Diagnostic Methods for Neimann-Pick Type C

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Niemann–Pick type C is a lysosomal storage disease associated with mutations in NPC1 and NPC2 genes. Niemann–Pick type C affects an estimated 1:150,000 people. Niemann-Pick type C (NPC) disease is an autosomal recessive lipid storage disorder characterized by progressive neurodegeneration. Approximately 95% of cases are caused by mutations in the NPC1 gene, referred to as type C; 5% are caused by mutations in the NPC2 gene, referred to as type C2.

The clinical manifestations of types C1 and C2 are similar because the respective genes are both involved in egress of lipids, particularly cholesterol, from late endosomes or lysosomes. Approximately 50% of cases present before 10 years of age, but manifestations may first be recognized as late as the sixth decade. Patients presented in their early forties with vertical supranuclear gaze paresis, dysarthria, and cognitive decline characterized by expressive aphasia, perseverative behavior, and impaired conceptualization and planning. They develop ataxia and athetoid movements, and sometimes facial dyskinesias and bradykinesia. A few Patients exhibit early cognitive symptoms in adolescence. Postmortem examination of the proband revealed frontal lobe atrophy and neuronal lysosomes with oligolamellar inclusions typical for NPC, but no visceromegaly.

The diagnosis of NPC is confirmed by biochemical testing that demonstrates impaired cholesterol esterification and positive filipin staining in cultured fibroblasts. Therefore Niemann–Pick type C is mainly diagnosed by assaying cultured fibroblasts for cholesterol esterfication and staining for unesterified cholesterol with filipin. The fibroblasts are grown from a small skin biopsy taken from a patient with suspected NPC. Biochemical testing for carrier status is unreliable. Most individuals with NPC have NPC1, caused by mutations in NPC1; fewer individuals have been diagnosed with NPC2, caused by mutations in NPC2. The diagnosis can be confirmed by identifying mutations in the NPC1 or NPC2 genes in 80–90% of cases. Molecular genetic testing of NPC1 and NPC2 detects disease-causing mutations in approximately 94% of individuals with NPC. Niemann-Pick disease type C2 is caused by homozygous mutation in the NPC2 gene on chromosome 14q24.

Since 2001 prenatal diagnosis by mutation analysis of an uncultured chorionic villus sample is available. In 2 patients with NPC2, homozygous mutations in the HE1 (NPC2) gene were identified. In 6 unrelated patients with NPC2, 5 different mutations in the NPC2 gene were identified. It was stated that a total of 15 disease-causing mutations had been identified in 22 unrelated families to date. E20X was the most common mutation, accounting for 34% of mutant alleles.

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