

Niemann-Pick Disease

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Niemann-Pick is an autosomal recessive genetic disorder resulting in abnormal lipid metabolism. It can result from a deficiency of the acid sphingomyelinase enzyme, leading to type A or B disease, or the NPC1 or NPC2 (also called HE1) proteins involved in cholesterol and fatty acid metabolism in lysosomes resulting in type C disease. The severity of the disease and age of onset vary, but it is always fatal.

Biochemistry and Molecular Biology of Niemann-Pick

Lipids like sphingomyelin and cholesterol are present in all cell membranes and are metabolized in lysosomes. Sphingomyelin appears to be involved in signaling cascades. Cholesterol is involved in the synthesis of many hormones and is an important component of cell membranes.²

Exogenous cholesterol, in the form of cholesterol esters, is taken up from the bloodstream as LDL via endocytosis, creating endosomes in the cell. Enzymes are sent to the endosomes and create lysosomes, which can break down the fatty acids and cholesterol esters contained within them. One of these enzymes is acid sphingomyelinase, which breaks down sphingomyelin, also found in lysosomes. The degraded components of sphingomyelin can be further broken down, or remade into sphingomyelin in the endoplasmic reticulum and golgi apparatus. Once the cholesterol esters are broken down to free cholesterol and fatty acids, the free cholesterol diffuses out of the lysosomes to the plasma membrane and endoplasmic reticulum. Free cholesterol in the cell activates mechanisms that downregulate LDL receptors, decreasing the amount of cholesterol taken up by the cell. If excess cholesterol is present in the cell, it is stored as cholesterol ester.^{1,2} In Niemann-Pick, these processes are disrupted.

Types A and B are characterized by a deficiency in acid sphingomyelinase (ASM), with type A having a larger deficit. This enzyme catalyzes the hydrolysis of sphingomyelin within lysosomes.² ASM deficiency results in an accumulation of sphingomyelin-containing lysosomes-like storage organelles.¹ These lysosomes build up forming lysosomal inclusions, giving the cells a characteristic foamy appearance.³ Accumulation of lysosomes eventually causes cell death.²

Type C disease results from a mutation in the NPC1 or NPC2 gene locus. The protein products of these genes are responsible for intracellular transport of exogenous cholesterol into and out of lysosomes. NPC1 is a transmembrane protein that spans the lysosomal membrane. It does not directly transport cholesterol. NPC2 is found within the lysosomes and can bind cholesterol. The exact function of these proteins is still under investigation, but when deficient, cholesterol metabolism is interrupted. Exogenous cholesterol esters are still taken up in LDL by the cell, packaged into lysosomes, and hydrolyzed to generate free cholesterol. However, it cannot leave the lysosomes to activate mechanisms that reduce LDL uptake. As a result, lysosomes accumulate within the cell and can cause cell death, as in disease types A and B.^{1,2,4,5}

In the brain, cholesterol is made endogenously, not absorbed as LDL. Here, the cholesterol is also trapped in organelles because of NPC1 and NPC2 mutations. The major components of the material trapped in these organelles are glycosphingolipids,

whose trafficking is disrupted in type C disease, although the mechanism remains unclear.^{1,2}

Genetics

Mutations of chromosome 11, at the gene locus encoding ASM, are responsible for disease types A and B. Type A is a more severe form where ASM activity is severely reduced or absent due to nonsense mutations producing truncated proteins or missense mutations that eliminate the enzymatic activity of the protein. Type B is a milder form caused by mutations that reduce the enzymatic activity of ASM or cause a reduced production of the protein fully functional protein. The amount of residual activity of the enzyme does not predict the severity of the disease.^{2,6} Specific mutations prevalent in certain populations have been found for Ashkenazi Jews, Saudi Arabians, Turks, Portuguese and Brazilians, and people of Scottish and English descent. The disease incidence in the general population is 1/248,000 live births.⁶

Type C disease is caused by mutations to the NPC1 gene on chromosome 18 or the NPC2 gene on chromosome 14. About 95% of type C disease is due to NPC1 mutations. Point mutations, deletions, and splice site mutations have been identified. It is found in 1/150,000 individuals, but is more prevalent in some populations including Acadians of Nova Scotia (type D disease, a specific allelic variant of type C), a Spanish-American population in southern New Mexico and Colorado, and a Bedouin group in Israel.⁷

Diagnostic Criteria

All forms of Niemann-Pick disease are initially diagnosed by recognition of certain characteristic symptoms. In newborns, these include ascites, or fluid in the abdomen, pulmonary infiltrates, and abnormal liver function tests, which may manifest as jaundice. These infants may be delayed in achieving normal developmental milestones such as sitting up and crawling on their own. In childhood, patients will present with symptoms such as hepatosplenomegaly, slow, uncontrolled muscle spasms (dystonia) or sudden bilateral muscular weakness (cataplexy), a loss in eye muscle control (ataxia), and seizures. Adults with the disease most often experience depression, bipolar disease, or schizophrenia.⁸

An initial diagnosis is confirmed through biochemical and/or genetic testing. Type A and B are diagnosed by measuring ASM activity in white blood cells. This test will not determine carrier status, as ASM activity appears to be normal in heterozygotes. In specific populations, such as Ashkenazi Jews, mutations in the SMPD1 gene can be tested for.² In fact, Niemann-Pick Disease is among the panel of over ten inherited diseases regularly tested for prenatally in this population. Other, less common mutations can be tested for with gene sequencing. Several laboratories across the United States provide such testing, which involves simply acquiring a tissue sample from anywhere in the body for DNA analysis.

Type C is diagnosed using fibroblast cells from a skin biopsy. Cells from affected individuals show a reduced ability to transport cholesterol due to an inability to esterify it. Filipin staining also reveals a cholesterol storage defect. Brightly stained spots appear surrounding the nucleus, indicating an accumulation of unesterified cholesterol. Genetic

testing is available from many laboratories for common mutations of the NPC1 and NPC2 genes.^{3,7}

Biopsies of bone marrow, spleen, and liver tissue were, until recently, commonly used diagnostic tools. In affected individuals, the appearance of foam cells would be the primary indicator of the disease. However, due to the lack of specificity of this finding for a differential diagnosis and the development of newer, less invasive testing, biopsies are rarely used anymore.³

Prognosis for Patients

The prognosis for patients with Niemann Pick Disease varies depending on the type that they have. However, besides rare variants of the disease, all those afflicted will die prematurely. Type A has a very rapid, progressive onset of neurological symptoms. Patients with Type A will generally die by the second or third year of life. Since Type B is associated with a more mild mutation of the ASM gene that does not completely impair its function, the symptoms do not occur as rapidly or as severely. The neurodegenerative features of Type A are not present in childhood, with the main symptoms being hepatosplenomegaly and short stature. However, during early adulthood, the central nervous system may begin to be affected, and the accumulation of lipids, particularly foam cells, in the liver spleen and lungs leads to a premature death. The progression of Type C is more similar to that of Type A, although the neurological symptoms do not appear as immediately, and early development can proceed normally. Beginning in late infancy, the disease becomes apparent. Accumulation of lipids in the cerebellum lead to balance problems, dystonia occurs with frequency, and finally, the child starts having seizures. These patients typically die between the age of 5 and 15.³

Possible Treatments

There are currently no cures or treatment for any of the forms of Neimann-Pick Disease. The only option for parents with children affected with this disorder is the management of specific symptoms. The seizures, cataplexy, and dystonia can be controlled with pharmaceuticals normally used for these conditions. In addition, airway secretions are managed with bronchodilators and antibiotics. Since nourishment can become an issue later in the progression of the disease, food is first softened and thickened, but eventually a feeding tube is required for sustenance. Physical, occupational, and speech therapies are also used to combat the lag in development.⁹

New potential treatments are being developed now in an effort to slow the progression of the disease, correct the damage caused to neural and organ tissues, and ultimately cure patients of the disease. One possibility is gene therapy, wherein normal copies of the SMPD1, NPC1, or NPC2 genes would be introduced into the patient and transcribe the normal, functioning gene products. The use of neuronal stem cells to replace damaged nerve cells is also under investigation. While in theory, these therapies could lead to a cure for Neimann-Pick, their full development is a long way off, complicated by the difficulty of carrying out clinical studies on patients who do not live past early childhood.⁹

Disease Risks for Other Family Members

All forms of Niemann-Pick Disease are inherited in an autosomal recessive manner.³ Therefore, in order for a child to be born with this disorder, he or she must receive one defective gene from each parent. This also implies that the parents of an affected child are obligate carriers and each have one mutated gene. Any new siblings of the affected child have a 25% chance of having two normal genes, a 50% chance of being an unaffected carrier, and a 25% chance of being homozygous for the mutant gene and having the disease. The time of onset for Niemann-Pick is generally consistent within a family, so if the proband has any older siblings who have not yet displayed symptoms of the disease, it greatly increases the chances that he or she is either a carrier, or homozygous for the normal gene, versus having the disease.⁷ Since both type A and type C are lethal before the child reaches reproductive age, the possibility of the proband passing the disease onto his or her children is generally not considered. However, since patients with type B can survive into adulthood, they should be advised that they have a 100% chance of passing one copy of a defective gene to their children. Therefore all of their children will be at least carriers of the disease and the probability of being affected will depend on the carrier status of the mate. This can be determined with carrier testing. Pregnant mothers can also have their unborn children tested for the disease using chorionic villus sampling at 10 to 12 weeks, or amniocentesis at 16 to 18 weeks.³ The parents of affected children contemplating having more children, and patients with the disease contemplating having children of their own should be counseled on the risk of disease, as described above, along with the possible range of severity, and available treatment and management options.

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