

# Niemann-Pick Disease (Acid Sphingomyelinase Deficiency)

## Background

Niemann-Pick Disease is a lysosomal storage disorder in the sphingolipid degradation group. There is a deficiency in the production of acid sphingomyelinase (ASM), the enzyme needed to metabolize sphingomyelin (a lipid). This leads to an accumulation of sphingomyelin and cholesterol in lysosomes. Excess sphingomyelin presents as fatty deposits on the liver, spleen, lungs, and in bone marrow, giving them a foamy, swollen appearance. These foamy cells, known as Niemann-Pick Cells, are the histological hallmark of Niemann-Pick Disease. Niemann-Pick is also known as Acid Sphingomyelinase Deficiency (ASM Deficiency) and has three clinical subtypes (A, B, C). The incidence of Niemann-Pick is 1 in 248,000 across all ethnicities. Type A has a higher frequency in people of Ashkenazi Jewish descent (incidence of 1 in 40,000; carrier frequency of 1 in 80). Type B is more common in the Maghreb region of Northern Africa, Saudi Arabia and Turkey.

## Clinical

Type A is defined by progressive neurological involvement, which is usually established within the first few months of life. Type A is a more severe disorder than Type B. Early symptoms include hepatosplenomegaly, recurrent vomiting, irritability, and chronic constipation. Developmental delay (infants do not progress to milestones beyond 10 months) and progressive weakness occur. Feeding becomes difficult as disease progresses, contributing to physical weakness. As the disease progresses, there is progressive failure to thrive, spasticity, ataxia, and myoclonic jerks. Characteristic cherry red spots on the macula, as well as corneal clouding, appear. Pulmonary infections are common and hospitalization may be necessary. Death typically occurs by three years of age.

Type B is not associated with neurological involvement. Symptoms can present at any age, even into adulthood. There is extensive involvement of the spleen, liver, and lungs. Common symptoms include hepatosplenomegaly, pulmonary insufficiency and infections, significantly stunted physical growth, delayed onset of puberty, and increased cholesterol levels. Patients may feel full sooner due to organomegaly, so supplements may be indicated to promote growth. Older patients may experience exercise intolerance. Annual pulmonary function tests are recommended. Bone age is delayed approximately 2.5 years behind chronological age. One third of these patients have cherry red spots on their macula. Patients with Type B should avoid contact sports due to concern of splenic rupture.

Niemann-Pick A and B are clinically distinguished from Type C. Niemann-Pick Type C results from a defect in cholesterol transport. Newborn screening for Type C is not available at this time.

## Testing

The diagnosis of Niemann-Pick Disease is made through enzyme assay analysis. The activity level of acid sphingomyelinase is measured in the peripheral blood using white blood cells or cultured fibroblasts. Gene analysis is available for the sphingomyelinphosphodiesterase 1 (SMPD1) gene, located on chromosome 11p15.1-p15.4. This can be useful in distinguishing between Type A and Type B. Type A has three common mutations (L302P, R496L, fsP330), which account for 90% of cases and are associated with the severe infantile form in the Ashkenazi Jewish population. A milder form of Type B is associated with the mutation deltaR608. Mutation analysis is also useful in genotype-phenotype correlation. Prenatal diagnosis is available via DNA analysis. Disorders with similar presentations include Gaucher Disease and GM1 gangliosidosis.

## Treatment

Current treatment involves symptom management. Fatty deposits on the liver may indicate the need for a transplant. Frequent meals are beneficial in promoting growth. Type B patients with pulmonary disease may become oxygen dependent. Splenectomies are contraindicated as they can lead to further deterioration of lung function. Treatment and follow-up care should be under the direction of multidisciplinary medical team that should include a metabolic geneticist trained in lysosomal storage disorders.

Hematopoietic stem cell transplantation has been attempted but it is not a proven treatment at this time. Enzyme replacement therapy is being tested in clinical trials, but it is not currently available as treatment for Niemann-Pick.

## Inheritance

Niemann-Pick Disease (chromosome 11p15.4) follows an autosomal recessive inheritance pattern; affected patients have two copies of a disease gene (or mutation). People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder.

As with all genetic diseases, genetic counseling is appropriate to help families understand recurrence risks and ensure that they receive proper evaluation and care.

## References

Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly W, Valle D, eds. *The Metabolic and Molecular Basis of Inherited Disease*. 8th Edition, 2001. McGraw-Hill. Chapter 136.