Title: Niemann-Pick Disease Subtypes and Ocular Manifestations

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Introduction: Niemann-Pick Disease (NPD) is an autosomal recessive disease that affects one in 250,000 individuals. It is associated with a partial or complete deficiency in acid sphingomyelinase, an enzyme that converts sphingomyelin into ceramide, a molecule essential for cell structure. The accumulation of sphingomyelin in lysosomes leads to cellular damage and dysfunction of the spleen, liver, bone marrow, and brain. Notably, this can present as ocular manifestations including cherry-red spots, macular halos, and corneal deposits. Because of these hallmark signs and symptoms, the role of the ophthalmologist is critical in diagnosing and managing NPD. As such, the purpose of this research is to discuss the pathophysiology, clinical features, ocular and nonocular manifestations, and management of NPD.

Pathophysiology: NPD can be divided into four distinct types – A, B, C, and E. Both NPD-A and NPD-B are associated with a mutation in SMPD1 (chromosome 11p15) resulting in a complete absence of acid sphingomyelinase. Both have similar manifestations including hepatosplenomegaly and macular cherry-red spots. NPD-A, the most severe of the four types, most commonly occurs in infancy presenting with feeding difficulties and loss of early motor skills. NPD-B presents in either infancy or childhood with skeletal abnormalities and thrombocytopenia. NPD-C is due to a defective protein genetically encoded by NPC1 (chromosome 18q11-12) and NPC2 (chromosome 14q24.3). NPD-C's clinical features are dependent on the onset which can occur in utero or throughout adulthood. From hydrops fetalis and ascites in-utero to ataxia, cognitive deterioration, and aspiration pneumonia in adulthood, NPD-C has the widest range of manifestations of the four types. Notably, vertical saccades gaze palsy is the hallmark symptom. NPD- E is the least common form that presents with neurological disease in adulthood.

Management: For all types of NPD, supportive care including physical therapy, occupational therapy, and regular nutritional assessment is vital for management. For NPD-A and NPD-B, olipudase-alfa (Sanofi) is a promising enzyme replacement therapy that can be of benefit due to its improvement of pulmonary function and reduction of spleen volume. For NPD-C, Miglustat (Janssen) has been shown to be of benefit by delaying neurological regression. Several other drugs are in clinical trials with promising potential that could improve clinical outcomes in patients with NPD.

Conclusion: NPD is a multi-system disease that requires a multidisciplinary team for management. On this team, the ophthalmologist can play a vital role by identifying key ocular manifestations of NPD early in the disease process and can spearhead the treatment course to minimize the risk of morbidity and mortality of patients with NPD.