

Niemann-Pick Diseases

Description

Niemann-Pick diseases are a group of fatal inherited metabolic diseases of childhood, first described by Albert Niemann and further characterized by Ludwig Pick. Niemann-Pick disorders are characterized by the buildup of toxic amounts of fatty substances called lipids, specifically sphingolipids and cholesterol, in various organs including the brain. Normally, specific enzymes in the body break down lipids, whereas people with Niemann-Pick disease either lack these enzymes or the enzymes do not function properly, causing lipids to accumulate within cells. As the lipids build up in the cell compartment called the lysosome, Niemann-Pick diseases belong to a larger group of diseases called lysosomal storage disorders.

Niemann-Pick diseases are sub-classified into the types A, B, C and D, which differ by the genes in which the disease mutations occur, the type and severity of symptoms, as well as the age of onset. Type A, which occurs in early infancy, is the most severe form of the disease. Symptoms include enlargement of the liver, spleen and lymph nodes, as well as significant damage to the brain. Type B usually begins in childhood, with milder symptoms and no brain damage. Types A and B are caused by mutations in a gene called SMPD1, which results in ineffective activity of the enzyme that breaks down the lipid sphingomyelin. Type C and D are caused by mutations in genes called NPC1 and NPC2, resulting in defective cholesterol transport in the brain. Types C and D may develop early or later in life, and are characterized by symptoms including learning difficulties, seizures, unsteady gait, slurred speech, difficulties with swallowing and eye movement, tremors and muscle loss, as well as liver and spleen enlargement.

Niemann-Pick diseases are passed on by an autosomal recessive mode of inheritance, which means that when both parents carry a copy of the disease-associated gene, there is a 25% chance that their child will be affected. Therefore, genetic testing is recommended for prospective parents who may be at a higher risk of being carriers of the disease-associated genes. For instance, the incidence of Niemann-Pick Type A is approximately 1 in 40,000 in Ashkenazi Jews, whereas Type D more commonly occurs in French Canadian populations from Nova Scotia. The overall incidence of Niemann-Pick disease is estimated to be approximately 1:100,000.

Diagnosis can be performed by biochemical or microscopic tests in people presenting with symptoms of Niemann-Pick disease. Blood and bone marrow samples can be used to measure the amount of the enzyme ASM, which is defective in patients with Niemann-Pick disease Types A and B. Types C and D are diagnosed by examination of the cholesterol storage capabilities of skin cells grown from patients. Genetic testing may also be performed to determine whether mutations exist in the genes that are defective in Niemann-Pick disease. Prenatal testing is also available in some centres.

Treatment

There are limited available treatments for Niemann–Pick disease, and supportive care through nutrition and physical therapies can improve the quality of life for patients. Additionally, for patients with peripheral organ pathology, specialists can assist in reducing the severity of symptoms.

Misglustat, registered as Zavesca, is an inhibitor of sphingolipid production that has recently been approved for treatment of Niemann-Pick C in Canada, the European Union, South Korea, Brazil, Russia and Australia. This drug does not cure the disease, but has been shown to slow neurological symptoms and disease progression in some patients.

The National Institutes of Health (NIH) and Therapies for Rare and Neglected Diseases (TRND) are in the process of initiating human clinical trials to test the efficacy of cyclodextrin as a treatment for Niemann-Pick type C. Cyclodextrin has shown immense promise in correcting cholesterol imbalances, reducing neurodegeneration and prolonging life in mouse models of Niemann-Pick C disease, and has been trialed in two patients in the United States.

Recently, experimental therapies including stem cell transplantation have been trialed in individuals with Type A and B disease, with varying degrees of success. While transplants have been successful at alleviating disease symptoms in two patients with Type B disease, complications due to the graft itself commonly arise as a consequence of treatment.

Prognosis

Niemann-Pick Type A is the most severe form of the disease, with an average life expectancy of 18 months. Type B represents a milder form of disease, and some patients live into late to mid teens, with a few surviving into adulthood. Prognosis for patients with Type C varies between individuals and may range between late childhood through the mid to late teens, with some patients living into adulthood.