Niemann-Pick disease type C.

Vanier MT.

Source

Institut National de la Santé et de la Recherche Médicale, Unité 820, Faculté de Médecine Lyon-Est Claude Bernard, 7 Rue G, Paradin, F-69008, Lyon, France. marie-t.vanier@inserm.fr

Abstract

Niemann-Pick C disease (NP-C) is a neurovisceral atypical lysosomal lipid storage disorder with an estimated minimal incidence of 1/120,000 live births. The broad clinical spectrum ranges from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. The neurological involvement defines the disease severity in most patients but is typically preceded by systemic signs (cholestatic jaundice in the neonatal period or isolated spleno- or hepatosplenomegaly in infancy or childhood). The first neurological symptoms vary with age of onset: delay in developmental motor milestones (early infantile period), gait problems, falls, clumsiness, cataplexy, school problems (late infantile and juvenile period), and ataxia not unfrequently following initial psychiatric disturbances (adult form). The most characteristic sign is vertical supranuclear gaze palsy. The neurological disorder consists mainly of cerebellar ataxia, dysarthria, dysphagia, and progressive dementia. Cataplexy, seizures and dystonia are other common features. NP-C is transmitted in an autosomal recessive manner and is caused by mutations of either the NPC1 (95% of families) or the NPC2 genes. The exact functions of the NPC1 and NPC2 proteins are still unclear. NP-C is currently described as a cellular cholesterol trafficking defect but in the brain, the prominently stored lipids are gangliosides. Clinical examination should include comprehensive neurological and ophthalmological evaluations. The primary laboratory diagnosis requires living skin fibroblasts to demonstrate accumulation of unesterified cholesterol in perinuclear vesicles (lysosomes) after staining with filipin. Pronounced abnormalities are observed in about 80% of the cases, mild to moderate alterations in the remainder ("variant" biochemical phenotype). Genotyping of patients is useful to confirm the diagnosis in the latter patients and essential for future prenatal diagnosis. The differential diagnosis may include other lipidoses; idiopathic neonatal hepatitis and other causes of cholestatic icterus should be considered in neonates, and conditions with cerebellar ataxia, dystonia, cataplexy and supranuclear gaze palsy in older children and adults. Symptomatic management of patients is crucial. A first product, miglustat, has been granted marketing authorization in Europe and several other countries for specific treatment of the neurological manifestations. The prognosis largely correlates with the age at onset of the neurological manifestations.

PMID:

20525256

[PubMed - indexed for MEDLINE]

PMCID: PMC2902432

Free PMC Article