Niemann–Pick Disease: From Genetic Defect to Clinical Manifestation

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Key points:

- Introduction
- Disease mechanism: Type A and B
- Disease mechanism: Type C
- Clinical presentation
- Diagnostic workup
- Outlook and Treatment

Introduction

Niemann–Pick disease (NPD) is a rare autosomal recessive lysosomal storage disorder characterized by abnormal accumulation of lipids, including sphingomyelin, cholesterol, and glycosphingolipids, within lysosomes.[1–3] The disease results from defects in lipid degradation or intracellular lipid transport and is primarily classified into acid sphingomyelinase deficiency (ASMD; Niemann–Pick disease types A and B) and Niemann–Pick disease type C, a disorder caused by impaired cholesterol trafficking.[4–7]

NPD has an estimated global incidence of approximately 1 in 250,000 live births, although its frequency varies among populations. Certain populations, particularly individuals of Ashkenazi Jewish ancestry, have a higher prevalence of pathogenic variants associated with ASMD, especially Niemann–Pick disease type A.[4]

The clinical spectrum of NPD is broad, ranging from severe infantile neurovisceral disease to later-onset forms with predominant visceral or neurological involvement. Due to its rarity and overlap with more common hepatic, hematological, and neurological disorders, diagnosis is often challenging and may be delayed. Early recognition through biochemical assays and molecular genetic testing is crucial for accurate diagnosis, appropriate management, and genetic counselling.[1,2]

Disease Mechanisms

Types A and B:

Niemann–Pick disease types A and B are caused by reduced activity of acid sphingomyelinase (ASM), an enzyme encoded by the SMPD1 gene on chromosome 11p15.4.[1,4] Under normal conditions, ASM breaks down sphingomyelin within lysosomes; however, deficient enzyme activity results in progressive sphingomyelin accumulation in cells of the monocyte–macrophage system, liver, and other affected tissues. Type A represents the more severe form, with almost absent ASM activity (<1%), leading to early-onset neurovisceral disease, rapid neurological decline, and shortened survival. Type B is associated with greater residual enzyme activity and follows a slower course, with clinical features mainly involving visceral organs, including hepatosplenomegaly, pulmonary disease, and dyslipidemia, while neurological involvement is uncommon.[4]

Type C:

Niemann–Pick disease type C differs from types A and B because the underlying defect involves intracellular cholesterol transport rather than sphingomyelin degradation. It is most commonly caused by variants in the **NPC1** gene (approximately 95% of cases) and less frequently by **NPC2** gene variants (approximately 5%).[2] The NPC1 and NPC2 proteins play an important role in moving cholesterol out of late endosomal and lysosomal

compartments. When this pathway is disrupted, unesterified cholesterol along with other lipids, including sphingomyelin and glycosphingolipids, accumulates within lysosomes.[1,2] This abnormal lipid storage particularly affects neurons and contributes to the progressive neurological manifestations characteristic of type C, such as cerebellar ataxia, cognitive decline, dystonia, and vertical supranuclear gaze palsy.[2,5]

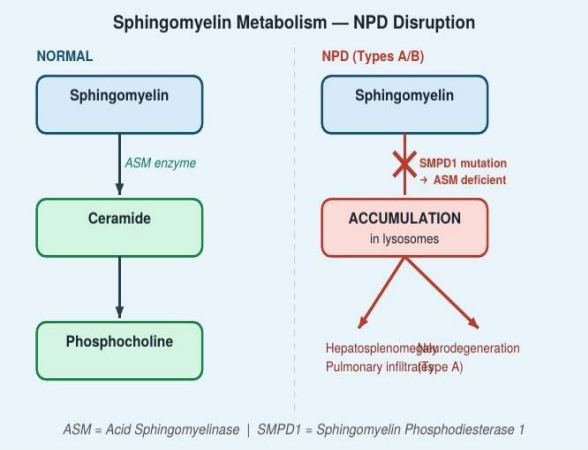


Figure 1: *Disrupted sphingomyelin catabolism pathway in NPD Types A & B. A.*[4]

Diagnostic Workup

Diagnosis of Niemann–Pick disease types A and B is based on demonstrating reduced acid sphingomyelinase (ASM) activity, usually measured in peripheral blood leukocytes or cultured fibroblasts. Confirmation is achieved through identification of pathogenic variants in the SMPD1 gene.[1,4] Bone marrow examination may show lipid-filled foam cells (storage macrophages), although this finding is not specific and should be interpreted alongside biochemical and genetic results.

The diagnosis of Niemann–Pick disease type C can be more challenging due to its variable clinical presentation. Filipin staining of cultured fibroblasts has traditionally been used to demonstrate intracellular accumulation of unesterified cholesterol; however, its role has increasingly been complemented by plasma oxysterol biomarker testing and NPC1/NPC2 gene sequencing.[2,6] These molecular and biochemical approaches have improved diagnostic accuracy, particularly in patients presenting later in life. Neuroimaging findings, including cerebellar atrophy in advanced disease, may provide additional supportive information but are not diagnostic on their own.[6]

Outlook and Treatment

Currently, there is no curative therapy for Niemann–Pick disease, and management focuses on slowing progression and controlling complications. **Miglustat** is approved in Europe for Niemann–Pick disease type C and may delay neurological deterioration.[2] **Olipudase alfa**, a recombinant acid sphingomyelinase replacement therapy, was approved by the FDA in 2022 for non-neurological manifestations of acid sphingomyelinase deficiency (types A and B), improving visceral involvement such as hepatosplenomegaly.[3] Supportive care includes management of respiratory complications, dyslipidemia, and nutritional issues. Emerging therapies, including gene-based approaches, remain under investigation.[4] Prognosis varies by subtype, with type A causing severe early disease, type B showing a slower progression, and type C being associated with progressive neurological decline.[2,5]

Conclusion

Niemann–Pick disease is a rare but clinically significant group of lysosomal storage disorders that may remain underdiagnosed due to variable presentation and overlap with more common conditions. It should be considered in patients with unexplained hepatosplenomegaly, thrombocytopenia, or progressive neurological symptoms when other causes have been excluded. Early diagnosis through biochemical and molecular testing allows appropriate management, genetic counselling, and monitoring of disease-related complications. Long-term neurological and neuropsychological follow-up is important, particularly in patients with central nervous system involvement.[7]

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