences, such as hearing her name being called and seeing shadows at night.

Physical exam

Lung and heart auscultation: Normal Abdomen: No pain, with bowel sounds present and liver palpable 5 cm from theright costal margin. Spleen also palpable. Neurological assessment: Ataxic gait and supranuclear horizontal gaze palsy, withoutother neurological changes.

Laboratory and Imaging Exams

No changes in the liver or coagulation profile. Skull tomography: Cerebellar atrophy and reduction in the volume of the corpus callosum. Due to psychotic symptoms, cognitive deficit and neuroimaging findings, the diagnostic hypothesis of Niemann-Pick disease type C (NPC) was made. Referral for specialized neurological evaluation confirmedthe suspicion. A skin biopsy with Filipin test was positive. Subsequent genetic testing identifiedmutations in the NPC1 gene, confirming the diagnosis of NPC.

Discussion

Niemann-Pick Disease (NPD) is a pathology of genetic origin characterized by the occurrence of neurovisceral lysosomal deposits. This condition progresses with different degrees of cellular infiltration in different organs such as the liver, lungs and brain, leading to organic aggression and culminating in states of insufficiency as a reflection of the presence of lipid deposits (BRASIL, 2020). The different presentations of DNP are divided into two groups: DNP types A and B (both resulting from acid sphingomyelinase deficiency) and DNP types C and D (arising from the absence of transport proteins produced by the NPC1 or NPC2 genes) (SCHUCHMAN, 2017). The spectrum of manifestations is broad, varying according to the clinical forms and the intensity of gene expression. Type A DNP can present with hydrops fetalis in the most severe perinatal forms or present with non-specific symptoms such as vomiting and diarrhoea in the first months of life. After a few months, findings such as hepatosplenomegaly, delayed neurocognitive development and significant neurodegenerative impairment emerge. on a progressive basis, so that a considerable portion of patients die between the second or third year of life (VANIER, 2013; SCHUCHMAN, 2017).

Type B DNP differs from type A in that it is typically non-neuropathic and has a greater tendency to chronicity. Added to this is the greater variability of clinical manifestations, both in intensity and quantity. The most common symptoms of type B are hepatomegaly and epistaxis, and there may also be impairment of lung cytoarchitecture, dyspnoea, visual changes and death in childhood. The tendency towards chronicity allows for greater survival for those with the condition, however, diagnoses tend to be later and difficult to define, as manifestations may be less evident and non-specific (VANIER, 2013). Type C is typically a fatal prenatal condition, but it can also affect new-borns, with a clinical picture marked by delayed neuro-psycho motor development and organic infiltration (especially in the liver and lung tissues). In some cases, the disease can occur late, in adult life, as a neurodegenerative condition with a tendency to chronicity. The estimated prevalence is 1:100,000 on the European continent.

Currently, there is still not enough information in the Brazilian literature to allow estimating the prevalence of type C DNP in Brazil (BRASIL, 2020). Diagnosis based on clinical findings is often difficult because it is a rare condition and little known by the general medical population. This is combined with the limited literature available and the lack of professionals with experience in managing this condition in the Brazilian scenario (MS protocol, 2020). Confirmation of the diagnosis is established

by verifying the deficiency of leukocyte acid sphingomyelinase in the bone marrow or genotyping for types A and B (VANIER, 2013). Genetic testing of mutations presents in the NPC1 and NPC2 genes allows confirmation of type C DNP (Patterson, 2000). Peripheral smear analysis is a possible, accessible and lower-cost way that also allows diagnosis (KARAMAN, 2011). Treatment requires a broad, individualized and multidisciplinary approach to the patient. The main targets are the relief of limitations derived from the disease, optimization of quality of life and prevention of complications. Specific therapy for DNP is still in experimental stages and lacks further evidence for widespread use and is therefore not widely recommended (BRASIL 2020; VANIER,2013).

The approach to these patients consists mainly of medication strategies for symptomatic relief, motor and respiratory physiotherapy, speech therapy, occupational therapy, psychological support, genetic counselling and surgical procedures (BRASIL, 2020; VANIER, 2013). People with DNP are susceptible to a variety of complications, the most common of which are respiratory and neurological. That said, it is essential that the care of these patients also includes specific prophylaxis for pulmonary infections, antibiotic therapy (when appropriate) and anticonvulsants. Progressive neurological impairment can affect swallowing and increase the risk of broncho aspiration and, therefore, it may be necessary to perform a definitive gastrostomy (BRASIL, 2020; VANIER, 2013).

In the present study, the objective is to elucidate the main aspects pertinent to the characterization of the pathology, covering the epidemiological, clinical, diagnostics and therapeutics. The relevance of this discussion is based on the high lethality associated with DNP and the uniqueness of this disease, an uncommon genetic condition, whose early diagnosis and intervention can directly interfere with the clinical outcome of its sufferers.

Conclusion

Acid Sphingomyelinase Deficiency (ASMD; alternatively known as Niemann-Pick Disease Types A, B, and A/B, OMID# 257,200 and 607,616) is an ultra-rare multisystem genetic disorder caused by pathogenic variants of the SMPD1gene and its exact pathophysiology *is* insufficiently understood (GEBERHIWOT T et al, 2023), is characterized by hepatosplenomegaly, thrombocytopenia, interstitial lung disease and dyslipidaemia with possible resulting premature cardiac and vascular disease, in the absence of evident neurological involvement. Bleeding episodes are common in part due to complications of thrombocytopenia and/or abnormal platelet function. Additional manifestations of chronic visceral ASMD disease may include chronic lung infections, anaemia and leukopenia, delayedgrowth and puberty, osteopenia with increased risk of fracture, and progressive liver fibrosis leading to liver dysfunction or failure (MCGOVERN MM et al, 2021). ASMD is not yet curable, but it is a treatable condition. Optimal disease management requires a multidisciplinary, multidisciplinary team based in a specialist centre, in close liaison with community care providers. The basis of therapy is to address existing/imminent complications and symptom management.

Once widely available on the market, enzyme replacement therapy (ERT) as a disease-modifying agent is expected to slow the progressionof non-CNS manifestations (GEBERHIWOT T et al, 2023). In this article, we describe the spectrum of manifestations of the disease, as well as its genetic nature and unknown pathophysiology. The results of this study reflect the atypical and unique characteristics of this disease, corroborate its rare nature as a condition among the existing universe of comorbidities, and highlight the complexity of its diagnosis and adequate follow-up.

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