

Niemann-Pick Disease [1]

By: Cooper-Roth, Tristan Keywords: [Human development](#) [2] [Congenital disorders](#) [3]

In 1914 Albert Niemann, a German pediatrician who primarily studied infant metabolism, published a description of an Ashkenazi Jewish infant with [jaundice](#) [5], nervous system and brain impairments, swollen lymph nodes (lymphadenopathy), and an enlarged liver and spleen (hepatosplenomegaly). He reported that these anatomical disturbances resulted in the premature death of the child at the age of eighteen months. After extensively studying the abnormal characteristics of the infant, Niemann came to the conclusion that the disease was a variant of Gaucher's disease. Gaucher's disease, described by the French dermatologist Philippe Gaucher in 1882, is a lipid storage disorder resulting in an excessive accumulation of lipids in the spleen, kidneys, liver, lungs, bone marrow, and brain. Niemann was able to connect the infant's disease to Gaucher's disease because it displayed similar symptoms: a noticeable accumulation of fatty substances in the brain, liver, and spleen.

In the 1920s, Ludwig Pick, a German pathologist, studied infants with similar lipid storage disorders, investigating the disease through autopsy and examination of the affected tissues. From past studies, Pick understood that Gaucher's disease was distinguished by a buildup of glucocerebrosides, composed of glucose and a ceramide fat, in the affected tissues. In contrast, Niemann and Pick's patients presented a buildup of sphingomyelins, composed of sphingosine, choline, a fatty acid, and a phosphoric acid. The results from Pick's studies provided him with an alternative conclusion; the disease was actually an entirely different lipid storage disease. From this point on, dysfunctional sphingomyelin storage was called Niemann-Pick disease (NPD) and is understood as a developmental disease.

In 1961 Allan Crocker and Sidney Farber divided NPD into four subcategories. Each form of the autosomal recessive disease acquired the letters A through D, depending on the patient's phenotype, the specific symptoms expressed, and the presence of unique cells. These unique cells are known as "foam cells" because of their foam-like appearance when displayed under a [microscope](#) [6]. This foam-like appearance is due to the accumulation of excessive amounts of low density lipoproteins (LDL) within the vacuoles of a cell called a histiocyte. Histiocytes are cells that are part of the reticuloendothelial system and are responsible for phagocytosis and antigen presentation. When excessive amounts of LDL (the main transporter of cholesterol and triglycerides from the liver to the peripheral tissues) are present, histiocytes function improperly.

NPD type A, an acute neuronopathic form, is characterized by a deficiency of acid sphingomyelinase, an enzyme responsible for breaking down sphingomyelin into its derivatives. This form of the disease was seen in the infant examined by Niemann and is known as the severe infantile form. Defective sphingomyelinase activity is caused by missense and nonsense mutations in the sphingomyelin phosphodiesterase-1 gene (*SMPD1*). With these mutations, the protein structure of sphingomyelinase develops irregularly and its function is either eradicated or greatly suppressed. In response to the [reduction](#) [7] in sphingomyelinase activity, the affected individuals of NPD type A experience a rapid neurologic degeneration from the accumulation of sphingomyelin in ganglion cells. Given the combination of rapid neurologic degeneration, lymphadenopathy, and hepatosplenomegaly, the individual is incapable of living past the age of three.

NPD type B is closely associated with type A due to a similar mutation in the *SMPD1* gene, but it does not involve the acute neurologic degeneration seen in type A. Type B patients do not experience this symptom because the mutated *SMPD1* gene still encodes for the protein make-up of sphingomyelinase, although it is a defective version with residual catalytic activity. Because of this residual activity, type B patients experience less severe sphingomyelin manifestations in the spleen, liver, and lungs. Thus, type B affected individuals are capable of surviving for a much longer period of time, as seen by clinical management, up to the age of fifty-five.

NPD types C and D are distinct from forms A and B because the genetic mutation is not found on the *SMPD1* gene; instead it is found on the *NPC1* and *NPC2* [genes](#) [8]. These particular [genes](#) [8], located on chromosome 18, are involved in constructing proteins responsible for cholesterol transportation in late endosomes, a major sorting compartment of the endomembrane system within eukaryotic cells, and lysosomes, organelles responsible for enzymatic breakdown of foreign and non-foreign particles in eukaryotic cells. With a disruption in either of these [genes](#) [8], the late endosome and lysosome of affected cells begins to accumulate sphingosine, a primary part of a sphingolipid and a component of cholesterol. Excessive accumulation of cholesterol in both the late endosome and lysosome results in irregular intracellular transport, cell signaling, and nerve conduction. Due to these abnormalities in cell physiology, the individuals affected by types C and D begin to experience progressive neurodegeneration typically at the age of two. NPD types C and D, referred to as the chronic neuronopathic form, have a variety of symptoms that may include grand mal seizures, loss of speech, ataxia, myoclonic jerks, dystonia, dementia, and vertical supranuclear gaze palsy. Although the neurodegeneration is quite severe, types C and D individuals suffer from less severe forms of hepatosplenomegaly, unlike types A and B, and the average life span of an individual with type C or D is 16.2 years.

Among the four types of NPD, the two easiest to detect and diagnose prenatally are types A and B. The detection of NPD

involves the culturing of amniocytes or chorionic villus cells and determining their sphingomyelinase activity. Most amniocytes affected by NPD type A express less than one percent normal sphingomyelinase activity (0.4 and 0.6 nmole/mg protein/hr versus the control mean of 61.7). To confirm the diagnosis of NPD *in utero*, skin fibroblast and liver cells are cultured from the fetus^[9] during the fourteenth week of gestation^[10]. The skin fibroblast cell culture is then tested for the level of cholesterol processing, and the liver culture is tested for the level of lipid storage. If the fetus^[9] exhibits any abnormalities in respect to these biochemical levels the patient is recommended to terminate the pregnancy^[11].

Sources

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Publisher

Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

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Last Modified

Wednesday, July 4, 2018 - 04:40

DC Date Accessioned

Friday, May 25, 2012 - 15:47

DC Date Available

Friday, May 25, 2012 - 15:47

DC Date Created

2010-10-11

DC Date Created Standard

Monday, October 11, 2010 - 07:00

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