Niemann-Pick disease

Niemann-Pick disease overview
Niemann-Pick disease is a term for a group of lysosome storage diseases that affect metabolism and that are caused by genetic mutations. The three most commonly recognized forms are Niemann-Pick Types A, B and C.

Niemann-Pick Types A and B (NPA and NPB), also called Acid Sphingomyelinase Deficiency (ASMD), are caused by the deficiency of a specific enzyme, acid sphingomyelinase (ASM). This enzyme is found in special compartments within cells called lysosomes and is required to metabolize a lipid called sphingomyelin. If ASM is absent or not functioning properly, sphingomyelin cannot be metabolized properly and is accumulated within the cell, eventually causing cell death and the malfunction of major organ systems.

NPA and NPB are both caused by the same enzymatic deficiency and there is a growing evidence that the two forms represent opposite ends of a continuum. People with NPA generally have little or no ASM production (less than 1% of normal) while those with NPB have approximately 10% of the normal level of ASM.

Forms of ASMD between these two extremes do occur, and the diagnosis is sometimes called intermediate NPD or Type A/B. There can be considerable overlap along the entire ASMD disease spectrum with symptoms ranging in onset, complexity and severity, and every patient's case is unique.

The clinical prognosis for NPA and NPB patients is very different. NPA is a severe neurologic disease that leads to an early death, usually by 2 to 4 years of age. In contrast, patients with NPB generally have little or no neurologic involvement and may survive into adulthood, though there may be health complications. Type B individuals usually have enlarged livers and spleens, and respiratory problems are common. The enlargement of organs and the respiratory problems can cause cardiovascular stress and can lead to heart disease.

There are approximately 1,200 cases of NPA and NPB world wide with the majority being Type B or an intermediate form.

Niemann-Pick Type C (NPC) is very different than Type A or B. NPC Patients are not able to metabolize cholesterol and other lipids properly within the cell. Consequently, excessive amounts of cholesterol accumulate within the liver and spleen and excessive amounts of other lipids accumulate in the brain. NPC causes a secondary reduction of ASM activity, which led all three types to be considered forms of the same disease.

There is considerable variation in when Type C symptoms first appear and in the progression of the disease. Symptoms may appear as early as a few months of age or as late as adulthood. Vertical gaze palsy (the inability to move the eyes up and down), enlarged liver, enlarged spleen, or jaundice in young children are strong indications that NPC should be considered. It is common for only one or two symptoms to appear in the early stages of the disease.

In most cases, neurological symptoms begin appearing between the ages of 4 and 10. Generally, the later neurological symptoms begin, the slower the progression of the disease.

Type C Niemann-Pick disease has about 500 cases diagnosed worldwide. It is believe, however, that the number of people affected by NPC is higher, but diagnostic difficulties do not allow an accurate assessment of the occurrence rate. NPC has been initially diagnosed as a learning disability, mild retardation, “clumsiness,” and delayed development of fine motor skills. It is not uncommon for a family to spend several years seeking a diagnosis before NPC is identified.

NPC is always fatal. The vast majority of children die before age 20 (and many die before the age of 10). Late onset of symptoms can lead to longer life spans but it is extremely rare for any person with NPC to reach age 40.

Niemann-Pick disease affects all segments of the population with cases reported from North America, South America,
Europe, Africa, Asia, and Australia. However a higher incidence of has been found in certain populations:
• Ashkenazi Jewish population (NPA and NPB)
• French Canadian population of Nova Scotia (type D – now considered a variant of NPC)
• Maghreb region (Tunisia, Morocco, and Algeria) of North Africa (NPB)
• Spanish-American population of southern New Mexico and Colorado (NPC)

**Diagnosis of Niemann-Pick disease**
All types of Niemann-Pick are autosomal recessive, which means that children with the disease have two copies of the abnormal gene. Each parent carries one copy of the abnormal gene without having any signs of the disease themselves. Siblings of the parents may also be carriers of the abnormal gene.

When both parents are carriers of the abnormal gene, there is:
- a 1 in 4 chance that a child will have the disease
- a 1 in 2 chance that a child will be a carrier
- a 1 in 4 chance that a child will not have the disease and will not be a carrier

Carrier detection testing for all families is not yet reliable.

The mutations for Types A and B have been extensively studied, particularly among the Ashkenazi Jewish population, and DNA tests for these forms of Niemann-Pick disease are available. Antenatal diagnosis (diagnosis in the fetus) of Niemann-Pick disease is available in a limited number of centers.

Dr. Wenda Greer of Dalhousie University has identified the genetic mutation related to Type D (now called the Nova Scotia variation of NPC). Carrier detection tests can be conducted for this mutation.

Carrier detection is possible for other families only after their specific mutation is identified. See the Diagnosis page for more details about genetic testing.

**Diagnosis of Niemann-Pick Type A.** NPA, like NPB, is diagnosed by measuring the level of activity of an enzyme called acid sphingomyelinase (ASM) in white blood cells. The test can be performed after taking a small blood sample from individuals suspected of having the disease and is available at many commercial laboratories in the United States and elsewhere. While this test will identify persons with Type A (as well as Type B), it is not very reliable for detecting persons who are carriers (who have only one non-functional copy of the ASM gene). Further, the test will show decreased activity of ASM, but it cannot always predict whether the individual will have type A or Type B or an intermediate variant of the disease; that requires clinical evaluation of the individual.

The Mount Sinai Department of Human Genetics has identified certain populations where specific mutations account for a high percentage of cases of ASM Deficiency*. For NPA, the mutations R496L, fsP330 and L302P account for over 95% of disease-causing genetic changes in the Ashkenazi Jewish population. Direct testing of individuals in this population for these 3 changes is used for carrier identification. In other populations, the mutations must first be identified in the affected individual before DNA carrier testing can be performed for family members. More recently, comprehensive analysis of the entire ASM gene structure has been used for carrier testing for partners of known Type A carriers. This is available at several US laboratories, including GeneDx in Gaithersburg, MD, Ambry Genetics in Aliso Viejo, CA and Emory Molecular Genetics Laboratory in Atlanta, GA.

If you have any questions about diagnostic or molecular genetic testing for Niemann-Pick Disease, or need assistance in arranging testing, please contact the NNPDF.


**Diagnosis of Niemann-Pick Type B.** NPB, like NPA, is diagnosed by measuring the level of activity of an enzyme called acid sphingomyelinase (ASM) in white blood cells. The test can be performed after taking a small blood sample from individuals suspected of having the disease and is available at many commercial laboratories in the United States and elsewhere. While this test will identify persons with Type B (as well as Type A), it is not very reliable for detecting persons who are carriers (who have only one non-functional copy of the ASM gene). Further, the test will show decreased activity of ASM, but it cannot always predict whether the individual will have type A or Type B or an
intermediate variant of the disease; that requires clinical evaluation of the individual.

Molecular genetic testing is now available commercially for Niemann-Pick disease, type B (or ASM Deficiency) at several laboratories, including GeneDx in Gaithersburg, MD, Ambry Genetics in Aliso Viejo, CA and Emory Molecular Genetics Laboratory in Atlanta, GA. Your health care provider should contact laboratory personnel to arrange for testing if you are interested. Once an affected individual has been tested and his or her mutations have been identified, it is then possible to diagnose Type B carriers by DNA testing within the individual's family.

The Mount Sinai Department of Human Genetics has identified certain populations* (shown below) where specific mutations account for a high percentage of cases. In these populations, it is possible to screen individuals for these specific mutations in order to identify carriers. In other populations, the mutations must first be identified in the affected individual before DNA carrier testing can be performed within a family, as noted above.

<table>
<thead>
<tr>
<th>Population</th>
<th>Mutations</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saudi Arabian</td>
<td>H421Y, K576N</td>
<td>85%</td>
</tr>
<tr>
<td>Turkish</td>
<td>L137P, fsP189, L549P</td>
<td>75%</td>
</tr>
<tr>
<td>Portuguese</td>
<td>S379P, R441X, R474W</td>
<td>55%</td>
</tr>
<tr>
<td>Brazilian</td>
<td>F480L</td>
<td></td>
</tr>
<tr>
<td>English/Scottish</td>
<td>A196P</td>
<td>42%</td>
</tr>
<tr>
<td>Other</td>
<td>DeltaR608</td>
<td>12%</td>
</tr>
</tbody>
</table>

If you have any questions about diagnostic or molecular genetic testing for Niemann-Pick Disease, type B or need assistance in arranging testing, contact the NNPDF.


**Diagnosis of Niemann-Pick Type C.** Niemann-Pick Type C (NPC) is a rare and extremely variable condition and therefore may not be recognized by some health care providers. For those specialists who do suspect this diagnosis in a patient, it can be determined by taking a small piece of skin ("skin biopsy"), growing the cells ("fibroblasts") in the laboratory, and studying their ability to transport and store cholesterol.

The transport of cholesterol in the cells is studied by measuring conversion of the cholesterol from one form to another ("esterification"). The storage of cholesterol is assessed by staining the cells with a chemical ("filipin") that glows under ultraviolet light. This can show whether the cholesterol is being stored inappropriately in lysosomes, the recycling centers of the cell. It is important that both the transport and storage tests be performed, since reliance on one or the other may lead to an incorrect diagnosis or a missed diagnosis of a variant form of NPC.

If a clinician suspects NPC in a patient, there are only 2 laboratories in the United States that do this diagnostic testing: 1) the Mayo Clinic Biochemical Genetics Laboratory in Rochester, MN and 2) the Lysosomal Disease Testing Laboratory at Thomas Jefferson University in Philadelphia, PA. It is important that the health care provider who is caring for your child contact the laboratory because laboratory personnel are not permitted to discuss testing directly with patients or their families. The health care provider will be given directions for collecting the sample and sending it to the laboratory so that it can be properly analyzed.

In 1997, the NPC1 gene was identified. Mutations, or disease-causing changes, in this gene are responsible for about 95% of all NPC cases. Since 1997, over 250 different genetic mutations related to NPC have been identified in this gene and in the second NPC gene, called NPC2. Overall, in about 95% of cases, it is possible to identify the genetic changes that have caused the disease if the diagnosis of NPC has first been confirmed by the testing outlined above. However, because there are so many unique mutations in these genes, and there are patients with classic NPC in whom mutations have not been identified, it is not optimal to use genetic testing as a general diagnostic tool. In addition, genetic testing can be performed to identify carriers in families where the mutation is known. More recently, it has also been used to help better define the carrier risk for partners of known carriers.

There are now three laboratories in the United States that perform genetic testing for NPC: 1) GeneDx in Gaithersburg,
MD, 2) Emory Molecular Genetics Laboratory, and 3) Mayo Clinic Molecular Genetics Laboratory. As with the diagnostic testing laboratories, the health care provider who is caring for your child should contact the laboratory for testing details.

For additional information about options for genetic testing, contact the NNPDF.

**Treatment options for Niemann-Pick disease**
The news concerning treatments for Niemann-Pick disease is improving but there is still much to do before definitive therapies are available. Just a few years ago, the cause of Niemann-Pick disease was unknown. Now the genetic sources of the disease have been identified and research is focusing on how the biochemical mechanisms work and how they can be corrected.

**Treatment options for NPA.** Presently, there are no treatments for Niemann-Pick disease Type A.

Supportive treatment can help manage the symptoms of NPB. Support may be needed from:
- A pulmonologist for respiratory problems
- A cardiologist for heart problems
- Liver and spleen specialists
- Nutritionists
- Physical therapists
- A gastroenterologist

**Treatment options for NPB.** Research into therapies for NPB has progressed rapidly since the early 1990’s. Mount Sinai School of Medicine is conducting research on bone marrow transplantation, enzyme replacement therapy, and gene therapy. These therapies have proven effective against NPB in the laboratory.

Bone marrow transplantation has proven effective in mouse models for many aspects of Type B when the transplant occurs early in life. Because bone marrow transplant is a complex medical procedure, it has only been conducted a few times on humans with Type B. The results of these transplants have been mixed.

Enzyme replacement therapy has been tested on mice and shown to be effective for NPB. It has also been used successfully in other lysosomal storage diseases, such as Gaucher Type I and Fabry’s. Genzyme Corp. and Mount Sinai Medical Center have begun a clinical trial of enzyme replacement therapy for older Type B patients.

**Treatment options for NPC.**

Click here to see the latest information for treatment options for NPC.

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