6. Diagnosis

- Laboratory diagnostic tests for NP-C are complex and can be difficult to interpret due to a variety of methodological factors.
- Diagnostic testing to confirm NP-C, following screening and differential diagnosis, should therefore be conducted by, or in consultation with, regional or national care centers specializing in the diagnosis of inherited metabolic disorders [26].

6.1. Biochemical testing

- The demonstration of impaired intracellular cholesterol transport by filipin staining in fibroblasts cultured from patient skin biopsies remains a key diagnostic test for NP-C (Fig. 4).
- In 80–85% of cases, fluorescence microscopic examination of NP-C positive cells typically reveals strongly fluorescent, cholesterol-filled perinuclear vesicles—the ‘classical’ cholesterol storage pattern [44]. Most other cases with a ‘variant biochemical phenotype’ show a less pronounced, more variable cholesterol storage [44,124,125].
- LDL-induced cholesteryl ester formation assays are no longer systematically used as a secondary biochemical test, as they are technically challenging (particularly in variant cases), costly and time-consuming [5].
- Biochemical tests cannot be relied upon to identify heterozygote carriers of NP-C in whom filipin test findings may either appear normal or display mild abnormalities, with changes similar to those seen in ‘variant’ cell lines [42,44].

6.2. Genetic testing

- NP-C is caused by autosomal recessive 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 [8,10,126,127].
- DNA sequencing should ideally be performed in parallel with filipin staining examinations, where possible (Fig. 4). Significant advances have been made in genetic sequencing of NPC1 and/or NPC2 gene mutations, but it is not yet possible to replace filipin staining with DNA sequencing as the primary diagnostic method.

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**Fig. 4.** Algorithm for the laboratory diagnosis of NP-C. *New test under clinical development* (see Section 6.3.2); **two subsequent filipin tests (not duplicate); 5-cell disease (ML-II and -III) gives a false positive result (but very different clinical features); 6ASM deficiency can give a similar filipin pattern; 7Not certainly pathogenic; 8DNA is usually needed to study the effect of splice mutations. Abbreviations: GD, Gaucher disease; ASM, acid sphingomyelinase; EM, electron microscopy; MLPA, Multiplex Ligation-dependent Probe Amplification (this technique evaluates copy number changes, and has allowed detection of large deletions in the NPC1 gene. It has also been useful to detect a false homozygous status with a deletion on the other allele). Note: a '+' sign or a '-' sign in this figure denotes 'positive' or 'negative', respectively, with respect to filipin staining.

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7. Treatment

- Progressive neurological manifestations in NP-C have a profound effect on the quality of life of both patients and their carers/family [132]. The correct, early identification of NP-C and the appropriate application of symptomatic and disease-specific therapies can dramatically improve quality of life for all those affected.
- In the absence of any curative treatment, quality of life represents a legitimate treatment goal in the management of NP-C [27], and can be addressed by 1) rigorous symptomatic treatment, and 2) miglustat therapy for existing neurological manifestations.
- Where applied, pharmacotherapies should be used according to individual approved drug indications.

7.1. Symptomatic therapies

7.1.1. Neurological manifestations

7.1.1.1. Seizures

- After full clinical appraisal of seizure semiology supported by EEG findings, the most appropriate drug should be selected according to identified seizure type.
- Drug doses should be increased until seizure control is achieved or adverse effects supervene, and it should be borne in mind that a seizure-free period could signal disease-related changes (e.g. loss of seizure-generating neurons). Antiepileptic drug therapy should therefore be reviewed in patients free of seizures for prolonged periods.
- If two or more drugs were used in appropriate doses for an adequate period are ineffective in controlling seizures, the likelihood of achieving control is poor.
- Patients who develop severe epilepsy generally have a worse prognosis and reduced lifespan compared with otherwise similar patients who are seizure free.

7.1.1.2. Cataplexy

- Tricyclic antidepressants or CNS stimulants have been shown to ameliorate cataplexy [58,59].

7.1.1.3. Dystonia and tremor

- These manifestations respond well to anticholinergic drugs, at least transiently, in some patients.
- Other drugs that can be effective include: trihexyphenidyl, benzodiazepines, and botulinum toxin (in selected cases). Gamma-aminobutyric acid derivatives may help in patients with advanced dystonia.
- In patients receiving antipsychotic therapy, low-potency atypical agents should be used to avoid worsening of dystonia, supplemented with sodium valproate as needed.

7.1.1.4. Dysphagia

- Swallowing function should be monitored closely, particularly in patients considered to be at risk of aspiration [39]. Patients should be closely monitored in the event of secondary lung involvement due to aspiration.
- Feeding management and/or dysphagia need to be tackled as early as possible; measures include softening or thickening of food and gastrostomy (to maintain adequate fluid and caloric intake).

7.1.1.5. Drooling

- Drooling can be a distressing manifestation in NP-C patients; oral atropine, parotid/submandibular injections of botulinum toxin,
hyoscine patches or glycopyrrolate bromide can be used to reduce the volume of secretions.

7.1.6. Sleep disturbances

- Narcolepsy, sleep inversion and/or obstructive sleep apnea may occur in addition to cataplexy, and can be treated with melatonin or positive airway pressure.

7.2. Cognitive impairment

- After careful assessment on relevant neuropsychological scales (see Section 5.3), appropriate support services should be provided for patients with cognitive impairment.
- There is no evidence that cognition-enhancing drugs can ameliorate cognitive impairment in NiP-C. However, treatment with miglustat may stabilize cognitive decline (see Section 7.2).

7.3. Psychiatric Illness

- Psychosis often responds to antipsychotic medication, although some NiP-C patients exhibit treatment resistance or even paradoxical worsening. Atypical antipsychotics and regular neurological monitoring are recommended in order to minimize aggravation of any pre-existing dystonia.
- Electro-convulsive therapy (ECT) has been successfully used in patients with catatonia [66].
- Mood stabilizers such as sodium valproate have been described as effective in the treatment of bipolar disorder [66,75], and depression is generally responsive to selective serotonin reuptake inhibitors [43,54].
- Family and end-of-life planning and support should be provided to all patients after diagnosis.

7.4. Systemic manifestations

- Gastrointestinal disturbances such as diarrhea are often seen in NiP-C. Diarrhea can be managed with anti-propulsive agents such as loperamide, and bowel-monitoring programs can be instituted to prevent constipation in affected patients [133].
- Primary lung involvement directly related to NiP-C disease is rare, but can be treated with aggressive bronchodilatation and, in some cases, chest physical therapy.

7.2. Disease-specific therapy

- Miglustat (N-butyldeoxynojirimycin; NB-DNJ; Zavesca®; Actelion Pharmaceuticals Ltd) is a small iminosugar molecule that acts as a competitive inhibitor of the enzyme, glucosylceramide synthase, which catalyzes the first committed step in glucosylceramide (GSL) synthesis [134,135].
- Miglustat is able to cross the blood–brain barrier [136], 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 [28]. It may also indirectly modulate intracellular calcium homeostasis related to sphingosine storage – a suspected initiating factor in the pathogenesis of NiP-C – through its effects on glucosylceramide levels [137–139].
- Miglustat was approved for the treatment of progressive neurological manifestations in pediatric and adult patients with NiP-C in the EU in 2009 [28], and has since been approved for this indication in a number of further countries.
- The approval of miglustat was based on data from a randomized clinical trial [32], long-term extension studies [30,31] and a retrospective observational cohort study [33], demonstrating stabilization of key neurological manifestations. Findings from clinical experience studies have since confirmed these therapeutic effects [35,38,39,140].
- The safety and tolerability of miglustat in NiP-C appear similar to that seen in GD1 [28,52,133,141], and were generally similar between pediatric and adult/juvenile patients. The most frequently reported adverse events were mild or moderate diarrhea, flatulence, weight loss and tremor [30–32,35].
- 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 previously described [133,142].
- The recommended dose of miglustat for adult and adolescent patients with NiP-C is 200 mg t.d.s. [28]. Dosing in patients aged 4–13 years should be adjusted according to body surface area (Table 2) [28].

7.3. Treatment goals with miglustat in NiP-C

- Due to the neurodegenerative nature of NiP-C, disease stabilization or a reduced rate of disease progression are likely the best attainable goals for long-term disease-specific therapy [26].
- Before disease-specific therapy with miglustat is commenced, patients and family members/carers should be informed of treatment expectations based on findings from previous clinical studies.
- It can take 6 months to 1 year to see discernible clinical benefits in NiP-C patients. In cases with slowly progressive forms of the disease (e.g. adult-onset patients), it can take longer to see treatment effects.

7.4. Whom and when to treat

- Physician judgment in partnership with fully informed parents and carers should remain paramount in determining which diagnosed patients should receive miglustat.
- All patients with neurological, psychiatric or cognitive manifestations at diagnosis should be offered miglustat therapy based on potential improvements in, or maintenance of, quality of life.
- Miglustat treatment can be initiated in patients aged <4 years who have a confirmed diagnosis of NiP-C and who have neurological symptoms.
- Before initiating miglustat therapy, young patients presenting with current cholestatic disease should first receive treatment to resolve systemic manifestations; miglustat does not treat cholestatic symptoms.
- A confirmed NiP-C diagnosis should not be taken as the only reason for immediate miglustat therapy, as neurological, psychiatric and/or cognitive symptoms can take a long time to appear (if at all in rare cases), and patient/carer education and planning are required.
- Patients diagnosed as a result of sibling screening or systemic symptoms should be monitored regularly for the appearance of neurological manifestations, and treatment should be considered at the first signs of neurological disease onset.

<table>
<thead>
<tr>
<th>Body surface area (m²)</th>
<th>Recommended dose</th>
</tr>
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<tbody>
<tr>
<td>&gt;1.25</td>
<td>200 mg three times a day</td>
</tr>
<tr>
<td>0.88–1.25</td>
<td>200 mg twice a day</td>
</tr>
<tr>
<td>0.73–0.88</td>
<td>100 mg three times a day</td>
</tr>
<tr>
<td>0.47–0.73</td>
<td>100 mg twice a day</td>
</tr>
<tr>
<td>≤0.47</td>
<td>100 mg once a day</td>
</tr>
</tbody>
</table>

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• Patients without neurological manifestations should not receive miglustat therapy, as some can remain asymptomatic for considerable periods of time [24,84,85].
• In cases where severe neurological impairment is already present at diagnosis, particularly in very young patients, miglustat is less likely to provide substantial therapeutic benefits [35].

7.5. Stopping therapy
• Miglustat treatment effects on neurological manifestations should be evaluated on a regular basis (e.g., every 6 months); and continuation of therapy should be re-appraised after ≥1 year of treatment [26,28].
• Gastrointestinal effects, the primary tolerability issue with miglustat, can be managed effectively using anti-diarrheal medication (e.g., loperamide) and/or dietary modification [28,133,142,143]. Temporary dose reduction may be of help in some patients [28].
• Treatment should be stopped whenever severe gastrointestinal disturbances occur despite dose reduction, dietary modification and symptomatic treatment.
• Discontinuation should be considered in patients who show progressive neurological deterioration leading to an unacceptable quality of life.
• Decisions to alter or stop miglustat therapy should be based on individual patient characteristics and in consultation with patients and family members.

7.6. Concomitant therapies in NP-C
• Most patients with NP-C generally receive multiple symptomatic therapies and supplements in clinical practice.
• Miglustat has a low likelihood for pharmacokinetic interactions with concomitant medications used in patients with NP-C; it does not inhibit or induce hepatic cytochrome P450 enzymes [28].

8. Disease monitoring
• Clinical evaluations following screening and confirmed diagnosis of NP-C should address each of the key neurological symptom types (see Sections 5.3 and 6).
• While it is most important to monitor 1) neurological function and 2) quality of life based on clinical judgment, the regular application of other ‘ancillary’ tests may be helpful, depending on their availability.
• Primary reasons for applying these tests are to provide objective support for key clinical observations, and to detect potential adverse effects of treatment.
• If the patient can cooperate, it is strongly recommended that video recordings of clinical examinations be taken according to a simple standardized video protocol (see Appendix A). This can help to evaluate neurological progression over years of follow up.

8.1. Physical examination
• Thorough physical examinations should be conducted every 6–12 months, and should include measurements of height and head circumference in children and adolescents.

8.2. NP-C disability rating scales
• Scales assessing impairments in key parameters of neurological disease progression in NP-C can provide useful information regarding disease progression and response to miglustat therapy [18,25,33].
• NP-C disability scales have been formulated that provide numeric scores ranging from best to worst for individual key neurological parameters, as well as overall composite scores that allow quantification of overall ‘functional disability’.
• Various NP-C disability scales are available [18,33,35,61]. The original disability scale formulated by Iura et al. [18], and subsequent modified versions [33,35], are the most widely used. The scale derived from data in the US NIH cohort [61] is comprehensive, requiring extensive laboratory investigations, and is suited for use in clinical practice. The more comprehensive scale has not been shown to offer greater clinical utility than simpler versions.

8.3. Specific neurological examinations
• Ocular–motor assessments should be conducted according to a standard assessment protocol (see www.NPC-SL.com/symptoms/neurological for example) at least once a year in childhood-onset patients to help monitor neurological disease progression.
• Swallowing should be monitored at least annually in all patients, but particularly those who present with dysphagia. Swallowing function can be assessed using simple food-type swallowing evaluations via video fluoroscopy (VFS) [36,39,140].
• Changes in ambulation can be monitored as part of standard general video assessments (see Appendix A), using simple 10-meter walk tests, or based on more formal clinical assessments such as the Hauser standard ambulation index [144].
• A variety of established tests are available for monitoring cognitive function (see Section 5.3), including the MMSE [96], ACE [99], NINCDS [100] and FAB [101]. Developmental scales can be used in infants and children.
• In patients with behavioral or psychiatric disorders, particularly those with juvenile and adolescent/adult-onset disease, neuropsychiatric evaluations such as the BPRS [94] or NPI [95] should be repeated at least annually.
• The type, magnitude and frequency of seizures (if present) should be closely documented at each clinical visit with reference to established guidelines on seizure semiology [97]; supported by EEG analysis if possible.

8.4. Systemic manifestations
• While organomegaly has not been shown to correlate with disease progression, abdominal ultrasound should be performed annually in patients with a history of previous systemic involvement, or with current splenomegaly or hepatosplenomegaly.

8.5. Laboratory assessments
• Plasma chitotriosidase 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 (see also Section 5.3). Preliminary data indicate that plasma oxysterols profiling may be of use in monitoring disease progression over time [114], but further data are required to establish the clinical utility of oxysterols as a potential monitoring method.

8.6. Imaging
• In some cases, brain imaging findings can be helpful in defining the presence or progression of neurological disease in NP-C, as well as responses to therapy.
• Magnetic resonance imaging (MRI) in NP-C patients with late-onset neurological disease often reveals cerebellar and/or cerebellar atrophy [24], and white matter hyperintensities in patients with early infantile-onset disease.
• Other brain areas that appear to be preferentially affected include the hippocampus, thalamus and striatum [145]. In addition, the
corpus callosum is commonly thinned [146], and patients may show some reduction in the midbrain area on mid-sagittal imaging [55].

- Proton magnetic resonance spectroscopic imaging (H-MRSI) is currently used in the diagnosis and follow-up of several other inborn errors of metabolism [147], and may be useful for monitoring disease progression and treatment responses in NP-C based on N-acetyl aspartate (NAA)/creatine and choline/creatine ratios [38,35,148].
- 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 [145, 149,150]. Changes in white matter appear to be widespread, affecting most major commissural, association and corticofugal/corticopetal tracts [145].
- Positron emission tomography (PET) is expensive and unlikely to be of practical use for clinical monitoring. However, this technique has been shown capable of quantifying progressive cerebral hypometabolism in NP-C patients [35,151].
- Magnetic transfer ratio (MTR) imaging has recently been reported as a possible method for quantifying brain changes in terms of both white matter and grey matter pathology in NP-C patients [152], but further data are required.

9. Future considerations

9.1. Potential future therapies

- A number of experimental strategies have been or are still being assessed for their potential use in the treatment of NP-C.

9.1.1. Strategies supported by human data

- Combinations of cholesterol-lowering agents reduce hepatic and plasma cholesterol levels, but there has been no reported evidence that this therapeutic approach can ameliorate neurological disease during clinical use [153,154].
- Unlike NPC1 protein, NPC2 protein has been shown to be secreted and recaptured. Hematopoietic stem cell transplantation may therefore be of clinical benefit in patients with NPC2 mutations, but clinical experience is very limited [155]. Hematopoietic stem cell or liver transplantation has not so far been effective in treating patients with NPC2 mutations.

9.1.2. Strategies supported by experimental data

- The interruption of apoptosis and related routes of cell death and dysfunction may be useful therapeutic targets in NP-C [27]. The overexpression of the GTPase enzyme, Rab 9, can reduce lipid accumulation in tissue culture and has been shown to prolong lifespan in a mouse model of NP-C [156–158]. Further data are required to assess this potential therapeutic approach.

- Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to slow the onset of neurological signs, as well as prolong lifespan in NPC1 mice [159]. Combination therapy with NSAIDs plus miglustat provided additive benefits, suggesting that NSAIDs could be a possible adjunctive therapy [159].

- 2-Hydroxy-β-cyclodextrin has been reported to reduce liver and spleen cholesterol, sphingomyelin, glycosphingolipids and sphingosine levels as well as brain cholesterol, gangliosides and sphingosine in animal models of NP-C [13,159–162]. These changes were associated with reduced liver dysfunction and neurodegeneration, and prolongation of survival.

- Curcumin has been reported to have beneficial effects on intracellular calcium homeostasis, lipid metabolism and survival in NPC1-mutant mice, but no clinical data are available.

9.2. Potential utility of oxysterol profiling

- Plasma oxysterol levels have been shown to be related to age at neurological disease onset in NP-C animal models and patients [113,114]. While these findings support the potential use of oxysterols as biomarkers for monitoring disease progression in NP-C, further prospective data from studies in humans are required.

- There are no current data on whether oxysterol levels correlate with filipin staining findings.

- Further data are also required regarding changes in oxysterol levels in response to miglustat therapy.

9.3. NP-C gene mutation database

- An international NP-C mutation database (http://npc.fki.ethz.ch) has been established. As more clinical and molecular data accrue, this database will facilitate genotype-phenotype correlations, and might also provide a clearer picture of ‘variant’ NP-C.

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Appendix A. Simplified 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) Hand movements
   - Opening and closing hands (5–10 times each)
   - Opposition movement of the thumb with each finger
   - Nose–finger test, eyes wide open (5–10 times each)

3) Standing and walking barefoot
   - Stand with feet together (15 s)
   - Standing with feet in tandem (15 s)
   - Walking + normal half-turn (15 s)
   - Walking with feet in tandem (15 s)

4) 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

5) Ocular movements
   - Voluntary saccadic eye movements: upward, downward, right, left (two cycles)
   - Eye pursuit (finger): upward, downward, right, left (two times, assessing velocity)

Note: Very young patients will unlikely be able to complete some of the tests specified earlier; video recording should be conducted with the consent of the parent or guardian in pediatric patients, or with the consent of the patient if he/she is an adult.

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Niemann–Pick type C: a potentially treatable disorder?

Ammar Kheder,1 Camilla Scott,2 Simon Olpin,2 Marios Hadjivassiliou1

ABSTRACT
Niemann–Pick disease refers to a group of autosomal recessive lipid storage disorders associated with a variable degree of neurological manifestations in addition to other organ involvement. Niemann–Pick disease is divided into types A–C. Of interest to neurologists is Niemann–Pick type C because of the association with neurological manifestations that are not confined to childhood. The clinical presentation of Niemann–Pick type C is variable, depending on age at onset. Neurological symptoms vary with age: hypotonia, delay in developmental motor milestones, falls, seizures, learning difficulties, ataxia with cognitive deficits and psychosis. The definitive diagnosis of Niemann–Pick type C requires demonstration of abnormal intracellular cholesterol trafficking using the filipin test. Therapeutic interventions are few but one that is of interest is miglustat, which has been approved for specific treatment of the neurological manifestations. It showed improvement in horizontal saccadic eye movement and a trend towards improvement or stabilisation in swallowing, hearing and walking. Niemann–Pick type C should be considered in patients with early-onset ataxia associated with progressive learning/cognitive difficulties even in the absence of vertical gaze palsy.

INTRODUCTION
Niemann–Pick disease refers to a group of autosomal recessive lipid storage disorders associated with variable degrees of neurological and other organ involvement (usually visceral).

A defect in cellular trafficking leads to lysosomal lipid accumulation in cells of different organs. Several lipids accumulate in the liver and spleen, including glycosphingolipids, phospholipids and sphingomyelin. Glycosphingolipid accumulates primarily in the central nervous system, causing the neurological manifestations.

The name recognises its first clinical description by the German paediatrician Albert Niemann and its pathological characterization by Ludwig Pick.1,2

Niemann–Pick disease is divided into types A–C.3 Type A is the infantile form with a high incidence among Ashkenazi Jews. Type B is less severe than A and is associated with visceral involvement and survival into adulthood.4 Niemann–Pick types A and B result from mutations on the same gene (SMPD1).

Niemann–Pick type C is of interest to neurologists because of its neurological manifestations that are not confined to childhood. Most patients presenting late (juvenile/adult form) typically have cerebellar involvement and a slowly progressive cognitive decline. Vertical supranuclear gaze palsy can be an early and useful diagnostic sign. Niemann–Pick type C is caused by mutations in either one of two genes, NPC1 and NPC2. It is not possible to distinguish clinically between these two genetic defects.

Niemann–Pick type C can present in infants, children or adults with an estimated prevalence of 1:150 000.5 There are currently about 100 cases in the UK.

CLINICAL CASES
Case 1
This 25-year-old man was referred for a second opinion. He had noticed difficulty with his writing from the age of 15 years, primarily due to tremor of his hand.

He subsequently developed problems with balance when walking. He had a few falls but did not require any walking aid. The tremor in his arms had evolved into clumsiness and his speech was becoming affected. His family commented on some cognitive decline but not bad enough to impair his ability to work as a night guard. There was no relevant family history.

On examination, his mini-mental state examination was normal. There was a full range of eye movements but non-sustained nystagmus on lateral gaze.
There was limb ataxia and he could only tandem walk with support. His reflexes were normal and plantars were flexor.

He had already undergone extensive investigations, including genetic testing for the common inherited ataxias, all of which were normal. His MRI of brain showed mild cerebellar (vermian) atrophy (figure 1). White cell enzymes showed elevated chitotriosidase. The combination of early-onset ataxia with cognitive involvement and elevated chitotriosidase raised the possibility of Niemann–Pick type C. Skin biopsy with filipin staining showed that 90% of all cells had cholesterol accumulation (figure 2). DNA analysis showed he was a compound heterozygote for NPC1 mutation (c.1133T>C, c.3591+4del). Following referral to the inherited metabolic disease centre, he started treatment with miglustat; while taking this, his condition remains stable.

**Case 2**

This 29-year-old woman attended for a further opinion. She had normal developmental milestones. At the age of 6 years, she had episodes of severe dizziness but recovered fully between attacks. During her teenage years she became clumsy and could not participate in sports. She began to struggle at school. Assessments at the time suggested elements of dyslexia and dyspraxia. She managed to graduate from a normal school with some extra support. In her early 20s she developed slurred speech, worsening gait difficulties and a tendency to fall. She also presented with symptoms of urinary frequency. At the time, there was no relevant family history.

![Figure 1. MRI from case 1 showing mild vermian cerebellar atrophy (arrow). The MRI brain appearances in Niemann–Pick type C are non-specific and occur in several different ataxias.](image1)

![Figure 2. Fluorescence microscopy showing a positive filipin test with skin fibroblasts from patient 2. The arrows point to strongly fluorescent cholesterol-filled perinuclear vesicles using fluorescence microscopy.](image2)

On examination, eye movements showed mildly restricted upgaze, broken pursuit and nystagmus on lateral gaze. She had significant gait ataxia and could not tandem walk. There was no suggestion of a peripheral neuropathy. She was emotionally labile.

Initial investigations including α-fetoprotein, serum vitamin E, genetic testing for spinocerebellar ataxia genes 1, 2, 3, 6, 7, 12, 17 and Friedrich's ataxia were all negative. MR scan of brain showed cerebellar atrophy. White cell enzymes were normal and chitotriosidase was not elevated. Muscle biopsy showed no evidence of mitochondrial disease. Cultured fibroblasts from skin biopsy showed cholesterol accumulation by filipin staining in 70% of the cells. Genetic testing confirmed the diagnosis of Niemann–Pick type C. She was a compound heterozygote for NPC1 mutation (c.3022A>C p.Ile1007Thr). She was referred to the inherited metabolic disease centre and started on miglustat.

**Case 3**

This 28-year-old woman—the younger sister of patient 2—was initially assessed in the ataxia clinic when she attended with her sister. She reported no balance problems. She was able to work as a secretary and had no history of trouble at school. Examination showed subtle signs of cerebellar dysfunction with mild gait ataxia. She was re-referred while her sister was undergoing investigations following an acute episode of psychosis requiring psychiatric input. During treatment with antipsychotics as an inpatient she was noted to be very clumsy, unsteady and with slurred speech. While undergoing inpatient psychiatric treatment, her sister was diagnosed with Niemann–Pick type C. As a result, she was also genetically tested for the condition and proved to be positive, with the same genetic defect as her sister.
NEUROLOGICAL RARITIES

CLINICAL FEATURES, DIAGNOSIS AND MANAGEMENT

The clinical presentation of Niemann-Pick type C varies with age at onset. Neurological symptoms also vary with age; hypotonia, delayed developmental motor milestones (early infantile period), ataxia, falls, seizures, learning difficulties (late infantile and juvenile period) and ataxia with cognitive deficits often follow a new onset of psychosis (adult form). In the perinatal and early infantile period there is often a history of jaundice (with hepatosplenomegaly) that often resolves spontaneously. This can be a useful diagnostic cue. Life expectancy is variable, with some patients living only a few days and others till their seventh decade. The majority of patients die before 25 years of age. The average age at death for patients presenting in adulthood is 38 years. Most patients presenting late (juvenile/adult form) have cerebellar involvement and slowly progressive cognitive decline. Vertical supranuclear gaze palsy is an early and useful sign. Dystonia sometimes occurs and about half of the patients develop seizures.

MRI is not particularly useful for the diagnosis, typically showing symmetrical cerebellar atrophy, a feature of many different ataxias.

Plasma chitotriosidase (a non-specific enzyme of storage diseases) can help to alert clinicians to the possibility of Niemann-Pick type C, but it is neither sensitive nor specific. Only one of the three cases described here had elevated chitotriosidase.

The definitive diagnosis of Niemann-Pick type C requires the demonstration of abnormal intracellular cholesterol trafficking. The filipin test is currently the most sensitive and specific assay, and is the key diagnostic test for Niemann-Pick type C before embarking on genetic testing. Filipin is a fluorescent antibiotic, which reacts with unesterified cholesterol giving a strongly fluorescent, stable cholesterol-filipin complex suitable for in situ detection. It requires the use of cultured skin fibroblasts. Skin fibroblasts are first delipidated and then exposed to a low-density lipoprotein (LDL)-enriched medium, after which the cells are fixed and stained with filipin. About 90% of Niemann-Pick type C cases show strongly fluorescent cholesterol-filled perinuclear vesicles on fluorescence microscopy. If the clinical suspicion is high and this test is negative, genetic testing is justified, as 10% of Niemann-Pick type C patients test negative on filipin staining.

Niemann-Pick type C has two disease gene loci: the NPC1 and NPC2 genes. About 95% of patients have NPC1 gene mutations, encoding the NPC1 protein, this is a large membrane glycoprotein predominantly located within the late endosomal membrane but is also transiently associated with lysosomes and the trans-Golgi network. It plays a role in LDL cholesterol intracellular trafficking, plasma levels and distribution. Disrupting this trafficking allows lipid accumulation with resulting neurological and hepatic manifestations.

NPC2 gene mutations and abnormalities of other as yet unidentified genes account for the remaining 5% of cases.

Management is largely supportive. This includes antiepileptic drugs for patients with seizures and botulinum toxin injections for those with dystonia. Physiotherapy may help the ataxia. Early diagnosis may help to identify special schooling needs for those patients with learning difficulties.

There are few therapeutic interventions but one merits further discussion: miglustat inhibits glycosphingolipids biosynthesis, decreases lipid storage and normalises lipid trafficking in B lymphocytes. In a randomised controlled study of 29 patients with Niemann-Pick type C aged ≥12 years, horizontal saccadic eye movement improved in those treated with miglustat 200 mg three times daily for 12 months versus those receiving standard care. There was also a trend towards improvement or stabilisation of clinically relevant secondary outcome measures, including swallowing, hearing and walking.

An international multicentre observational cohort study evaluated neurological disease progression retrospectively in patients treated with miglustat in clinical practice (n=66), using a modified disease-specific disability scale. While most patients had impaired function and disease progression before miglustat therapy, most remained stable or improved during treatment, and there was a significant reduction in the annual rate of progression in composite disability scores.

The most frequently reported adverse events were mild or moderate diarrhoea, flatulence, weight loss and tremor. Gastrointestinal adverse events and mild-to-moderate weight loss (50% of patients, overall) tend to decrease over time.

The Health Technology Assessment NIHR programme recently reviewed these studies and any case reports using miglustat in Niemann-Pick type C. The panel estimated the cost of caring for an adult patient with Niemann-Pick type C as £3800 per year. The mean annual cost of the use of miglustat was £94108. Using a longitudinal regression modelling of the costs, the panel found no significant association between time on miglustat and either total National Health Service, social-care and hospital-care costs, or non–hospital care costs for patients with Niemann-Pick type C. The panel acknowledged that any analysis of the association between the use of miglustat and clinical outcome were hampered by both the small numbers recruited (due to the rarity of the disease) and the lack of data regarding key outcomes for those that participated. In the case of our three patients, all have been referred to the National service for Niemann-Pick disease and are all currently on miglustat. Their condition remains stable.

An important message is that in patients with early-onset ataxia associated with progressive learning/cognitive difficulties, clinicians should consider Niemann-Pick type C even in patients without...
vertical gaze palsy. This is even more important now that there is a potential treatment.

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