

NIEMANN PICK DISEASE

INTRODUCTION

Niemann Pick disease is an autosomal recessive genetic disorder that results from defects in acid Sphingomyelinase. Types A and B are due to Sphingomyelinase deficiency while Type C is a lipid trafficking defect causing cholesterol to accumulate in the liver and spleen. Niemann Pick disease is a form of sphingolipidosis, a subgroup of lysosomal storage disorders. The diagnosis is established by markedly decreased Sphingomyelinase activity in nucleated cells.

NORMAL RANGE

Sphingomyelinase (nmol/hr/mg)	Remarks
>3	Normal activity
1.5-3	Possibility of carrier state likely
<1.5	Deficient activity

CLINICAL PRESENTATION

Type A (Acute Neuropathic Form)

- Neonatal period is usually normal
- Vomiting or diarrhea or both usually appears in the first week of life.
- Progressive failure to thrive by 3-4 months of age and sometimes earlier
- Hepatosplenomegaly and Lymphadenopathy
- Hypotonia, progressive loss of acquired motor skills, lack of interest in the surroundings by 5-10 months of age
- A cherry red spot in the retina, but may not be present until an advanced stage
- Seizures rare
- Death usually occurs between 1.5-3 years of age.
- Have little or no sphingomyelinase activity (less than 1% of normal)
- Cases with a milder systemic involvement, slightly protracted onset of neurological symptoms and slower course are also observed.

Type B (Non- Neuropathic)

- Most presenting sign is Splenomegaly or Hepatosplenomegaly in late infancy or childhood
- Can present from birth until late adulthood
- Risk of splenic rupture
- A small number of patients develop liver failure and may require liver transplantation
- Pulmonary involvement is often the main complaint in adults. Pulmonary disease is progressive and may range from dyspnea on exertion (frequent) to oxygen dependency.
- Enlarged organs and pulmonary complications can cause cardiovascular stress and lead to heart disease.

- In children, retarded body growth is a common finding between the ages of 6 - 16 years.
- Skeletal age and puberty are often delayed.
- Joint/limb pain, bruising, headache, abdominal pain and diarrhea are also observed
- Do not have neurological involvement and are intellectually intact.
- Sphingomyelinase activity is approximately 10% of the normal.

Type C (NPD-C)

- Autosomal recessive lipid storage disorder
- Mutations seen in NPC1 & NPC2 genes
- Progressive neurodegeneration

Type D (NPD-D)

- Genetic isolate from Nova scotia
- Biochemically & clinically indistinguishable from NPD-C
- New terminology is NPD-C1

Type E & F (NPD-E & NPD-F)

- Adult onset
- Insidious with slower progression

Intermediate form of Sphingomyelinase deficient Niemann Pick Disease

- Heterogeneous category
- Some patients closer to Type A with a late infantile, juvenile or adult neurological onset
- Such patients have slow progressive disease that may include cerebellar ataxia, extrapyramidal involvement or psychiatric disorder
- Some patients are closer to type B, with minimal nervous system involvement (often peripheral neuropathy) and /or mild mental retardation.

INCIDENCE

All types of disease are pan-ethnic. Majority of cases are type B or an intermediate form. The overall incidence is about 1 in 40,000-50,000 live births worldwide.

HIGH RISK FACTORS

- Genetic mutations - Niemann-Pick disease types A and B are caused by mutation in the SMPD1 gene while Type C is caused by mutation in NPC1 (95% cases) or NPC2 (5% cases) genes
- Consanguinity
- Family history - in families with an affected child, there will be 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and 25% chance of being unaffected and not a carrier.

PATHOLOGY

Accumulation of lipid laden macrophages / foam cells / sea blue histiocytes specially in liver & spleen.

LABORATORY DIAGNOSIS

Biochemical testing – Acid Sphingomyelinase activity of <10% in peripheral blood lymphocytes or cultured skin fibroblasts confirms the diagnosis.

Bone Marrow Examination – Presence of lipid laden macrophages

Molecular testing

- Sequence analysis of SMPD1 mutation in 99% cases
- Targeted mutation analysis for NPD-A & NPD-B mutations