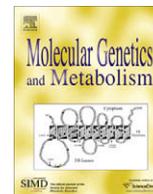




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Commentary

Recommendations on the diagnosis and management of Niemann-Pick disease type C

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ABSTRACT

Niemann-Pick disease type C (NP-C) is a lysosomal storage disease in which impaired intracellular lipid trafficking leads to excess storage of cholesterol and glycosphingolipids in the brain and other tissues. It is characterized clinically by a variety of progressive, disabling neurological symptoms including clumsiness, limb and gait ataxia, dysarthria, dysphagia and cognitive deterioration (dementia). Until recently, there has been no disease-modifying therapy available for NP-C, with treatment limited to supportive measures. In most countries, NP-C is managed through specialist centers, with non-specialist support provided locally. However, effective patient support is hampered by the absence of national or international clinical management guidelines. In this paper, we seek to address this important gap in the current literature. An expert panel was convened in Paris, France in January 2009 to discuss best care practices for NP-C. This commentary reviews current literature on key aspects of the clinical management of NP-C in children, juveniles and adults, and provides recommendations based on consensus between the experts at the meeting.

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Introduction

Niemann-Pick disease type C (NP-C)¹ is a panethnic, autosomal recessive neurodegenerative disease with a minimal incidence calculated as 1:150,000 live births [1–5]. This is probably an underestimate, however, with the incidence more likely to be around

1:120,000 live births, based on the number of diagnosed cases versus births during the past 20 years (Vanier, unpublished data). The disease is characterized by a variety of progressive, disabling neurological symptoms including clumsiness, limb and gait ataxia, dysarthria, dysphagia and cognitive deterioration (dementia) [1,6–8]. In the terminal phase of the illness, patients are typically immobile, tube-fed,

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¹ Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; GD1, Gaucher disease type 1; GM2/GM3, gangliosides M2 and M3; GSL, glycosphingolipid; HSEM- α , horizontal saccadic eye movement asymptotic peak velocity; H-MRS, proton magnetic resonance spectroscopy imaging; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NP-A/NP-B/NP-C, Niemann-Pick disease types A, B, C; NPC1/NPC2, specific gene mutations in patients with NP-C; SEM, saccadic eye movement; VSEM, vertical saccadic eye movement; VSGP, vertical supranuclear gaze palsy.

and demented [6,7,9]. NP-C imposes an emotional and economic burden on patients, families and society that is disproportionate to its relative infrequency.

Unlike Niemann-Pick disease A and B, which are caused by a primary deficiency of the enzyme, acid sphingomyelinase, NP-C is associated with mutations of the genes, *NPC1* and *NPC2*, with no primary defect in catabolic enzymes. *NPC1* gene mutations are present in 95% of cases, and *NPC2* mutations are present in approximately 4%; the remainder of patients are biochemically proven cases who do not have identified mutations [10–13]. At the cellular level, these mutations give rise to characteristic abnormalities in the intracellular transport of cholesterol, glycosphingolipids and sphingosine [14–21]. Impaired function of the *NPC1* and *NPC2* gene products, which normally function cooperatively in intracellular lipid transport [1,14], leads to the accumulation of these lipids in the late-endosomal/lysosomal intracellular compartment, and excess bulk build up in various tissues. Unesterified cholesterol, sphingomyelin, bis(monoacylglycero)phosphate, glycosphingolipids and sphingosine are stored in excess in the liver and spleen, while levels of glucosylceramide, lactosylceramide and above all, GM2 and GM3 gangliosides are markedly increased in the brain [8,19,20,22–24].

NP-C has an extremely heterogeneous clinical presentation characterized by a wide range of symptoms that are not specific to the disease, and which arise and progress over varied periods of time [6–8]. This complicates diagnosis, and is likely an important factor in the under-detection of the NP-C and, in some cases, its misdiagnosis. Even after multiple clinical screening tests to distinguish NP-C from other neurological diseases, confirmation of a diagnosis requires involved biochemical and molecular-genetic laboratory testing [1,2]. The diagnosis of NP-C can therefore be a prolonged process, and necessitates awareness by specialists in many disciplines [8,9,25]. In the first decade of life, the most common presentations are neurological, although early-onset patients are often diagnosed based on isolated systemic manifestations [26,27]. Many cases are also diagnosed in adulthood (as late as the seventh decade of life) [8,28–30]. The age at onset of neurological symptoms has a major influence on disease progression; if neurological symptoms arise early in life, the rate of deterioration is generally faster and premature death occurs sooner [7,28,31].

Until recently, no disease-modifying therapy has been available for NP-C. Therapy has been limited to supportive measures, including pharmacotherapy to alleviate neurological symptoms [9,32]. Specific, disease-modifying therapies are required that can stabilize patients by slowing or stopping the progression of neurological symptoms. The recent approval of miglustat, based on preclinical evidence [33], a prospective clinical trial [34–36] and a retrospective cohort study [31], is a significant step toward addressing the unmet therapeutic needs in NP-C.

The rarity of NP-C, the marked heterogeneity and the non-specificity of its clinical symptoms, the prolonged and technically demanding nature of its diagnosis, and the relative current lack of clear agreement regarding disease and therapeutic monitoring, together present significant challenges to the clinical management of the disease. In most countries, NP-C is managed through specialist centers, with non-specialist support provided locally. Effective patient support is hampered by the absence of national or international clinical management guidelines.

An expert panel was convened in Paris, France in January 2009, to discuss best care practices for NP-C. This document reviews current literature on key aspects of the clinical management of NP-C in children, juveniles and adults, and provides recommendations based on consensus at the meeting. While published data on the epidemiology, monitoring and treatment of NP-C are relatively scarce, efforts have been made here to provide guidance based on relevant, published evidence.

General notes

Disease types and nomenclature

- NP-C, in which the primary biochemical defect is impaired lipid transport, is distinct and separate from Niemann-Pick disease types A and B (NP-A and NP-B), which are caused by a primary deficiency of acid sphingomyelinase.
- NP-C is caused by mutations in either one of the two genes, *NPC1* or *NPC2*. Patients with *NPC1* or *NPC2* mutations are not distinguishable clinically, and symptomatic disease management is identical. Undetected causal gene mutations may also exist.
- For the remainder of this report, discussion relating to the screening, diagnosis and non-specific (supportive) therapy of the disease will refer to 'NP-C' patients as a whole. Where patients possessing *NPC1* and *NPC2* mutations are discussed in terms of specific therapy or other mutation-specific facets, the subtype names 'NPC1' and 'NPC2' are used.
- The term, Niemann-Pick disease type D (NP-D), which originally distinguished a genetic isolate from Nova Scotia from other patients with NP-C, should no longer be used. NP-D is biochemically and clinically indistinguishable from NP-C, and describes a group of patients with a common founder mutation in the *NPC1* gene [8,37].

Pattern of occurrence

- NP-C is a panethnic condition, arising sporadically and with similar frequencies across all populations, regardless of ethnic ancestry. Genetic isolates have been identified which show a higher than average incidence of the disease [8,38].

Prognosis

- Essentially all patients with NP-C die prematurely, although disease progression rates and life expectancy vary greatly, primarily dependent on the age at onset of neurological symptoms.
- In some very rare cases, patients can survive into the sixth or even seventh decade of life, and to date, some reported cases have never exhibited neurological abnormalities.
- Estimates of age at onset and prognosis based on studies conducted in the USA and Europe are summarized in Table 1 [6,7,39].

Referral to specialist centers

- Patients with NP-C can initially present first to a wide range of healthcare professionals, including neonatologists, family practitioners, pediatricians, pulmonologists, medical geneticists, hematologists, pediatric gastroenterologists, child and adult neurologists, internists and psychiatrists.
- Patients found to be at risk of NP-C following screening should be referred to regional or national care centers specializing in the diagnosis and treatment of lysosomal storage disease. If patients are not able to travel to such centers, specialists should be consulted and kept up to date on patient progress.

Patient associations and research foundations

- Patient organizations and research foundations play a vital role in providing support to both patients and relatives, raising awareness of the disease and communicating current, accurate and practically useful data to families and healthcare professionals.

Table 1

Estimates of age at diagnosis and prognosis in NP-C patients categorized from the age at onset of neurological disease.

| | Age group | Mean (range) | |
|---------------------|-----------------|------------------------|-----------------------|
| | | Age at diagnosis | Age at death |
| Spain [39] (n = 45) | Early infantile | 1.5 yrs (3 mo–3 yrs) | 4 yrs (3.5–5 yrs) |
| | Late infantile | 5 yrs (6 mo–7 yrs) | 11 yrs (7–15 yrs) |
| | Juvenile | 11 yrs (1.5–23 yrs) | 16 yrs (11–21 yrs) |
| | Adult | 24 yrs (20–30 yrs) | – |
| UK [6] (n = 44) | Early infantile | 5 mo (4–6 mo) | 4 yrs (3.5–4.5 yrs) |
| | Late infantile | 10 mo (9–11 mo) | 7 yrs (5.5–10 yrs) |
| | Juvenile | 9 yrs (1 mo–2 yrs) | 18 yrs (5–40 yrs) |
| | Adult | 17 yrs (14–20 yrs) | 33 yrs (27–37 yrs) |
| France* (n = 70) | Early infantile | 1.3 yrs (1 mo–3.5 yrs) | 3.8 yrs (1.6–6.5 yrs) |
| | Late infantile | 4 yrs (1 mo–7 yrs) | 10 yrs (6.5–14 yrs) |
| | Juvenile | 9 yrs (8 mo–16 yrs) | 19 yrs (13–34 yrs) |
| | Adult | 27 yrs (3 mo–58 yrs) | 44 yrs (28–49 yrs) |
| USA [7] (n = 87) | Overall | 10.4 yrs (9.3 yrs) | 16.2 yrs (11.1 yrs) |

* Unpublished data from the French Committee for the Evaluation and Treatment of Niemann-Pick diseases (CETNP).

- The promotion of further research by provision of a functioning infrastructure of relevant contacts and resources, including national specialist treatment centers, is crucial to advancing knowledge regarding therapy and disease management in rare diseases such as NP-C.
- Below is a list of the major bodies providing support for NP-C within Europe:

(1) Patient associations

- France: Vaincre les Maladies Lysosomales; <http://www.vml-asso.org/>.
- Germany: Niemann-Pick Selbsthilfegruppe e.V; <http://www.niemann-pick.de/news.php>.
- Italy: Associazione Italiana Niemann-Pick Onlus; <http://www.niemannpick.org/>.

Table 2

Characteristic clinical signs and symptoms in NP-C, by age at onset.

| Age at onset | Systemic manifestations | Neurological manifestations |
|---|--|--|
| Pre-/peri-natal period (≤ 3 mo) | Fetal hydrops Hepatosplenomegaly Fetal ascites with or without persistence after birth Prolonged cholestasis (frequent) Hepatosplenomegaly Respiratory failure Hepatic failure | Usually not recognized |
| Early-infantile period (3 mo to <2 yrs) | Isolated hepatosplenomegaly or Hepatosplenomegaly | Delayed developmental motor milestones Central hypotonia Hearing loss VSGP ^a (usually not recognized) |
| Late-infantile period (2 to <6 yrs) | Isolated organomegaly or Organomegaly (usually present) | Frequent falls, clumsiness Progressive ataxia, dystonia, dysphagia, dysarthria Central hypotonia Hearing loss Seizures (partial or generalized) Cataplexy VSGP ^a (usually present) |
| Juvenile (classical) (6–15 yrs) | Isolated organomegaly or Organomegaly (not always present) | School failure, learning disability Behavioral problems Frequent falls, clumsiness Progressive ataxia, dysarthria, dystonia, dysphagia Myoclonus Cataplexy Seizures (partial and/or generalized) VSGP ^a (usually present) |
| Adolescent and adult (>15 yrs) | Organomegaly (not always present) or Isolated splenomegaly in adults has been described in exceedingly rare cases | Clumsiness Cataplexy Psychiatric signs ^b Cognitive decline, dementia, learning disability VSGP ^a (usually present) Slowly progressing motor symptoms ^c Myoclonus Seizures (partial and/or generalized) |

^a VSGP, vertical supranuclear gaze palsy – increased latency in initiation of vertical saccades, with gradual slowing and eventual loss of saccadic velocity.^b Schizophrenia (psychosis), depression.^c Ataxia, dystonia, dysarthria, dysphagia.

- Netherlands: Volwassenen en Kinderen met Stofwisselingsziekten (VKS); <http://www.stofwisselingsziekten.nl/>.
- Spain: Fundacion Niemann-Pick de Espana; <http://www.fnp.es/>.
- UK: Niemann-Pick disease group; <http://www.niemannpick.org.uk/>.

(2) Research foundations

- European Study Group on Lysosomal Diseases (ESGLD); www.esgl.org.

Screening and diagnosis

Characteristic signs and symptoms

- NP-C is a neurovisceral condition; clinical features that indicate a possible diagnosis of NP-C involve systemic, neurological and psychiatric symptoms.
- Clinical NP-C phenotypes can be broadly grouped based on age at disease onset. Generally accepted categories characterize the presentations of NP-C as pre/peri-natal [12,26,28,40,41], early infantile [28,39,42], late infantile and juvenile [7,43–48], and adolescent/adult [2,6,29,30,49,50]. Table 2 summarizes characteristic signs and symptoms by age at onset.
- In terms of natural history, NP-C neurological symptoms occur along a continuous spectrum [6,28,39,40,44], with considerable overlap between the age categories listed in Table 2.
- Specific points regarding key signs and symptoms of NP-C are noted below.

(1) Systemic symptoms:

- NP-C is a significant cause of neonatal cholestatic liver disease with associated splenomegaly, and of isolated splenomegaly or hepatosplenomegaly in childhood. Prenatal or perinatal-onset NP-C is usually only detected after investigations of systemic manifestations such as fetal hydrops, ascites, prolonged cholestasis, and cholestatic hepatopathy, which can arise in isolation [26].
- Hepatosplenomegaly in older-onset patients, if present, is usually asymptomatic and often goes unrecognized. The organomegaly may be palpable, but ultrasound examination is advisable to accurately determine the presence of organomegaly. Medical histories often reveal a past history of unexplained hepatic or splenic enlargement during childhood.
- Pulmonary infiltration with foam cells is mostly restricted to patients with early-onset disease.

(2) Ophthalmological abnormalities:

- Retinal pigment abnormalities, which are characteristic of certain lysosomal storage disorders, do not occur in NP-C. In particular, macular cherry-red spots have not been associated with the disease, in contrast to NP-A and B.
- Abnormal saccadic eye movements (SEM) are often the earliest neurological sign seen in NP-C. In most patients, the initial SEM deficit is in the vertical plane (VSEM), affecting patients' abilities to look downwards, upwards, and ultimately both. Subsequently, horizontal gaze (HSEM) is affected. Over time, these changes lead to complete supranuclear gaze palsy, where patients' abilities to read, interpret and navigate visual cues in the environment or in social interaction are limited [51,52]. Vertical supranuclear gaze palsy (VSGP) is acknowledged as a characteristic sign of NP-C.
- SEM abnormalities are most commonly detected from the late-infantile period onwards.

(3) Neuropsychiatry

- Neuropsychiatric manifestations generally appear from the late-infantile period onwards. Juvenile patients (aged 6–15 years) often experience difficulties at school and/or behavioral problems. In later-onset disease, progressive neuropsychiatric manifestations are seen, and show considerable variability between patients [8,29,30]. Older patients also generally experience difficulties in further education or work.
- Progressive cognitive decline is invariable, and ranges from subtle impairment of executive function that is only detectable by specific psychometric testing, to overt, profound dementia ultimately manifesting as pronounced apathy and mutism.
- Psychosis is a common presentation in patients with later-onset disease, and can be misdiagnosed as schizophrenia or other forms of psychosis if other neurological symptoms are not present or recognized [53]. Other common psychiatric presentations include agitation, hyperactivity, sleep disorders, bipolar disorder or depression. Although these symptoms are poorly specific if seen in isolation, association with cognitive decline, visual hallucinations, aggravation with neuroleptic drugs or catatonia are more indicative of an underlying organic disorder.

Initial (screening) assessments

- Screening evaluations in patients suspected to have NP-C should be conducted with the goal of distinguishing the disease from other lysosomal storage disorders, and should be guided by the onset and evolution of signs and symptoms over time.
- Although the clinical presentations of NP-C differ between children and adults, screening and diagnosis can be conducted using similar methods in all patients.
- Recognizing that the initial tests performed may be limited by the availability of equipment and expertise locally, all suspected NP-C patients should ideally undergo the initial tests listed in Table 3.

Table 3

Assessments for patients with suspected NP-C.

| | |
|----------------------|---|
| Medical history | Date of first-ever neurological manifestation Splenomegaly, splenectomy Neonatal cholestasis Abnormal muscle tone or posture Incoordination Poor school performance or limited working ability Seizures/cataplexy ^a |
| Clinical examination | Comprehensive neurological examination ^b Identification of characteristic signs and symptoms ^c Vital signs, body weight, height, and head circumference Eye movement evaluations (for abnormal SEM) Psychometric assessment Psychiatric evaluation Hearing test(s) ^d Ultrasound evaluation of liver and spleen size Nerve conduction studies to look for evidence of peripheral neuropathy |
| Laboratory tests | Full blood count and coagulation screen Lipid profile, transaminases (AST and ALT), urea and electrolytes Plasma chitotriosidase Bone marrow histology ^e (could be useful but not mandatory) Skin electron microscopy ^f |

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; SEM, saccadic eye movements.

^a Cataplexy in NP-C ranges from subtle signs (minor head-drop or falls, often confused with seizures), to full collapse in response to humorous stimuli.

^b Including muscle tone and strength tests, motor reflexes, assessments of movement (ataxia and dystonia), and swallowing evaluations.

^c see Table 2.

^d Audiogram and/or brainstem evoked potentials.

^e Only used in some expert centers, and may require general anesthesia.

^f Where available (see *Histology*).

- Important points relating to a number of the listed screening assessments are covered in the following brief sections.

Plasma chitotriosidase

- Plasma chitotriosidase is considered a marker of disease severity and a screening parameter in other lysosomal storage diseases (e.g., Gaucher disease) [54,55]. However, the utility of chitotriosidase in monitoring of NP-C is not established.
- Plasma chitotriosidase can be useful in screening patients for NP-C, particularly in children with isolated hepatosplenomegaly. However, this marker enzyme is neither sensitive nor specific for NP-C [56].
- Plasma chitotriosidase is generally more elevated in young patients than in adults. However, around 6% of the general population is chitotriosidase-negative [57].

Routine laboratory analyses

- Routine laboratory biochemistry profiles including standard blood biochemistry, plasma lipids and unconjugated bilirubin are generally normal in NP-C patients, but can be altered in those with hypersplenism or cholestatic liver disease.
- Mild thrombocytopenia can sometimes be seen in patients with splenomegaly.
- Low HDL-C is a common, but not universal, finding.

- While plasma transaminases are generally normal, aspartate aminotransferase (ASAT) activity can be elevated, but generally returns to normal over time.

Histology

- Examination of tissue samples by light microscopy can identify the presence of characteristic (but not specific) foam cells and/or sea-blue histiocytes in the bone marrow, spleen, liver, lung and lymph nodes [8,43,58]. In some cases, subtle involvement of the skin, skeletal muscle and the eyes can be detected [8,59]. Light microscopy, without electron microscopy of liver biopsy specimens, may miss NP-C presenting with neonatal cholestatic liver disease.
- Electron microscopy of skin biopsies [59] (or of a liver biopsy) may demonstrate polymorphous cytoplasmic bodies (PCBs), which are virtually pathognomonic of NP-C. Accurate interpretation of skin biopsies requires meticulous handling and preparation of tissues, and the involvement of an experienced pathologist [8].

Laboratory diagnosis

- Currently, biochemical tests that demonstrate impaired intracellular cholesterol transport and homeostasis are considered the primary diagnostic tests for NP-C.

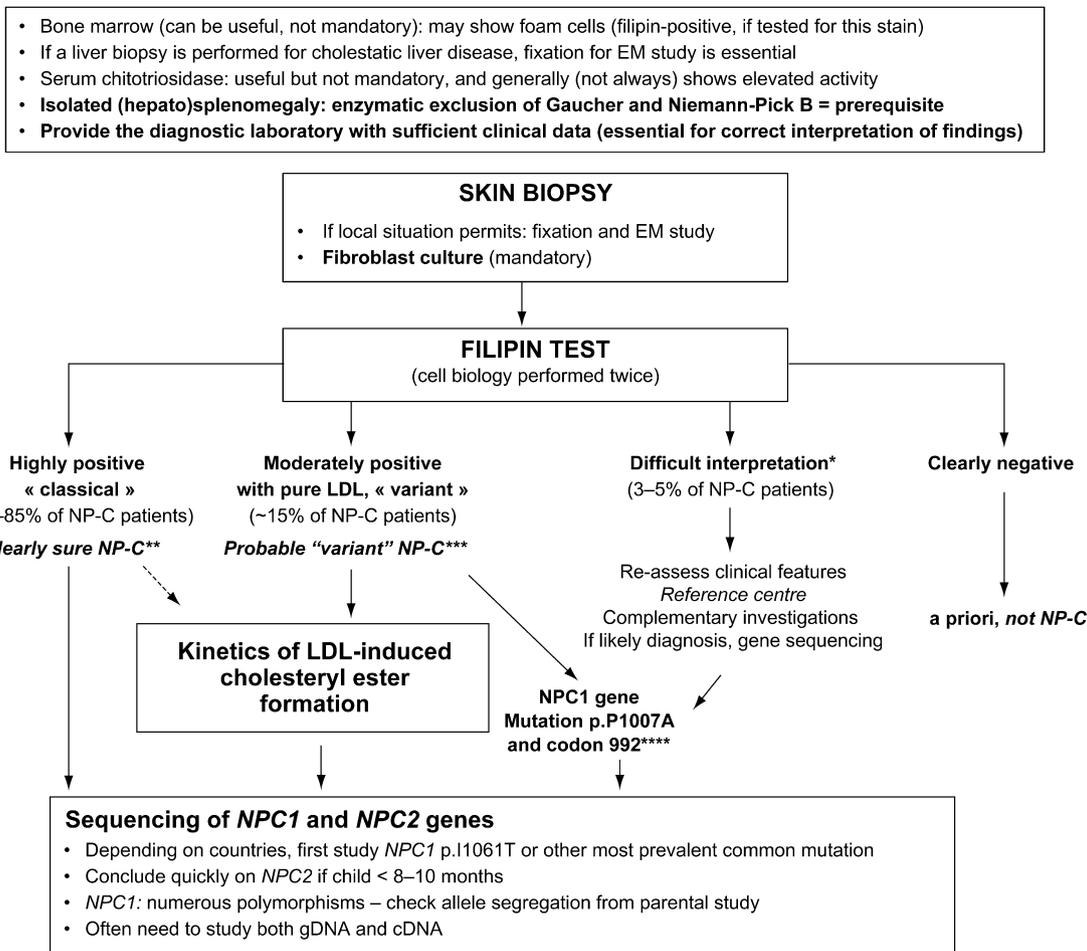


Fig. 1. Laboratory diagnostic algorithm. *Sphingomyelinase deficiency (including late-onset type A) may give a dubious filipin pattern, with normal kinetics of LDL-induced cholesteryl ester formation – most cell lines in this group (dubious filipin pattern) are eventually categorized as ‘not NPC’ after genetic studies; **false positive: I-cell disease (but very different clinical features); ***heterozygotes may show a pattern (filipin staining and kinetics of LDL-induced cholesteryl ester formation) similar to that in ‘variant’ patients; ****in many countries, NPC1 p.P1007A or different missense mutations on codon 992 constitute the most frequent ‘variant’ mutations. *Note:* Genetic studies can also be undertaken if clinical symptoms are very suggestive of a diagnosis of NP-C, even with a negative result from filipin testing.

- The presence of a disease-causing mutation on each of two alleles in *NPC1* or *NPC2* genes combined with characteristic clinical findings will confirm a diagnosis. Novel mutations may require further investigations.
- The laboratory diagnostic algorithm in Fig. 1 summarizes processes that should ideally form the basis of confirmed diagnoses in NP-C.
- Laboratory diagnostic tests for NP-C are not straightforward, must include both positive and negative controls, and are often difficult to interpret due to a variety of methodological factors. Testing should therefore be conducted in specialized centers. A quality control process to standardize diagnostic testing between centers would be highly desirable.
- The precise diagnostic evaluations undertaken in patients suspected to have NP-C, following screening, can depend on regional availability of resources and expertise.

Biochemical diagnostic testing

- The biochemical diagnosis of NP-C requires living cells – usually a skin fibroblast culture. The filipin test is currently the most sensitive and specific assay, and is considered the key biological diagnostic test for NP-C. Fibroblasts are cultured in an LDL-enriched medium, after which the cells are fixed and stained with filipin. Fluorescence microscopic examination of NP-C-positive cells typically reveals numerous strongly fluorescent (cholesterol-filled) perinuclear vesicles. This ‘classical’ storage pattern is observed in approximately 85% of cases. A lesser (and variable) level of storage is seen in about 15% of cases, who are described as having a ‘variant biochemical phenotype’. Diagnostic interpretation is often difficult in these patients, carrying a risk of false-positive or false-negative findings [60,61]. However, incubating cultured cells with LDL under specific conditions can optimize the filipin test and facilitate identification of ‘variant’ cell lines [61].
- Measurement of the LDL-induced rate of cholesteryl ester formation in cultured fibroblasts constitutes a useful secondary test. [60,61]. Patient cell lines with a ‘classical biochemical phenotype’ show null or very low rates of cholesterol esterification. Patient cell lines with a ‘variant biochemical phenotype’ display only mildly impaired esterification. Results from this test might therefore be inconclusive and in such patients, genetic mutation analysis is important to confirm diagnosis (see *Genetic testing*). Because this test is complex, costly and time-consuming, mutation analysis is often initiated directly when filipin study is clearly positive (see Fig. 1).
- Biochemical tests cannot be relied upon to identify heterozygote carriers of NP-C. The filipin test may be completely normal. A significant proportion of obligate carriers may display mild abnormalities, with similar changes to those seen in ‘variant’ cell lines.
- Prenatal diagnosis using biochemical testing has several pitfalls, and is not applicable in all families [62,63]. It is possible only in very few centers. All efforts should therefore be made to perform prenatal diagnosis of NP-C using the molecular genetic approach (see *Genetic testing*).
- Filipin staining of bone marrow smears examined in parallel with Giemsa-stained smears, revealing cholesterol-loaded foam cells, may provide a rapid screening test for NP-C, but should not be considered as a definitive assessment.

Genetic testing

- NP-C is caused by the autosomal recessive inheritance of mutations in either of two genes; *NPC1* (located to chromosome 18, q11–q12) or *NPC2* (located to chromosome 14; q24.3).

- Over 95% of NP-C patients have pathological *NPC1* mutations, with approximately 4% of patients expressing disease-causing mutations in *NPC2*; the remaining patients appear to possess as yet unidentified gene mutations [10–13]. Molecular genetic testing of *NPC1* and *NPC2* genes is offered in a number of specialized laboratories.
- Identification of *NPC1* mutations can in some instances be difficult and may require combined studies of gDNA and cDNA. Because there are numerous polymorphisms in these genes, interpretation of novel missense mutations should be undertaken with caution. The ‘variant’ biochemical phenotype is associated with certain *NPC1* mutations [11].
- Genetic testing can be vital in confirming diagnoses in patients with a ‘variant’ biochemical phenotype, and is currently considered essential for prenatal diagnosis [8,63].
- Genetic studies can also be undertaken if clinical symptoms are very suggestive of a diagnosis of NP-C, even with a negative result from filipin testing (see *Biochemical diagnostic testing*).

Carrier detection and prenatal diagnosis.

- Once mutations have been identified in the index case of a family, a parental study should be performed to ensure allele segregation. This also allows reliable detection of heterozygote carriers in family members.
- Counseling should be provided with the results of positive genetic tests for NP-C to provide information on the nature, inheritance and family planning implications of the disease.
- Prenatal diagnosis should be offered to couples with a previous affected child. Identification of mutations in every new NP-C case for which parents may request prenatal diagnosis should be a priority. DNA from both parents also needs to be studied, ideally before final genetic counseling.
- Prenatal diagnosis is best achieved using chorionic villus sampling (CVS) at 10–12 weeks. Molecular genetic analysis is the preferred strategy, and can be applied to uncultured CVS. Prenatal diagnosis by primary biochemical testing requires cell culture (see *Biochemical diagnostic testing*), and is only reliable if the affected individual in the family has a ‘classic biochemical phenotype’. Today, this method should be considered as a last resort [62,63].

Differential diagnosis

- Because of its wide range of clinical manifestations, the differential diagnosis for NP-C is broad, particularly if the phenotype is fragmentary.
- Systemic symptoms such as neonatal jaundice and isolated splenomegaly, and neurological symptoms such as dystonia, dementia, cataplexy and supranuclear gaze palsy can arise in a variety of other diseases, including other inherited errors of metabolism such as GM2 gangliosidosis and Gaucher disease type 3 [64].

Neuropathology

- Neuropathology can provide disease-specific information but can only be obtained by brain or rectal biopsy, and is therefore not suitable for NP-C screening.
- Characteristic neuropathological features include neuronal lipid storage, meganeurite formation, ectopic dendritogenesis, neuroaxonal dystrophy, neuronal loss, and neurofibrillary tangles [65–69].
- Biochemical lipid analysis of frozen tissues, preferably spleen but also liver and brain, performed by an expert laboratory, can quickly provide disease-specific information.

Treatment

- Until recently, there was no disease-modifying treatment for NP-C. Supportive therapies are variably effective for the alleviation of clinical manifestations of NP-C, and can improve patients' quality of life. High-quality general pediatric and medical care is essential to maximize quality of life in patients with NP-C.
- Palliative pharmacotherapy is available for dystonia, cataplexy, seizures, sleep disorders, gastrointestinal symptoms and, rarely, lung involvement [9,32].
- Following the approval of miglustat, treatment can be aimed toward stabilizing neurological disease.

Symptomatic therapies

Therapies for CNS manifestations

- Tricyclic antidepressants or CNS stimulants may control cataplexy [8,45,46].
- Anti-epileptic drugs can control or diminish the frequency of seizures.
- Dystonia and tremor respond well to anticholinergic drugs in some patients, and botulinum toxin can also be effective in selected cases.
- Melatonin can be used to treat insomnia. Formal evaluation by a sleep specialist may be helpful in some cases.
- Behavioral problems such as hyperactivity, hallucinations and agitation should be addressed by the patient's support team, with specialist psychiatric consultation when available and appropriate.

Management of systemic manifestations

- Patients with NP-C become malnourished as dysphagia progresses. Feeding and swallowing ability should be carefully monitored as patients are at risk of silent aspiration. Softening or thickening of foods is often beneficial in those with swallowing difficulties. Most patients with NP-C eventually require a gastrostomy tube to maintain adequate fluid and caloric intake.
- Patients with dysphagia often drool; this can sometimes be controlled by small doses of orally administered atropine, or parotid and submandibular glandular injections of botulinum toxin.
- Gastrointestinal signs are often seen in NP-C, and diarrhea can be frequent in both treated and non-treated patients. Anti-diarrhea medications and dietary modification can help, and a bowel-monitoring program should be maintained to prevent constipation.
- Secondary lung involvement due to aspiration frequently complicates dysphagia. Prophylactic antibiotic therapy may avoid pulmonary infection in these patients. Primary lung involvement directly related to NP-C disease is rare, but can be treated with aggressive bronchodilation and, in some cases, chest physical therapy. There are no controlled data from clinical trials to support the use of these interventions.

Disease-specific therapies

Treatment goals with disease-specific therapies

- Treatment goals in disease-modifying therapy for NP-C are based on its presumed and known neuropathology. Overall neurological function may be considered proportional to the sum pool of CNS neurons in networks that retain functional capacity. This pool forms the primary therapeutic target in a progressive neurodegenerative disorder such as NP-C.

- Because a fraction of the neuronal pool will likely already be irreversibly damaged or lost by the time diagnosis is made and disease-specific treatment initiated, disease stabilization or a reduced rate of disease progression is likely the best attainable goal for long-term therapy.
- Because of the variability of disease progression at different ages, treatment plans and expectations should be tailored to the individual.

Approaches supported by experimental (in vitro or animal model) data

Cell-signaling targets.

- Mobilization of endosomal cargoes may be a potential target for small-molecule therapies that are capable of penetrating intracellular compartments. Direct or indirect overexpression of the GTPase, Rab 9, can reverse the NP-C phenotype, with restoration of lipid transport in tissue culture [70,71]. A recent study showed that overexpression of Rab 9 reduced stored lipids and prolonged lifespan in a mouse model of NP-C [72].
- Data suggest that interruption of apoptosis and related routes of cell death and dysfunction may be useful therapeutic targets in NP-C [9,32].
- More evidence is required to assess the utility of cell-signaling target-based approaches in NP-C.

Neurosteroids.

- Neurosteroids can affect neuronal growth and differentiation and can modulate a variety of neurotransmitter receptors. In the *NPC1* mouse model, early intraperitoneal infusion of allopregnanolone in β -cyclodextrin appeared to delay some of the neuropathological signs of disease progression and neurological symptom onset, and to prolong survival [73–75].
- Further data are required to assess the possible role of neurosteroids in NP-C therapy.

Sterol-binding agents.

- Recent data show that early treatment of *NPC1*-mutant mice with 2-hydroxy- β -cyclodextrin resulted in strikingly reduced cholesterol concentrations in liver and spleen, ameliorated liver dysfunction and neurodegeneration, and notably prolonged survival [76].
- Further data are required regarding the possible role of such agents in NP-C therapy.

Curcumin.

- Curcumin may have beneficial effects on intracellular calcium homeostasis and, secondarily, on lipid metabolism in *NPC1*-mutant mice [77].
- Elevation of cytosolic calcium with curcumin normalized *NPC1* disease cellular phenotypes and prolonged survival in a mouse model of *NPC1* [77].
- Data from clinical studies with curcumin are required to better characterize its effects.

Approaches supported by clinical data

Tissue and organ transplantation.

- There is no evidence that the gene product of *NPC1* is transducible between cells, whereas *NPC2* protein has been shown to be secreted and recaptured [13,78].
- There is therefore some indication that bone marrow transplantation may be of clinical benefit in patients with *NPC2* mutations, although clinical experience with this intervention is currently very limited.

- Pre-clinical and clinical studies have established that, while bone marrow or liver transplantation may partially normalize tissue storage of cholesterol and sphingomyelin, they are not effective in treating neurological symptoms in patients with *NPC1* mutations [79–82].

Cholesterol-lowering agents.

- Strategies to reduce intracellular cholesterol storage have been tested, based on the hypothesis that cholesterol is an offending metabolite in NP-C. Although combinations of cholesterol-lowering agents reduce hepatic and plasma cholesterol levels, there has been no reported evidence of amelioration of neurological disease during clinical use [83,84].

Miglustat.

- Most progress in NP-C therapeutics has been made in assessing the potential role of miglustat (N-butyldeoxyjirimycin; NB-DNJ; Zavesca®, Actelion Pharmaceuticals Ltd.) for slowing or stabilizing disease progression.
- Miglustat is a small iminosugar molecule that acts as a competitive inhibitor of the enzyme, glucosylceramide synthase, which catalyses the first committed step in glycosphingolipid (GSL) synthesis [85,86]. Miglustat reduces the potentially neurotoxic accumulation of gangliosides GM2 and GM3, lactosylceramide and glucosylceramide. Miglustat does not inhibit the synthesis of sphingomyelin (an important ubiquitous sphingolipid) or galactosyl ceramide (a key component of myelin). Miglustat treatment does not lead to accumulation of ceramide [87].
- Miglustat might also indirectly modulate intracellular calcium homeostasis through its effects on glucosylceramide levels [88]. Impaired calcium homeostasis related to sphingosine storage may be an initiating factor in the pathogenesis of *NPC1* [77].
- Miglustat is able to cross the blood–brain barrier [89], and was shown to reduce GSL accumulation and cellular pathology in the brain, delay onset of neurological symptoms, and prolong survival during pre-clinical studies [33].
- Miglustat is available for the treatment of patients with mild-to-moderate type 1 Gaucher disease (GD1) for whom enzyme replacement therapy is unsuitable throughout the EU [90], the USA [91] and in a number of other countries. It was granted orphan drug designation for the treatment of NP-C in the European Union and United States in 2006 and 2008, respectively. In January 2009, the EU Commission extended its indication to the treatment of progressive neurological manifestations in adult patients and pediatric patients with NP-C [90].
- An RCT (OGT-918-007) [36] assessed the efficacy, safety and tolerability of miglustat 200 mg t.i.d. in juvenile and adult patients aged ≥ 12 years ($n = 29$), compared with standard care. A parallel pediatric sub-study assessed miglustat in children ($n = 12$) aged from 4 to 12 years. Long-term data from open-label extension treatment (up to 66 months) have also been reported [34,35]. Horizontal saccadic eye movement velocity (HSEM- α) was improved (*versus* standard care) over 12 months [36] and stabilized over 24 months [35] in children, juveniles and adults. Benefits were also seen for swallowing, ambulation, and cognition [35,36]. Overall, 72.4% of patients treated for ≥ 12 months had stabilized disease, based on a composite assessment of HSEM- α , ambulation, swallowing and cognition [92].
- An international, multicentre, observational cohort study evaluated neurological disease progression retrospectively in patients treated with miglustat in clinical practice ($n = 66$) [93], using a modified disease-specific disability scale [39] (see *Functional disability as an overall measure of neurological deterioration*). While most patients had impaired function and disease progression prior to miglustat therapy [93] the majority remained stable

or improved during treatment, and there was a significant reduction in the annual rate of progression of composite disability scale scores during a median (range) of 533 (18–1646) days' treatment; 75.4% of patients were classified as 'good responders', and the proportion of good responders increased in later-onset forms [93].

- The effects of miglustat on the systemic manifestations of NP-C have not been investigated in clinical trials, but no effects have been reported to date.
- The safety and tolerability of miglustat in NP-C appear similar to that seen in GD1 [94–96], and were generally similar between pediatric and adult/juvenile patients with NP-C. The most frequently-reported adverse events were mild or moderate diarrhea, flatulence, weight loss and tremor [35]. Gastrointestinal adverse events and mild-to-moderate weight loss (seen in 50% of patients, overall) tend to decrease over time on continued therapy, and can be managed as described in *Treatment alterations and stopping therapy*). Growth rates are not altered in pediatric or juvenile patients [35]. Mild reductions in platelet counts that were not associated with bleeding were observed in some patients, and monitoring of platelet counts is recommended in these patients [90]. As recommended in the summary of product characteristics, miglustat should not be used during pregnancy or by breast-feeding women. Studies in rats have shown that miglustat adversely affects spermatogenesis and sperm parameters, and reduces fertility [97,98]. Conversely, a pilot study conducted in normal men showed no effect of miglustat on sperm concentration, motility or sperm morphology after 6 weeks of therapy [99]. Until further information is available, male patients should cease miglustat before seeking to conceive, and maintain reliable contraceptive methods [90].
- The recommended dose of miglustat for the treatment of adult and adolescent patients with NP-C is 200 mg t.i.d. [90]. Dosing in patients between 4 and 12 years should be adjusted according to body surface area (Table 4) [90]. There is limited experience with the use of miglustat in patients with NP-C under 4 years of age.

Whom to treat

- Palliative pharmacotherapy should be offered to alleviate common neurological or gastrointestinal symptoms of NP-C, as per individual approved drug indications.
- To date, miglustat is the only approved, disease-specific therapy for the treatment of NP-C. Fig. 2 can be used as a guide in making decisions to treat with miglustat. Miglustat is not formally contraindicated in any of the patient types listed.
- Treatment should be started immediately in patients with any type of neurological manifestations. In patients who do not have neurological manifestations but for whom there is a known family history and disease course, treatment should be commenced at or before the anticipated time of neurological symptom onset (Fig. 2).
- Patients with early-infantile onset NP-C, and those with severe dementia in the terminal stage of the disease are less likely to benefit from treatment with miglustat and decisions to start treatment should be made on a case by case basis.

Table 4
Recommended miglustat dose alteration according to body surface area [90].

| Body surface area (m ²) | Recommended dose |
|-------------------------------------|--------------------------|
| >1.25 | 200 mg three times a day |
| >0.88–1.25 | 200 mg twice a day |
| >0.73–0.88 | 100 mg three times a day |
| >0.47–0.73 | 100 mg twice a day |
| ≤ 0.47 | 100 mg once a day |

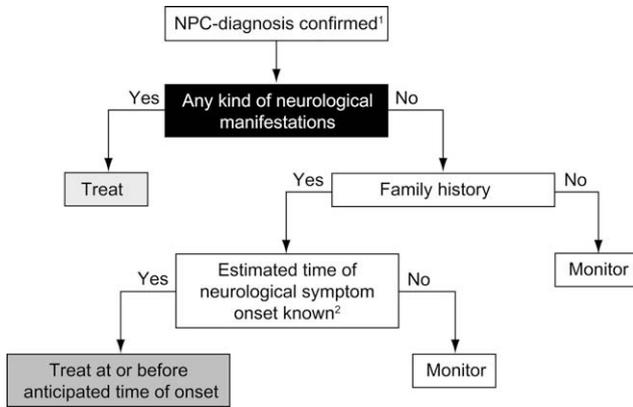


Fig. 2. Protocol for initiation of miglustat treatment in NP-C. ¹Biochemical and/or molecular-genetic diagnosis, with or without systemic or other clinical signs and symptoms. ²Patients asymptomatic or with isolated splenomegaly, and with one or more older siblings in whom the time of neurological symptom onset and rate of progression are known.

- Regional legal and regulatory criteria for initiating disease-specific therapy need to be taken into account in treating NP-C; these factors are beyond the scope of the current consensus recommendations.

When to start treatment

- Palliative pharmacotherapy should be supplied as and when the common neurological or gastrointestinal symptoms of NP-C arise, based on clinical judgment (see *Symptomatic therapies*).
- Disease-specific therapy with miglustat should be commenced as soon as possible in patients as indicated in Fig. 2 (see also *Whom to treat*).
- In patients with early-infantile onset disease, it can take 6 months to 1 year to see discernable clinical benefits. In patients with later-onset disease, it can take 2–3 years to see clinical benefits.

Treatment alterations and stopping therapy

- Palliative pharmacotherapy should be stopped based on treating physicians' judgment.
- In general, miglustat therapy should be continued as long as patients continue to derive discernable therapeutic benefits with an acceptable profile of tolerability/safety.
- Given the high variability of NP-C in terms of symptomatology and rates of progression, decisions to alter or discontinue treatment with miglustat should be based on individual patient characteristics, in consultation with patients and family members.
- Gastrointestinal effects are the chief tolerability issue with miglustat, and can usually be managed with symptomatic therapy (e.g., loperamide) or dietary modification (initiation of a diet low in lactose and other carbohydrates) [90,94]; temporary dose reduction may be of help in some patients [90].
- In cases of perceived lack of response, dose manipulation can be undertaken with careful consideration of risk versus benefit and patient tolerability.

Multiple therapies in NP-C

- Most patients with NP-C receive multiple drugs and supplements in clinical practice; miglustat does not inhibit or induce hepatic cytochrome P450 enzymes [90].
- Significant pharmacokinetic interactions with drugs that are substrates of hepatic cytochrome P450 enzymes are considered unlikely.

Disease monitoring

Monitoring disease progression and response to treatment

- Initial, baseline clinical evaluations following screening and confirmed diagnosis of NP-C (see *Initial (screening) assessments* and *Laboratory diagnosis*) should address each of the key neurological symptom types, bearing in mind the typical phenotypes seen per age-at-onset group (see Table 2).
- Table 5 provides an overall summary of evaluations that should be conducted at baseline (diagnosis or treatment start) and during regular follow up.
- A standardized video recording of a clinical examination assessing speech, walking, dysmetria, writing, dystonia and eye movements is useful in monitoring disease progression (see Appendix A).

Functional disability as an overall measure of neurological deterioration

- In order to monitor disease progression and evaluate patient responses to treatment, it is important to quantify the degree of patient disability resulting from neurological impairment.
- Iturriaga et al. [39] formulated a scale based on impairments in four key neurological parameters: ambulation, manipulation, language and swallowing. Deficits in each of these parameters

Table 5

Baseline and follow-up evaluations for NP-C.

| Assessment | Baseline | Frequency at follow up |
|---|----------|------------------------|
| <i>General</i> | | |
| Complete physical examination (including body weight, height ^a , head circumference ^a) | ✓ | Every 6 months |
| <i>Clinical parameters of neurological disease</i> | | |
| NP-C functional disability scale ^b | ✓ | Every 6 months |
| Global function video recording ^c | ✓ | Every 6–12 months |
| Assessment of seizures ^d | ✓ | Every 6–12 months |
| <i>Other measures</i> | | |
| Neuropsychiatric evaluations ^e | ✓ | Every 6–12 months |
| Hearing ^f | ✓ | Every 6–12 months |
| Serial evoked potential recordings | ✓ | Every 6–12 months |
| Ophthalmologic assessment (SEM) ^g | ✓ | Every 6–12 months |
| <i>Laboratory measures^h</i> | | |
| Routine biochemistry (ASAT, ALAT) | ✓ | Every 6–12 months |
| Hematology (blood counts) | ✓ | Every 6–12 months |
| Plasma chitotriosidase ⁱ (optional) | ✓ | Every 12 months |
| Abdominal ultrasound ^j | ✓ | Every 12 months |
| <i>Imaging^k</i> | | |
| MRI or H-MRS (optional) | ✓ | Every 12 months |

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; MRI, magnetic resonance imaging; MRS, proton magnetic resonance spectroscopy imaging; SEM, saccadic eye movements.

- ^a In children and adolescents only.
- ^b NP-C functional disability scale measures ambulation, manipulation, speech and swallowing (see *Functional disability as an overall measure of neurological deterioration*) [93].
- ^c Global functional ability videoed with parent/guardian consent in children.
- ^d Seizure type, magnitude and frequency.
- ^e Full neurological examination plus brief psychiatric evaluation using history and MMSE or similar.
- ^f Hearing assessed by audiogram or brainstem evoked potentials.
- ^g Conducted according to standard ophthalmologic assessment protocol (see *Characteristic signs and symptoms* and Appendix A).
- ^h Important in patients with systemic disease manifestations (e.g., cholestatic jaundice or pronounced splenomegaly).
- ⁱ Plasma chitotriosidase activities (optional) have not been shown to correlate with progression of neurological disease.
- ^j Organomegaly detected through abdominal ultrasound has not been shown to correlate with disease progression.
- ^k If feasible, in patients with slowly progressing disease, dependent on clinical judgment for application of general anesthesia and resource availability.

were assigned numeric scores ranging from best to worst. Disability on each parameter is assessed, and overall, composite scores with equal weighting for each of the four scale parameters are derived that represent overall ‘functional disability’ [39].

- Assessments of functional disability in patients with NP-C using this scale provide useful longitudinal, long-term follow up information. Although it has yet to undergo formal validation studies, the scale has been shown to be capable of discerning differences in severity and annual progression rates between different age subgroups of patients with NP-C (Table 6) [31].
- As with any score-based clinical assessment, patient performances are subject to normal variation. Scale scores should therefore be recorded in order to reflect patients’ best level of performance in the preceding week or month.

Additional, specific neurological symptom tests

- While the NP-C functional disability scale provides an overall assessment of disease progression, several specific tests exist that can be employed to evaluate certain domains in more detail. These are listed below. Neurological examinations should be video recorded to provide objective reference points.
- **Mobility:** The Hauser Standard Ambulation Index [100], which measures patients’ ability to walk 25 feet (7.62 m), is considered a useful measure of ambulation. Patients’ performance is rated on a 10-point scale with scores ranging from 0 (asymptomatic, fully active) through 5 (requires bilateral support and walks 25 feet in >20 s) to 9 (restricted to wheelchair; unable to transfer independently).
- **Motor function/control:** Optional tests (depending on availability) such as kinematic analysis by accelerometry (for tremor) and surface electromyography (for general movement abnormalities) can provide additional useful information.
- **Swallowing:** Deficits in swallowing, which occur late in the disease course in all patients, can be assessed using simple food-type swallowing evaluations (with sample foods of different consistencies such as water, puree, soft lumps and solids) or radiographic imaging analysis based on video fluoroscopic studies (VFS).

Other monitoring tests

Eye movements.

- As at screening (see *Characteristic signs and symptoms*), clinical examination of eye movements can be performed according to standardized protocols (see *Appendix A*).

Table 6

NP-C functional disability rating scale [39].

| Ambulation | Score | Language | Score |
|--|-------|-----------------------------------|-------|
| Normal | 1 | Normal | 1 |
| Autonomous ataxic gait | 2 | Mild dysarthria ^d | 2 |
| Outdoor assisted ambulation | 3 | Severe dysarthria ^e | 3 |
| Indoor assisted ambulation | 4 | Non-verbal communication | 4 |
| Wheelchair bound | 5 | Absence of communication | 5 |
| Manipulation | | Swallowing | |
| Normal | 1 | Normal | 1 |
| Slight dysmetria/dystonia ^a | 2 | Occasional dysphagia | 2 |
| Mild dysmetria/dystonia ^b | 3 | Daily dysphagia | 3 |
| Severe dysmetria/dystonia ^c | 4 | NG tube or gastric button feeding | 4 |

Abbreviations: NG, nasogastric.

^a Autonomous manipulation.

^b Requires help for tasks but able to feed self.

^c Requires help for all activities.

^d Understandable.

^e Only comprehensible to certain family members.

- Specialized ophthalmic assessments of SEM can be conducted based on video-recorded eye movements, and subsequent computerized measurements of peak velocity, amplitude and duration of either or both of horizontal/vertical SEM [101].

Psychometric evaluation scales.

- NP-C patients experience a variety of progressive neuropsychiatric symptoms, the most common being cognitive impairment (dementia).
- Various clinical tools are available for psychometric assessment in patients with NP-C, and expertise with different scales varies between regions.
- The Mini-Mental State Examination (MMSE) is a widely-used, generic measure of cognition [102] that has been validated for use in children [103,104]. While it is relatively insensitive in the detection of dementia in NP-C, it has been used in studies assessing neuropsychiatric decline associated with the disease.
- The Frontal Assessment Battery (FAB) evaluates cognitive domains that are commonly affected in NP-C, particularly in patients with later-onset disease with predominantly frontal dementia [105].
- Developmental scales can be used in assessments of infants and children.

Imaging.

- While optional, magnetic resonance imaging (MRI) in patients with slowly progressing disease may show cerebral atrophy and/or marked atrophy of the superior/anterior cerebellar vermis, and lesser degrees of cerebral atrophy late in the course of the illness [29]. Other visible abnormalities may include thinning of the corpus callosum and increased signal from the centrum semiovale, reflecting secondary demyelination.
- Patients with early-infantile neurological disease onset may show pronounced white matter signal hyperintensity in T2-weighted MRI images.
- Proton magnetic resonance spectroscopic imaging (H-MRSI), by evaluation of choline/creatine ratios, has been proposed as a more sensitive imaging technique to monitor disease progression in NP-C based on limited uncontrolled observations [106]. In patients with NP-C, the N-acetyl aspartate/creatine ratio is significantly reduced in the frontal and parietal cortices, centrum semiovale and caudate nucleus, and the choline/creatine ratio is increased in the frontal cortex and centrum semiovale. The use of H-MRSI has been established for the diagnosis and follow up of several inborn errors of metabolism, and has the attraction of providing objective, quantitative data [107,108].
- Preliminary data using H-MRSI in three patients treated with miglustat suggested beneficial effects of treatment on brain chemistry [107], but further studies are required to establish the utility of this technique.
- Diffusion Tensor Imaging (DTI), which measures white matter integrity as a function of water diffusion in the brain, may also prove useful in monitoring white matter changes in NP-C [109].

Biochemical markers.

- Currently there are no reliable, validated biochemical markers of neurological disease severity/progression in NP-C.
- While non-specific for NP-C, routine plasma biochemistry analyses are considered important in monitoring the safety and tolerability of treatment.
- Plasma chitotriosidase can be a useful disease screening marker in NP-C (see *Plasma chitotriosidase*), but it currently has no application as a disease-monitoring parameter as there are no data to show a correlation between plasma chitotriosidase and progression of neurological disease.

Summary points

- NP-C is a rare, panethnic, neurodegenerative disease with variable systemic manifestations. Published estimates of prevalence have varied widely [1–5]. An incidence close to 1:120,000 was calculated in France based on the number of diagnosed cases versus births during the past 20 years (Vanier, unpublished data).
- The primary biochemical defect is severely impaired intracellular lipid transport [14–21], and is caused by mutations in either one of the two genes *NPC1* (in 95% of cases) or *NPC2* (in around 4% of cases) [10–13]; undetected causal gene mutations may also exist.
- NP-C has an extremely heterogeneous clinical presentation [8,9,25]. Symptomatology, disease progression rates and life expectancy vary greatly and are strongly influenced by age at onset of neurological symptoms [7,28,31].
- Clinical NP-C phenotypes can be broadly grouped based on age at disease onset: pre-perinatal (≤ 3 months), early infantile (3 months to 2 years), late infantile (2–6 years), juvenile (6–15 years), adolescent/adult (> 15 years) (Table 2) [2,6,39]. In reality there is a considerable overlap between these categories.
- Initial screening of patients with suspected NP-C can be conducted using similar methods in all patients, according to the protocol in these consensus recommendations (Table 3).
- The key laboratory diagnostic test for NP-C is filipin staining of cultured (patient) skin fibroblasts, to demonstrate free cholesterol accumulation in lysosomes secondary to impaired intracellular cholesterol transport (Fig. 1) [60,61]. LDL-induced cholesterol esterification rate assay is a useful complementary evaluation [60,61]. Molecular genetic testing of *NPC1* and *NPC2* genes is essential to offer early and reliable prenatal diagnosis, and to confirm diagnosis in patients with a variant biochemical phenotype [11].
- Supportive therapies are variably effective for the alleviation of numerous clinical problems associated with the disease [8,32].
- Until recently, there were no available disease-specific therapies for the treatment of NP-C. With the recent approval of miglustat [90], and the possible development of additional disease-specific therapies [9,32], treatment can be aimed toward stabilizing neurological disease.
- Decisions to treat NP-C patients with miglustat should be guided by the scheme included in these consensus recommendations (Fig. 2).
- Patient disease course and response to therapy should be followed up regularly (every 6–12 months) based on investigations listed in Table 5. The NP-C functional disability scale is considered a useful measure (Table 6).
- There is an unmet need for reliable markers to monitor NP-C. There are no reliable, validated biochemical markers of neurological disease progression. Imaging techniques have potential, but further evaluation is required [106–109].

Future considerations

This is the first guideline proposed for the management of this rare inherited disease, and it is intended that this resource will be updated in the future as new data become available. Intensive research into the epidemiology, pathophysiology, diagnosis, and treatment of NP-C is ongoing at a number of expert centers. Further important findings on disease screening and the use of monitoring techniques in NP-C are expected over the coming year.

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Appendix A. Standard video protocol for clinical assessment

- (1) Speech (30–45 s)
 - Say a sentence; for example, “Hello, today is a beautiful day” (three times)
 - (2) Sitting on a bed, feet not touching the floor, arms extended forward (45 s)
 - (3) Hand movements
 - For the following exercises, the patient should be seated comfortably (feet and trunk support allowed if necessary)
 - Tapping movements (thumb–index grip) (5–10 times each)
 - Opening and closing hands (5–10 times each)
 - Fast alternating hand movements (5–10 times, both hands together)
 - Opposition movement of the thumb with each finger
 - Nose–finger test, eyes wide open (5–10 times each)
 - (4) Feet
 - Tapping foot on the floor (10 times each)
 - Heel–shin (5 times each)
 - (5) Standing and walking barefoot
 - Spontaneous standing (15 s)
 - Stand with feet together (15 s)
 - Standing with feet in tandem (15 s)
 - Walking and normal half-turn (15 s)
 - Walking with feet in tandem (15 s)
 - (6) Writing/drawing (dominant hand)
 - Write a sentence, for example “Today is a beautiful day”. For younger children, make a drawing or a spiral
 - Filming the page
 - (7) Ocular movements
 - Voluntary saccadic eye movements: upward, downward, right, left (two cycles)
 - Eye pursuit (finger): upward, downward, right, left (two times, assessing velocity)

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