Niemann-Pick Disease

Contents

Niemann-Pick disease has been used to designate a heterogeneous group of autosomal recessive lysosomal lipid storage disorders (acid sphingomyelinase deficiency) (types A and B), with common features of hepatosplenomegaly and sphingomyelin storage in reticuloendothelial and parenchymal tissues, with or without neurological involvement. Niemann-Pick type C disease (NP-C) evolved from that of a sphingomyelin storage disorder to that of a cholesterol storage disorder (Pentchev et al. 1994).

Synonyms and Related Disorders

Acid sphingomyelinase deficiency; Niemann-Pick disease types A, B, C

Genetics/Basic Defects

1. Niemann-Pick disease types A and B
    1. A rare lysosomal storage disease.
    2. Inherited as autosomal recessive traits.
    3. Result from allelic mutations in the sphingomyelin phosphodiesterase (*SMPD*) genes, located within the chromosomal region 11p15.4.
    4. Caused by deficient activity of acid sphingomyelinase (ASM).
    5. The acid sphingomyelinase defect leads to the accumulation of sphingomyelin in the cells of the liver, spleen, bone marrow, lungs, and, in some patients, brain (Schneider and Kennedy 1967; Marathe et al. 1998; Rodriguez-Lafrasse and Vanier 1999; Schuchman and Desnick 2001a, b).
2. Niemann-Pick disease type C (Vanier 2010)
    1. Biochemically, genetically, and clinically distinct from type A disease and type B disease
    2. Caused by autosomal recessive inheritance of mutations in two genes, *NPC1* (18q11.2) in 95% of cases or *NPC2* (14q24.3) in about 4% of cases, resulting in a disruption of intracellular cholesterol transport and accu-

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mulation of excessive amounts of cholesterol within liver and spleen and other lipids in the brain

Clinical Features

1. Niemann-Pick disease type A (Vanier 2010; Adolina 2014)
   1. A severe neurodegenerative disease with little or no enzyme activity.
   2. Ashkenazi Jewish predilection (gene frequency estimated to be 1:100).
   3. Overall frequency of types A and B: 1:250,000 (Meikle et al. 1999).
   4. Onset in infancy.
      1. Abdominal enlargement due to hepatosplenomegaly
      2. Feeding difficulties
      3. Macular cherry-red spot
   5. Progressive loss of acquired motor skills.
   6. Peripheral neuropathy (Gumbinas et al. 1975; Landrieu and Saïd 1984).
      1. Hypotonia
      2. Absent reflexes
   7. Increased accumulation of sphingomyelin in ganglion cells of the central nervous system leads to neurologic disturbances and mental retardation generally resulting in death by 3 years of age (McGovern et al. 2006).
2. Niemann-Pick disease type B (Guillemot et al. 2007; McGovern et al. 2013)
   1. A milder disease with the same gene defect as type A but has more residual enzyme activity
   2. Panethnic
   3. Characterized by phenotypic heterogeneity
   4. Broad range of severity
   5. Ocular manifestations (primary retinal including macular halos and cherry-red maculae) (Lowe et al. 1986; McGovern et al. 2004a)
   6. Onset in preteen years with the enlargement of the liver and spleen (hepatosplenomegaly)
   7. In adulthood, infiltrative pulmonary disease and ataxia are the major complications
   8. Other features
      1. Hyperlipidemia
      2. Liver dysfunction
      3. Cardiac disease
      4. Excessive bleeding and bruising
      5. Recurrent respiratory infections
      6. Retinal stigmata
      7. Growth retardation/developmental delay
      8. Skeletal manifestations
         1. Osteoporosis
         2. Osteopenia
      9. Peripheral neuropathy
   9. Absence of central nervous system involvement in most patients
   10. Serious morbidities: clinically significant hepatic, cardiac, and pulmonary disease especially in pediatric population
   11. Major causes of death: pneumonia/respiratory failure
3. Niemann-Pick disease type C (Patterson et al. 2012)
   1. Perinatal fetus.
      1. Fetal hydrops
      2. Fetal ascites
   2. Neonates/infants.
      1. Prolonged neonatal cholestatic icterus appearing in the first days or weeks of life (most cases resolve spontaneously by 2–4 months of age), usually associated with progressive hepatosplenomegaly in approximately 50% of patients (Vanier et al. 1988; Kelly et al. 1993; Yerushalmi et al. 2002)
      2. Ascites and severe liver disease resulting from infiltration of the liver
      3. Respiratory failure resulting from infiltration of the lungs
      4. Infants with severe early infantile neurologic onset form
         1. Hepatosplenomegaly almost invariably present
         2. Central hypotonia
         3. Developmental delay of motor milestones
         4. Loss of acquired motor skills, followed by pronounced spasticity with pyramidal tract involvement
         5. Intentional tremor frequently present

3. Mid-to-late childhood: classic presentation occurs during this period.
    1. Insidious onset of ataxia
    2. Vertical supranuclear gaze palsy (a clinical hallmark, often the initial sign)
    3. Dementia
    4. Action dystonia
    5. Seizures
    6. Dysarthria
    7. Dysphagia
    8. Develop pyramidal signs and spasticity at a late stage
    9. Eventual disabling
    10. Death usually occurring in the late second or third decade from aspiration pneumonia
4. Adults.
    1. Dementia
    2. Psychiatric signs
        1. Psychosis including paranoid delusions, auditory or visual hallucinations, and interpretative thoughts
        2. Depressive syndrome
        3. Behavioral problems with aggressiveness
        4. Social isolation
        5. Others

Diagnostic Investigations

1. Radiology.
    1. Type A: chest X-ray and CT scan for demonstrating interstitial lung disease.
    2. Type B:
        1. Chest X-ray and CT scan demonstrate interstitial lung disease (presence of "crazy paving" sign: ground-glass opacities, intermixed thickened interlobular septa and intralobular lines) (Mendelson et al. 2007).
        2. MRI of the brain: may show pronounced cerebellar and mild supratentorial atrophy (Obenberger et al. 1999).
    3. Type C: MRI at late stages of the illness may reveal marked atrophy of the superior/anterior cerebellar vermis, thinning of the corpus callosum, mild cerebral atrophy, and increased signal in the periatrial white matter reflecting secondary demyelination; MRS (magnetic resonance spectroscopy) may be more sensitive than standard MRI (Tedeschi et al. 1998).
2. Pulmonary function test. The lack of correlation between functional pulmonary impairment and the findings at radiography and thin-section CT may be due to the pathologic basis of the lung abnormalities in type B Niemann-Pick disease.
3. Biochemical/histological analyses (Mendelson et al. 2007; Schuchman 2007; Cruse 2013).
    1. NPD type A
        1. Absence of residual acid sphingomyelinase activity and subsequent lysosomal accumulation of sphingomyelin (Graber et al. 1994)
        2. Decreased high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia, and increased LDL cholesterol (McGovern et al. 2004b)
        3. Large lipid laden foam cells: observed in the reticuloendothelial system of the spleen, bone marrow, lymph nodes, blood vessels, peripheral nerve Schwann cells, central nervous system, and retinal cells (Wenger et al. 1981)
        4. Electron microscopy: reveals lysosomal inclusions and myelin inclusions in peripheral nerves, indicating a severe myelinopathy (Landrieu and Saïd 1984)
    2. NPD type B
        1. Demonstration of reduced ASM activity in isolated leukocytes and/or cultured skin fibroblast
        2. High triglycerides and LDL cholesterol
        3. Low HDL cholesterol (most consistent laboratory finding)
        4. Thrombocytopenia secondary to hypersplenism in most patients
        5. Liver involvement: infiltration of foamy histiocytes, ballooning of hepatocytes, and fibrosis (Takahashi et al. 1997)
    3. NPD type C (Patterson et al. 2012)
        1. Impaired cholesterol esterification

2. Positive filipin staining in cultured fibroblasts
4. Molecular genetic analysis
   1. NPD types A and B: identification of *SMPD1* gene mutation
   2. NPD type C: molecular testing of *NPC1* and *NPC2* detects disease-causing mutations in approximately 94% of individuals with NPD type C

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: 25%
   2. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis
   1. Type A or B
      1. Measure sphingomyelinase activity in amniotic fibroblasts (Wenger et al. 1978; Vanier 2002)
      2. Molecular genetic testing if both disease-causing *SMPD1* alleles have been identified in an affected family member (McGovern and Schuchman 2011)
   2. Type C (Patterson et al. 2012)
      1. Chorionic villus sampling at 10–12 weeks or fetal cells obtained by amniocentesis at 15–18 weeks: available for pregnancies at 25% risk for type C.
      2. Biochemical testing can be done only when the proband has the typical biochemical phenotype.
      3. Molecular genetic testing: possible when the two disease-causing *NPC1* or *NPC2* mutations have been identified in the proband.
3. Carrier testing: available by molecular testing if the *NPC1* or *NPC2* gene mutation has been identified in the proband
4. Management (Vanier 2010)
   1. Symptomatic management
      1. Antiepileptic drugs for seizures.
      2. Anticholinergic agents for dystonia and tremor.
      3. Physiotherapy for spasticity and prevention of contractures.
      4. Melatonin may be used to treat insomnia.
      5. Special schooling.
      6. Proper management of infections.
      7. Gastrostomy for feeding difficulties.
   2. Bone marrow transplantation
      1. Regression of hepatomegaly and lung infiltration (Hsu et al. 1999).
      2. Unfortunately neurologic status continues to deteriorate.
   3. Liver transplantation with cirrhosis does not influence the course of neurologic deterioration (Gartner et al. 1986).
   4. A rationale supporting early hematopoietic stem cell transplantation in NPC2 patients because the NPC2 protein is soluble, secreted, and recaptured (Verot et al. 2007; Bonney et al. 2010).
   5. Miglustat.
      1. A controlled clinical trial was initiated in neurologically symptomatic patients, first in adolescents and adults (12 years and above) (Patterson et al. 2007), then in children (4–12 years). Overall, the disease course stabilized in 72% of patients treated for 1 year or more.
      2. In January 2009, the European Union has extended the indication of miglustat to the treatment of progressive neurological manifestations in adult and pediatric patients with NP-C, and the drug is now approved for this indication in several other countries. This represents the first specific treatment for NP-C.
      3. An international, multicenter observational cohort study in 66 patients treated off-label with miglustat (Iturriaga et al. 2006; Pineda et al. 2009) further showed a significant reduction in the annual rate of progression of the disease in a majority of patients. Late-onset forms generally appeared as the best responders. A further case series from Spain has been documented (Pineda et al. 2010).
      4. Longer term studies will be important to better evaluate the disease progression

following the stabilization phase (Jacklin et al. 2010).

5. It has been recommended to treat patients as soon as they show neurological manifestations of any type.
6. Miglustat, however, is not expected to have an effect on the systemic manifestations of NP-C.

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Fig. 1 This is an 18-year-old Caucasian female who was seen because of abnormal neurologic symptoms. Early developmental milestones were on target. At 1 year of age, she was noted to walk with an unusual gait. She began staggering and waggling, accompanied with pronate wrists and "stiff arms." As she gets older, she started to have slurring speech, drooling, and choking when drinking or eating. She was also noted to have vertical gaze palsy especially with downward motion, seizures, ataxia, and loss of previously attained speech. The ophthalmology evaluation revealed inferior and superior rectus paralysis and monitor myopia. Her brother has similar clinical symptoms. He has abnormal cholesterol esterification studies with less than 10% of normal cultured fibroblast control assay results. Niemann-Pick type C mutation analysis from his fibroblast culture revealed a heterozygous sequence change in exon 8: c.1211G > A (DNA change of p.2903A > G), which is a known pathogenic mutation. He also has a heterozygous sequence change in exon 19: c.2903A > G. The significance of this sequence change is unknown. Fibroblasts from this patient displayed depressed but not absent cholesterol esterification (20% of normal control cells). Filipin staining of free cholesterol was also seen although not as dramatic as a bona fide Niemann-Pick type C patient. Her Niemann-Pick type C mutation analysis revealed the same heterozygous sequence changes in exon 8 and exon 19. The molecular findings of this patient and her brother are consistent with Niemann-Pick disease type C (Courtesy of Dr. Susonne Ursin)