INTRODUCTION

Since the early 1980s, the “Niemann–Pick disease” group of disorders has been divided into two distinct entities: (1) acid sphingomyelinase deficiencies (encompassing types A and B); and (2) Niemann–Pick disease type C (encompassing types C and D), resulting from the deficiency of either the NPC1 or the NPC2 transport proteins (Vanier and Suzuki, 1996).

ACID SPHINGOMYELINASE-DEFICIENT NIEMANN–PICK DISEASE (OR PRIMARY SPHINGOMYELINOSES; NIEMANN–PICK DISEASES TYPES A AND B)

The acid sphingomyelinase-deficient Niemann–Pick disease (ASM-deficient NPD or ASM deficiency (Schuchman, 2007)) is an autosomal recessive lipid storage disease resulting from mutations in the SMPD1 gene. The ASM lysosomal enzyme deficiency leads to progressive accumulation of sphingomyelin in systemic organs in all types of the disease, and in brain in the neuronopathic forms. A secondary accumulation of other lipids also occurs (Vanier and Suzuki, 1996). ASM deficiencies have historically been categorized into a severe, acute neuronopathic form, or type A, and a non-neuronopathic form, or type B. Intermediate cases have been described, indicating that the clinical spectrum is a continuum. Type A, frequent in the Ashkenazi Jewish population, is very rare in other populations. Type B is panethnic. Its incidence has been estimated at 1/200,000 births in France. Intermediate forms seem more common in central Europe.

Clinical forms

CLASSICAL NIEMANN–PICK DISEASE TYPE A

The neonatal period is often normal, with vomiting or diarrhea (or both) most commonly appearing in the first months of life. Failure to thrive often motivates a first consultation, leading to the discovery of a usually prominent hepatosplenomegaly (a constant sign). Hypotrophy is observed in 70% of cases. Some patients may show a minor dysmorphism, and a brownish skin pigmentation. Neurological examination is normal until 5–10 months of age. The child then shows hypotonia, progressive loss of acquired motor skills, loss of interest in the surroundings, and reduction of spontaneous movements. Slowed nerve conduction is generally present. The first evidence of psychomotor regression may be overlooked due to the severity of visceral signs and poor general condition. Macular cherry-red spots are a typical feature, but often not present until an advanced stage. The initial axial hypotonia is later combined with bilateral pyramidal signs. The patients will show an increasing spasticity, then abolished deep tendon reflexes. Seizures may occur but are not a major sign. The child often becomes cachectic. Recurrent respiratory infections are a common complication. Death classically occurs between 1.5 and 3 years of age (Vanier and Suzuki, 1996; McGovern et al., 2006). Some patients have a slightly protracted onset of the neurological symptoms and a slower course.

NIEMANN–PICK DISEASE TYPE B

Type B is a chronic, non-neuronopathic form, with an extremely variable degree of systemic involvement. The age of discovery, typically in late infancy of childhood, may vary from birth until late adulthood. A majority of patients survive until late adulthood (McGovern et al., 2008). Some children have a severe systemic disease, eventually leading to premature death (Labrune et al., 1991; Wasserstein et al., 2004; Pavlu-Pereira et al., 2005). Splenomegaly or hepatosplenomegaly constitute the presenting symptom in approximately 80% of the patients. Bruising
and epistaxis are frequent. Hypersplenism may occur in a small proportion of patients. Splenectomy is seldom necessary and should be avoided. In adults, radiographic abnormalities of the lung may be the presenting sign. Pulmonary involvement is common at all ages, and can be associated with a widely variable impairment of respiratory function (Mendelson et al., 2006). Radiographically, it manifests as a reticulonodular pattern, interlobular septal thickening, and ground-glass density. In adults with a long follow-up, pulmonary involvement is often the main complaint, ranging from dyspnea on exertion (frequent) to oxygen dependency. In children, retarded body growth is a common finding between the ages of 6 and 16 years. Skeletal age and puberty are often delayed (Vanier and Suzuki, 1996; McGovern et al., 2008). Alterations of liver function are in general mild, but a few cases have been described with liver cirrhosis and liver failure (Labrune et al., 1991). Hypercholesterolemia with marked decrease of HDL cholesterol is common even in children. Other features associated with the disease are joint/limb pain, bruising, headache, abdominal pain, or diarrhea. Ophthalmological changes include macular halo but also cherry-red spots (McGovern et al., 2008).

**Intermediate forms of acid sphingomyelinase-deficient Niemann–Pick disease**

This is a heterogenous category. Some patients are closer to type A with a late infantile, juvenile, or adult neurological onset and a slowly progressive disease that may include cerebellar ataxia, extrapyramidal involvement, or psychiatric disorders (Pavlu-Pereira et al., 2005). Others are closer to type B, with minimal nervous system involvement (often peripheral neuropathy) and/or mild mental retardation (Wasserstein et al., 2004, 2006).

**Laboratory diagnosis**

Bone marrow usually reveals the presence of foamy histiocytes or sea-blue histiocytes. Chitotriosidase activity is generally moderately increased. The diagnosis is established by demonstration of a deficiency in activity of acid sphingomyelinase in white blood cells or cultured skin fibroblasts. The choice of a method with high specificity and sensitivity is critical. Genotyping is useful for subsequent genetic counseling and may help to predict a phenotype (note that in neuronopathic forms, decreased peripheral nerve conduction velocities are an early sign). Well over 100 mutations of the *SMPD1* gene are known. In Ashkenazi Jewish type A patients, three mutations account for > 90% of alleles. The common p.R610del mutation is “neuroprotective” (always associated with a B phenotype).

Prenatal diagnosis is possible by measurement of sphingomyelinase activity or DNA testing on uncultured or cultured chorionic villus sampling, or cultured amniocytes.

**Management and therapy**

To date, management of all types of ASM-deficient NPD is still symptomatic. Major feeding problems are common in type A. In follow-up of type B patients, pulmonary function testing is important. Bone marrow transplantation has shown no evidence of neurological improvement in type A patients. Splenectomy should be a last resort in type B patients, as it may worsen the interstitial pulmonary disease. Some type B patients will need various levels of oxygen therapy and many adults are treated by hypcholesterolemic drugs.

Type B patients are appropriate candidates for enzyme replacement therapy by recombinant acid sphingomyelinase. The proof of concept was obtained in a preclinical trial and safety data from a phase I clinical trial have been released (McGovern et al., 2011). The phase II trial is planned for the near future.

**Niemann–Pick disease type C**

Niemann–Pick C disease (NP-C) is an autosomal recessive atypical lysosomal lipid storage disorder due to mutations of either the *NPC1* (95% of families) or the *NPC2* gene. In both cases the metabolic lesion is similar and involves a unique impairment in processing and utilization of endocytosed cholesterol that explains the complex lipid storage observed in extraneural tissues. The disease is often described as a cellular cholesterol trafficking defect but the situation is more complex in the brain, where neurons accumulate mostly GM2 and GM3 gangliosides, and much less cholesterol. The full functions of the NPC2 and NPC1 proteins have not yet been elucidated. Main features of the neuropathology include neuronal storage, prominent neuronal loss (especially of Purkinje cells), ectopic dendrites, neuroaxonal dystrophy, and Alzheimer-like changes. No clinical or biochemical feature clearly distinguishes patients belonging to the largely dominating NP-C1 group (*NPC1* mutations) or to the very rare NP-C2 group (*NPC2* mutations). The disease is panethnic and has an estimated incidence of approximately 1/100 000 live births (Vanier, 2010). The historical Niemann–Pick type D is now included in the NP-C1 group.

**General clinical features**

The clinical presentation of NP-C is extremely heterogeneous, with an age of onset ranging from the perinatal period until well into adult age (as late as the seventh decade of life). Similarly, the lifespan of the patients varies between a few days until over 60 years of age, although a majority of cases die between 10 and 25 years. NP-C is classically a neurovisceral condition. Visceral involvement (of liver, spleen, and sometimes lung) and neurological or psychiatric manifestations arise at
different times, and they also follow completely independent courses. Systemic disease, when present, always precedes onset of neurological symptoms, but the systemic component may be absent or minimal in approximately 15% of all patients, and close to half of the adult-onset patients, at least at the time of diagnosis. Apart from a small subset of patients who die at birth or in the first 6 months of life from hepatic or respiratory failure, and exceptional adult cases, all patients will ultimately develop a progressive and fatal neurological disease. In typical patients, the neurological disorder consists mainly of cerebellar ataxia, dysarthria, dysphagia, and progressive dementia, and the majority of cases show a characteristic vertical supranuclear gaze palsy (VSGP). Cataplexy, seizures, and dystonia are other quite common features, and psychiatric disturbances are frequent in late-onset patients. The proper recognition of VSGP is essential, but this sign is often overlooked at an early stage, because slow pursuit is often maintained although saccade velocity is already impaired. Cataplexy (with or without narcolepsy), usually laughter-induced, is another more specific symptom. Except for the perinatal period, the systemic disease is usually not very severe. The splenomegaly has been noted to fluctuate and to decrease with time. Severe lung involvement has been reported in a few patients (mostly NP-C2). Note that the age of onset of the systemic symptoms is not related to that of the neurological disease (the latter can occur many years, or even decades, later) (Patterson, 2003; Vanier and Millat, 2003; Wraith et al., 2009; Vanier, 2010).

Clinical forms

Patients are often classified by age of onset of disease. For periods other than perinatal, some patients present with systemic involvement only, while others (with often pre-existing systemic involvement) start their neurological disease at this time. Because the age of neurological onset usually correlates with the general later course of the disease and lifespan (unlike systemic symptoms), a classification of patients by neurological forms is often more useful to compare natural histories. The main clinical features are summarized in Figure 176.1.

**Fig. 176.1.** Schematic representation of the clinical aspects of Niemann–Pick C disease. Particular emphasis is given to the main initial neurological manifestations. (Modified from Vanier, 2010.)
PERINATAL PRESENTATION

Fetal hydrops (rapidly fatal) or fetal ascites can occur. In about 40% of patients, a prolonged neonatal cholestatic icterus is present in association with progressive hepatosplenomegaly. It most often resolves spontaneously (only hepatosplenomegaly remains, until the first neurological signs appear). In about 10% of these cases, however, it worsens and leads to liver failure; children with this rapidly fatal neonatal cholestatic form usually die before 6 months of age. A few infants present with a severe respiratory insufficiency (together with hepatosplenomegaly or liver disease) that may also be fatal. Patients with NP-C do not show neurological manifestations during the neonatal period, but note that those dying from a severe perinatal form may have siblings with a neurological form (Vanier and Suzuki, 1996).

NEUROLOGICAL FORMS

Early infantile neurological onset form. Hepatosplenomegaly (often with a history of neonatal icterus) has been present since early life. Delay of developmental motor milestones from the age of 8–9 months and central hypotonia constitute the first neurological symptoms, which become more evident between 1 and 2 years of age. The subsequent course includes a loss of acquired motor skills, proportionally less marked mental regression, followed by spasticity with pyramidal tract involvement. Most patients never learn to walk. Intention tremor is frequent; VSGP is often absent or not recognized. Seizures are uncommon. Brain imaging shows signs of leukodystrophy and cerebral atrophy. Survival rarely exceeds 5 years.

Late infantile and juvenile neurological onset forms. These constitute the large majority of cases. In patients with neurological onset between 3 and 5 years (late infantile), systemic symptoms have generally been present for a varying period. Language delay is frequent. The child often presents with gait problems, frequent falls, and clumsiness, due to ataxia, and progressive VSGP. Cataplexy frequently develops. Impairment in mental development becomes obvious. In patients with neurological onset between 5–6 and 12–15 years (juvenile), a moderate splenomegaly is frequent but reported absent in at least 10% of cases. School problems with difficulties in writing and impaired attention or dyspraxia are common. VSGP is present. The child becomes clumsier, shows learning disabilities, and often develops cataplexy. Ataxia becomes obvious. Action dystonia is frequent. In both forms, about half of the patients develop seizures of various types. As ataxia progresses, dysphagia and dysarthria appear. Cognitive impairment is variable. At a later stage, dysarthria and swallowing problems worsen, motor impairment is major. Patients develop pyramidal signs and spasticity. Death most often occurs between 7 and 12 years of age in the late infantile form. The lifespan varies from late teens until age 30 or later in patients with juvenile onset.

Adolescent and adult neurological onset form. This often manifests as an attenuated juvenile form with an insidious onset, but in at least one third of cases, patients show a psychiatric presentation that may remain isolated for several years. Psychiatric signs are most often consistent with psychosis. At this stage the neurological examination may be normal. Splenomegaly is absent in close to half of the patients. Some patients show severe ataxia, dystonia, and dysarthria with variable cognitive dysfunction, whereas psychiatric symptoms and dementia dominate in others. Movement disorders (58%) are more frequent than in the juvenile form; epilepsy is rare (15%) (Sevin et al., 2007). The later course is similar to that in the juvenile form.

Laboratory diagnosis

Foam cells and sea-blue histiocytes are often present in bone marrow. The primary laboratory diagnosis is based on the demonstration of impaired intracellular cholesterol transport in cultured cells (skin fibroblasts). The “filipin test” (see Ch 172 and Fig. 172.2) constitutes the most sensitive assay. LDL-induced cholesterol esterification has now been superseded by mutation analysis. NP-C cells stained by filipin show numerous strongly fluorescent (cholesterol-filled) perinuclear vesicles. This “classical” pattern is observed in 85% of cases. A lesser level of storage (determined by specific mutations) or “variant” pattern occurs in the remaining cases, for which mutation analysis may be required for final diagnosis. It is, in fact, advisable to undertake gene testing in every diagnosed patient, since molecular genetic study is now the highly preferred strategy for prenatal diagnosis. Over 300 NPC1 mutations are known to date. Only two of these are frequent, p.I1061T and p.P1007A. NPC1 and NPC2 mutations correlate with the neurological form of the disease, not with the systemic manifestations. Prenatal diagnosis is optimally achieved by molecular genetics on uncultured or cultured chorionic villi, or cultured amniocytes (Wraith et al., 2009; Vanier, 2010).

Management and therapy

Management remains largely symptomatic. Gastric stomy is often required. Cataplexy often responds to protriptyline, clomipramine, or modafinil. Bone marrow transplantation has been unsuccessful in NP-C1 but there is a rationale in NP-C2 (unlike NPC1, the NPC2 protein is secreted and recaptured). Among experimental therapies tested in animal models, the best results were...
obtained with miglustat or cyclodextrin (Vanier, 2010). Clinical trials have been conducted using miglustat and this drug is currently approved in Europe and in a number of other countries for the treatment of neurological manifestations of NP-C. Published reports have concluded that miglustat globally slows the progression of disease in a majority of not too advanced patients. Late-onset forms generally appeared as the best responders (Wraith and Imrie, 2009; Patterson et al., 2010; Wraith et al., 2010). A major problem in developing therapies towards the brain dysfunction in NP-C is the unknown nature of the primary target(s).

Two additional diagnostic and management guidelines papers based on expert opinion have been published (Patterson et al., 2012; Wijburg et al., 2012). A screening test based on the study of plasma oxysterols (Porter et al., 2010) is under evaluation. A clinical trial with intracerebroventricular administration of 2-hydroxypropyl-beta-cyclodextrin has been initiated.

REFERENCES


