ARTÍCULO DE REVISIÓN

NIEMANN-PICK DISEASE

Enfermedad de Niemann-Pick

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ABSTRACT

Niemann-pick disease (NPD) is a group of lysosomal storage diseases that overlap in some clinical features such as hepatosplenomegaly and/or central nervous system involvement. There are three distinctive types of NPD; two that are an acid sphingomyelin deficiency (types A and B), and a cholesterol-binding protein disfunction (type C). Type A patients present hepatosplenomegaly and neurodegeneration, while type B patients also have hepatosplenomegaly and lungs alterations, but no sign of central nervous system involvement. Type C patients have different clinical features depending on the age of disease onset.

RESUMEN

La enfermedad de Niemann-pick (NPD) compone un grupo de enfermedades de almacenamiento lisosomal que se parecen en cuanto a sus manifestaciones clinicas, como hepatosplenomegalia y/o degeneración del sistema nervioso central. Hay tres tipos de NPD; dos que presentan una deficiencia de esfingomielinasa (tipos A y B), y uno que presenta una disfunción en proteínas de transporte de colesterol. Los pacientes con tipo A presentan hepatosplenomegalia y neurodegeneración, mientras que los pacientes con tipo B también presentan hepatosplenomegalia más alteraciones en los pulmones, pero sin signos de afectación neurológica. Los pacientes con tipo C tienen diferentes manifestaciones clinicas, dependiendo de la edad en la que se presenta la enfermedad.

1. INTRODUCTION

Niemann-Pick disease (NPD) is a genetic lysosomal storage disorder that accumulates different types of lipids in specific organs and structures. It was first described by the german pediatrician Albert Niemann in 1914, mistaking the patient's symptoms with Gaucher disease (another lysosomal storage disorder). The patient was an 18-year-old female jew with hepatosplenomegaly and a progressive neurogenerative disorder leading to death weeks after being incorrectly diagnosed with Gaucher disease.[1] In 1927, pathologist Ludwig Pick analyzed children that presented neurodegenerative disorders[1,2] and the same symptoms Niemann described in his patient. He differentiated the disorder from Gaucher disease naming it Niemann-Pick disease.[1] Allen Crocker and Roscoe Brady described the biochemical aspects of NPD and classified it in four types: A, B, C and D in 1961 and 1966.[1,3]

NPD is classified according to the genetic mutation and clinical features. NPD types A and B are caused by an acid sphingomyelinase (ASM) deficiency due to a mutation in the SMPD1 gene. NPD type A and B are differentiated by severity and presence or absence of neurological symptoms.[4] NPD types C and D are caused by a deficiency involving lysosomal cholesterol-binding proteins and mutations in NPC1 or NPC2 genes.[5,6] NPD type D is considered a variant of type C, therefore they are both contemplated as type C.[1]

NPD is inherited in an autosomal recessive manner. ASM is produced from the SMPD1 gene located in 11p15.4, inherited from the maternal chromosome. The degree of clinical manifestations depends on the type of SMPD1 mutation (more than 180 mutations have been found in this gene). NPD type A has a global prevalence of 1:250,000 newborns, but there is a higher incidence in Ashkenazi Jews (1:40,000). NPD type A is the most frequent form of NPD, presented in 75% of cases.[2] There are 3 specific mutations that are seen in 90% of Ashkenazi Jews with NPD type A (p.Arg496Leu, p.Leu302Pro and c.996delC).[2,3] Another specific mutation (deltaR608) was found in 15-20% of NPD type B individuals in Western Europe and North America.

NPD type C is due to a mutation in either NPC1 (95% of cases) or NPC2 (5% of cases) genes that encode for NPC1 and NPC2 cholesterol-binding proteins.[6,7,8] NPC1 gene is mapped from chromosome 18q11-q12 with more than 300 mutations. Mutant allele p.I1061T is the most frequent and correlates with a juvenile neurologic onset. NPC2 gene is mapped from chromosome 14q24.3 with one mutation (E20X) that appears frequently, even though many others have also been described. The true prevalence of NPD type C is unknown, but it is estimated to be between 0.66 and 0.83 per 100,000 births.[8]

2. DISEASE OVERVIEW

NIEMANN-PICK TYPE A AND B

SMPD1 gene mutation causes an acid sphingomyelinase (ASM) deficiency. ASM is a lysosomal enzyme that maintains sphingolipid homeostasis. It catalyzes the hydrolytic cleavage of sphingomyelin producing phosphocholine and ceramide. Sphingomyelin is a major component of cell membranes and myelin shed, and the principal accumulating lipid in patients with Niemann-Pick disease (NPD) types A and B.2 Insufficient ASM activity leads to sphingomyelin accumulation in the monocyte-macrophage system and other cell types (hepatocytes, dermal fibroblasts, vascular endothelial cells, vascular smooth muscle cells, perineurium, and Schwann cells).[2,4]

Clinical features in types A and B are due to lipid abnormalities in cell membranes. Sphingomyelin and other substrates can build up over

time and cause cell and tissue damage. The primary organs affected in all ASM-deficient patients are the liver, spleen and lungs.[2,4]

Pathologic analysis reveals lipid loaded cells (foam cells) in the liver, spleen, lungs, lymph nodes, adrenal cortex and bone marrow. Foam cells have a "bubbly" appearance when histologically analyzed, as we see in **Figure 1**. In the liver, foam cells are present in hepatocytes, Kupffer cells and bile duct epithelium. Liver biopsies reveal some degree of fibrosis, which usually leads to cirrhosis. In the lungs, lipid filled macrophages and neutrophils can be found.[4]

NPD type A patients usually present an atrophic brain. Ganglion cells are swollen and present a pale and vacuolated cytoplasm. There is a loss of cells in the cerebral and cerebellar cortices and some areas of white matter show demyelination. Foam cells are present in leptomeninges, tela choroidea, endothelium, and perivascular spaces of cerebral blood vessels.[4]

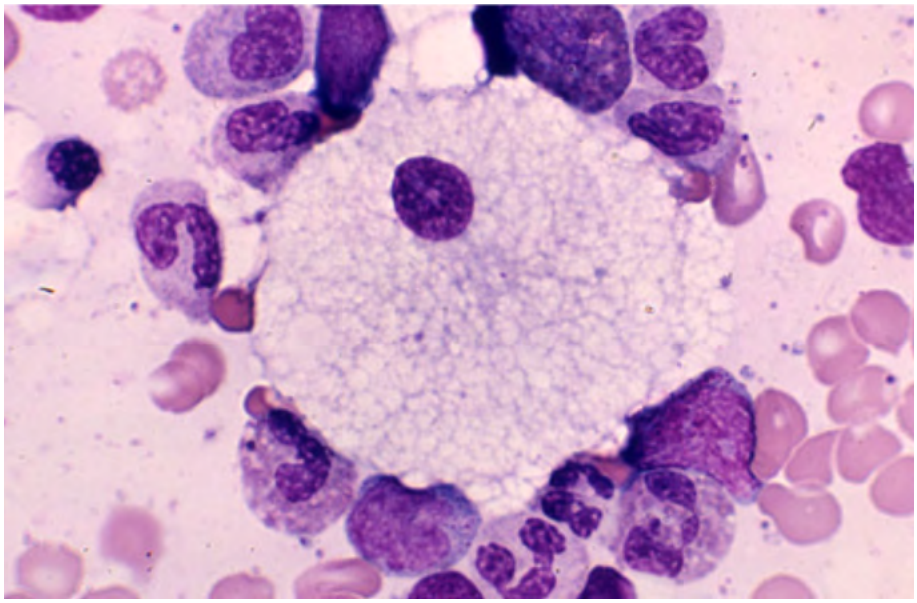

FIGURE 1. *Niemann-Pick cell. Characteristic foamy macrophage, cell contains sphingomyelin and cholesterol.*[9]

3. NIEMANN-PICK TYPE C

The biochemical defect in type C NPD is an abnormality in cholesterol transport due to a mutation in NPC1 or NPC2 gene.[1-8,10] Cholesterol-binding proteins (NPC1 and NPC2) become inefficient and fail to transport cholesterol out of the lysosomes.[5,6,8] Cholesterol and sphingomyelin accumulate in lysosomes.[10] Cholesterol is an important substance needed in cell membranes, failure to transport cholesterol leads to membrane cholesterol deficiency ending in dysfunction and apoptosis.[6]

Lipid accumulation is different in the brain than in other organs. The liver and spleen accumulate unesterified cholesterol and sphingomyelin. This accumulation explains the dysfunction of intracellular metabolism of lipids. The brain accumulates glycosphingolipids that causes neurologic dysfunction and as the disease progresses neuronal death becomes prominent.[6,8] The participation of cellular cholesterol transport abnormalities in the pathophysiology of NPD type C remains unknown.[8]

4. CLINICAL FEATURES

Type A Niemann-Pick disease (NPD) has an early onset. Patients present hepatosplenomegaly and failure to thrive within the first year of life. **Figure 2** shows a cherry-red spot in the maculae that is presented in 50% of the patients.[1,2] NPD type A is characterized by a progressive neurodegenerative course with profound hypotonia. It can be diagnosed within the first 6 months of life if hepatosplenomegaly is present. From month 6 to 15 development plateaus. There is a rapid progression of psychomotor deterioration and most patients never develop the ability to sit independently.[2] Death mostly occurs during the third year of life.[1,2,7]

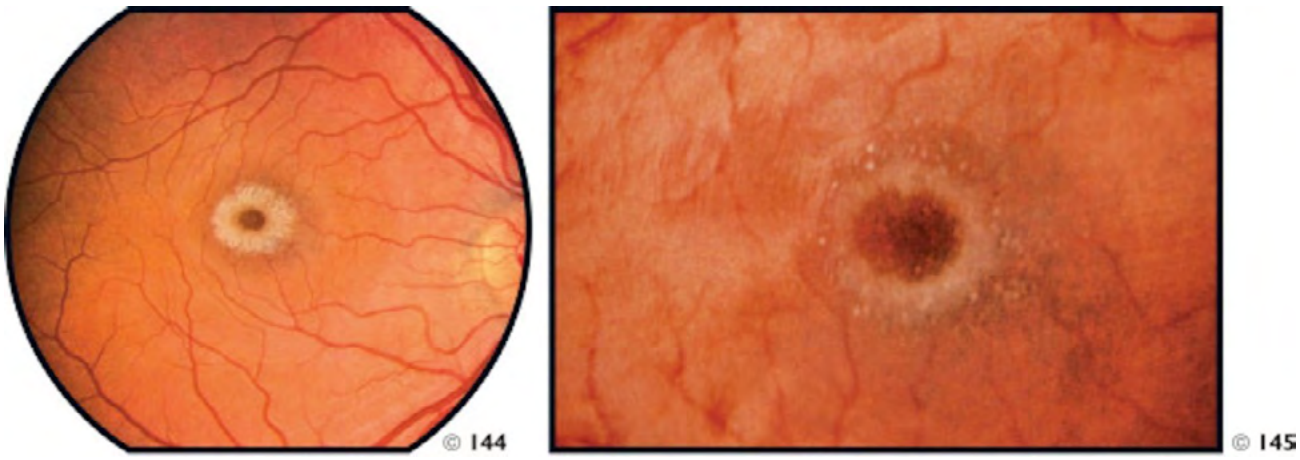

FIGURE 2. *Typical cherry-red spot on macula.*[11]

Type B NPD has a variable onset[5] and there are no signs of central nervous system involvement.[2] This makes it less severe than type A.[7] Hepatosplenomegaly is present and accompanied by liver failure. The lungs are frequently involved in type B NPD, therefore pulmonary function is compromised. A cherry-red spot can be identified in a few cases.[2] There is sphingomyelin accumulation in bone marrow and lungs. There is a high chance the patient can survive to adulthood.[5,7]

The classic presentation of NPD type C occurs in mid-to-late childhood with the subtle onset of ataxia, vertical supranuclear gaze palsy, dementia, dystonia and seizures, and it may present at any age. Neonates can present ascites (buildup of fluid in the abdominal cavity) and lung or liver infiltration. Many infants die at this stage and those who survive are hypotonic and present delayed psychomotor development.[6] Organomegaly is present in infants, but then decreases over time.[8] Adolescents and adults may present neurological disease with a slower progression. Adults are more likely to show psychiatric symptoms (dementia).[6] Lifespan of NPD type C patients also varies from a few days until over 60 years of age, although the majority of patients die between ages 10 and 25.[8]

5. DIAGNOSIS

Because Niemann-Pick disease (NPD) is rare, diagnosis may be missed during the initial stage of the disease. NPD should be suspected in patients with hepatosplenomegaly, development delay and a cherry-red spot on macula. Diagnosis is difficult to accomplish with clinical presentation and has to be confirmed over biochemical or molecular genetic testing.[4]

Quantifying acid sphingomyelinase (ASM) activity in leukocytes or fibroblast is the standard confirmatory diagnostic procedure. Sequencing the SPMD1 gene is also an option to confirm the diagnosis, but it should not be used as a first line diagnostic indicator. Presence of vacuolated cells in peripheral blood or bone marrow is also indicative of the disease only if there is deficient enzyme activity. The differential diagnosis of ASM deficiency include Gaucher disease and type C NPD.[2]

Clinical diagnosis of NPD type C is easy in patients who have the typical symptoms (splenomegaly, ataxia, and supranuclear vertical gaze palsy). Although clinical presentations may vary with age. The demonstration of impaired intracellular cholesterol transport and homeostasis is the primary diagnostic test for NPD type C. This test requires living cells (skin fibroblast). Fibroblasts are cultured, fixed, stained and examined using fluorescence microscopes. Gene testing is advised with every new diagnosed patient to confirm diagnosis and identify type of mutation.[8]

In neonates and young infants NPD type C should be differentiated from idiopathic neonatal hepatitis. In children and adults other conditions that cause cerebellar ataxia, dystonia, cataplexy and supranuclear gaze should be considered.[8]

6. TREATMENTS

There are no curative therapies for patients with Niemann-Pick disease (NPD). Treatment is limited to symptom management and supportive care.[4,8] Experimental treatments like bone marrow transplant and enzyme therapy are yet to be approved as a method to cure NPD.[4]

CONCLUSION

Niemann-Pick disease (NPD) is a rare lysosomal storage disorder caused by a genetic mutation inherited in an autosomal recessive matter. It is a progressive and life-threatening disease. Today, we know that there are three distinctive types of NPD: A, B and C. NPD type A and B are caused by an acid sphingomyelinase deficiency and type C is caused by a cholesterol-binding protein disfunction.

NPD is characterized by having lipid accumulations inside of lysosomes and/or cells. The lipid accumulations cause clinical manifestations such as organomegaly and neurodegeneration. There is no cure for NPD and the only treatment includes symptom management. Death is highly anticipated with this disease and patients can only receive palliative care.

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