bilitation of neurological disease after miglustat therapy (mean [95%CI] composite score, 0.44 [0.34, 0.55] units/ year).

Discussion and conclusion

There is agreement that disease stabilization is the best attainable therapeutic goal in patients with NP-C exhibiting neurological manifestations [42]. These observational cohort study data indicate that miglustat stabilizes neurological disease in the majority of patients with NP-C, as indicated by improvement or stabilization of all four key parameters of neurological disease progression (ambulation, manipulation, language and swallowing) analyzed in this study. The data from the observational period prior to miglustat treatment indicated a deterioration of all four neurological parameters assessed, prior to therapy. In line with previous data [2,17,22], disease progression was greater in the early childhood-onset group and lower among juveniles/adults.

Overall, the pattern of changes observed on all four neurological parameters during treatment with miglustat are consistent with findings from the clinical trial with miglustat, which indicated long-term therapeutic benefits in children and in juvenile/adult patients with NP-C [38-40]. While the majority (up to 65%) of patients in the overall cohort experienced deterioration prior to therapy, 75% were categorized as stable/improved following a mean (SD) of 1.5 (1.1) years after miglustat treatment. The composite disability score also indicated overall stabilization of neurological disease.

In this cohort, patients’ response to miglustat therapy was dependent on their age at diagnosis. Disease progression rate decreased during miglustat treatment in all age groups. Treatment effect appeared greatest in juveniles/adults, but a reduction in progression rate was also observed in patients diagnosed in early childhood. In addition, the magnitude of treatment effect was greater in patients with progressive neurological disease between diagnosis and treatment start. The minority of patients who
showed deterioration during miglustat therapy were those who were at a more advanced stage of the disease. As suggested by findings from a recent study modeling the disease course of NP-C [43], these patients were less likely to benefit from miglustat owing to significant irreversible neuronal damage that had likely occurred before initiation of miglustat.

This retrospective observational study, conducted among international, expert centers, is subject to a number of limitations and inherent sources of potential bias. While it was not possible to include a control group in the study design owing to the retrospective nature of this analysis, the subset of 19 patients with extended pre-treatment data could be considered as a within-subject control group, confirming the finding from the main cohort that invariable disease progression occurred prior to miglustat therapy, and supporting the finding of reduced progression after initiation of miglustat. The regional distribution of patients included in the analysis was variable, but this is likely related to the different national organization of healthcare for rare diseases among the countries of the participating centers. While it is unknown if this could have affected study outcomes, we consider this patient cohort to be representative of the overall treated NP-C population. Baseline patient characteristics (age at onset, gender distribution) were comparable with those described in other studies [12,17]. Moreover, the overall cohort of 66 patients represents the majority of the estimated population of diagnosed NP-C patients treated with miglustat in the clinical setting.

All centers known to treat NP-C patients with miglustat were identified and invited to participate. Participation was on a voluntary basis, and each participating center included data from all patients undergoing treatment, without exclusion. Of note, the discontinuation rate among patients included in this worldwide study was comparable with that recently reported in NP-C patients treated with miglustat as part of an ongoing European post-marketing surveillance (PMS) program [44]. In addition, the efficacy analysis included data from all patients in whom miglustat treatment was stopped. It is therefore unlikely that our observational study population was subject to selection bias based on positive treatment benefit. Of note, standard care remained unchanged during the pre-treatment observation period.

Presently, there are no clinical tools that have been validated for monitoring disease progression in NP-C. The disease-specific disability scale offered a valuable and easy-to-use tool for standardizing clinical assessments across the participating centers. It incorporates four well recognized parameters of neurological disease progression in NP-C that are considered clinically relevant across all patient age groups, and has previously been used in a Spanish cohort of 30 patients with NP-C (three peri-natal, 13 infantile, 11 juvenile and three adult cases) [23]. In the present study, this scale allowed the identification of distinct differences in disease progression rate among patient subgroups, both on and off treatment with miglustat. An international disease registry for NP-C patients will be implemented soon and will include this scale as one of the standard monitoring assessments. This will yield further, valuable long-term information on the utility of this scale in monitoring disease progression and treatment response.

An innate limitation of the disability scale is that it does not capture psychiatric manifestations; psychiatric impairment is a common manifestation among adolescent and adult patients with NP-C [20,21]. However, while our cohort did contain a significant number of such patients, inclusion of a psychiatric symptom parameter would have skewed the composite score data because not all patients would exhibit psychiatric symptoms, particularly very young patients with early-onset disease. Further, prospective studies would be required to address psychiatric manifestations in addition to the standard four parameters assessed here.

Based as it is on data from clinical site experience, this cohort represents the largest sample of patients with NP-C studied to date. There are relatively few published reports of findings from 'real-world' experience with miglustat. Our findings support those from case studies. For instance, Chien et al. [45] reported improved swallowing over a time course of 6 months in one patient, and reported improved ambulation over 6–12 months in a second. Santos et al. [46] reported notably improved ambulation in a Brazilian case study following 12 months of miglustat therapy. Galana et al. [47] reported general clinical improvement/stabilization and improved brain function in three patients included in a French case series.

Collection of data on the safety/tolerability of miglustat in NP-C was not in the scope of this study. However, the mean dose of miglustat used in this cohort of patients was similar to that used in a previous clinical trial investigating the efficacy and safety of miglustat in patients with NP-C [38,40]. The safety/tolerability of miglustat 200 mg t.i.d. in patients with NP-C evaluated in this clinical trial was shown to be consistent with that seen during previous trials in Gaucher disease type 1, where half the clinical dose (100 mg t.i.d.) is used [37]. The safety/tolerability profile of miglustat has also been shown to be comparable between pediatric and adult/juvenile patients with NP-C [38,40]. Further safety/tolerability data have been collected in the ongoing miglustat PMS study.

In conclusion, there is consensus that stabilization of neurological disease is the best attainable therapeutic goal in NP-C patients presenting with neurological manifestations, which reflect underlying irreversible neuronal loss/damage. This study indicates that miglustat can stabilize neurological disease in most patients, particularly in juveniles and adults. Age at diagnosis influenced response to treatment, and clinical benefit (i.e. slowing of disease progression) was also seen in the earliest childhood forms.

Acknowledgments and disclosures

The authors would like to thank Peter Schieber from Actelion Pharmaceuticals Ltd., for his help in data collection, and extend gratitude to the following investigators, for their contributions of patient data: Dr. D. Cassimani, Leuven, Belgium; Dr. M. Cochran, Tuscon, USA; Dr. P.M. Fernhoff, Atlanta, USA; Dr. R. Greenslein, West Hartford, USA; Dr. C. Haase, Jena, Germany; Dr. B. Heron, Paris, France; Dr. R. Lachmann, London, UK; Dr. M. Noetzel, St. Louis, USA; Dr. M. Schmitz dos Santos, Curitiba, Brazil; Dr. L.S. Smith, Rotterdam, the Netherlands; Dr. M. Clayton, London, UK; Dr. F.A. Wilburg, the Netherlands; Dr. S. Winter, California, USA; Dr. A.L. Yanai, Mato Grosso, Brazil.

This research was supported by Actelion Pharmaceuticals Ltd. Alpha-Plus Medical Communications provided medical writing assistance, paid for by Actelion Pharmaceuticals Ltd. Dr. Wraith is supported by the Manchester Academic Health Sciences Centre (MAHSC) and the NIHR Manchester Biomedical Research Centre. All authors read, contributed to and approved this paper, and the decision to submit this report to peer review, for publication, was reached by consensus among all listed authors.

References

Clinical experience with miglustat therapy in pediatric patients with Niemann-Pick disease type C: A case series

M. Pineda a,*, M.S. Perez-Poyato a, M. O’Callaghan a, M.A. Vilaseca a, M. Pocovi b, R. Domingo c, L. Ruiz Portal d, A. Verdú Pérez e, T. Temudo f, A. Gaspar g, J.J. García Peñas h, S. Roldán i, L. Martín Fumero j, O. Blanco de la Barca k, M.T. García Silva l, J. Macías-Vidal a, M.J. Coll a

a Departments of Pediatric Neurology and Clinical Biochemistry, Hospital Sant Joan de Déu, Barcelona, and Centre for Biomedical Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Spain
b Department of Biochemistry, Molecular and Cellular Biology, University of Zaragoza, Zaragoza, Spain
c Hospital Virgen de la Arrixaca, Murcia, Spain
d Hospital Virgen del Rosario, Seville, Spain
e Hospital Virgen de la Salud, Toledo, Spain
f San Juan General Hospital, Oporto, Portugal
g Hospital Santa María, Lisbon, Portugal
h Hospital Niño Jesús, Madrid, Spain
i Hospital Virgen de las Nieves, Granada, Spain
j Hospital Ntra. Sra. Candelaria, Tenérife, Spain
k Hospital de Vigo, Pontevedra, Spain
l Pediatric Unit for Rare Diseases, Hospital 12 de Octubre, Madrid, Spain

ARTICLE INFO

Article history:
Received 20 October 2009
Received in revised form 25 November 2009
Accepted 25 November 2009
Available online 20 November 2009

Keywords:
Niemann–Pick disease type C (NP-C)
Miglustat
PET
Disability
Chitotriosidase, CCL18

ABSTRACT

Niemann–Pick disease type C (NP-C) is an inherited neurovisceral lysosomal lipid storage disease characterized by progressive neurological deterioration. Different clinical forms have been defined based on patient age at onset: perinatal, early-infantile (EI), late-infantile (LI), juvenile and adult. We evaluated the efficacy and tolerability of miglustat in 16 symptomatic NP-C patients, with comparative reference to one neurologically asymptomatic, untreated patient. All patients were categorized according to age at neurological disease onset and were assessed using a standardized clinical assessment protocol: disability and cognitive function scales, positron emission tomography (PET), and biochemical markers. PET and disability scale evaluations indicated that cerebral hypometabolism and neurological symptoms were stabilized during treatment in juvenile-onset NP-C patients. EI and LI NP-C patients, who had higher disease severity at baseline (treatment start), showed increased disability scores and progressive cerebral hypometabolism during follow-up. Similarly, while cognitive scale scores remained relatively stable in patients with juvenile NP-C, cognition deteriorated in EI and LI patients. Plasma chitotriosidase (CHT) activity was lower in the juvenile NP-C subgroup than in EI and LI patients, and generally increased in patients who discontinued treatment. Plasma CCL18/GPRC and CHT activities indicated greater macrophagic activity in EI and LI patients versus juveniles. Miglustat was generally well tolerated; frequent adverse events included diarrhea and flatulence, which were managed effectively by dietary modification and loperamide. Overall, miglustat appeared to stabilize neurological status in juvenile-onset NP-C patients, but therapeutic benefits appeared smaller among younger patients who were at a more advanced stage of disease at baseline.

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Introduction

Niemann–Pick disease type C (NP-C) is a neurovisceral lysosomal lipid storage disease characterized by progressive neurological deterioration. NP-C is caused by mutations in either one of the two genes, NPC1 or NPC2, which encode proteins involved in the regulation of normal intracellular lipid trafficking through sequen-

tial activities within a common pathway [1–4]. Expression of the mutant genes leads to severely impaired intracellular lipid transport and marked accumulation of both unesterified cholesterol and several glycosphingolipids in a variety of tissues and organs, in particular the brain [2,3,5,6]. NP-C has a highly variable clinical presentation. The symptomatology and rate of disease progression are strongly influenced by age at disease onset [7,8], and different clinical forms have been described on this basis. In the perinatal form, patients die from liver failure within the first months of life. Other forms are defined based
on the following ages at onset: early-infantile (EI) form, <2 years; late-infantile (LI) form, 3–5 years; juvenile form, 5–16 years; adult form, >16 years. Clinical symptoms include progressive neurological deterioration and visceral organomegaly. Neurodegeneration begins with clumsiness and progressive ataxia followed by a range of symptoms that can generally include dysmetria, vertical supranuclear opthalmoplegia, cataplexy, seizures, dystonia, pyramidal signs, dysphagia and dementia [8,9].

The biochemical diagnosis of NPC is currently based on the demonstration of impaired low-density lipoprotein (LDL) cholesterol trafficking in cultured fibroblasts from patients, by cytochemical visualization of accumulated free cholesterol after filipin staining [9]. Recently, CCL18 pulmonary and activation-regulated chemokine (PARC), termed hereinafter as ‘CCL18’, has been reported as a potential new surrogate marker for monitoring symptomatic patients with Gaucher disease (GD) [10]. On average, this protein is elevated 29-fold in GD patients, without overlap between patient and control values. Chitotriosidase (ChT) is a human chitinase that shows markedly elevated activity in a variety of lysosomal storage disorders [11]. It is secreted by activated macrophages and is thought to play a role in defense against chitin-containing pathogens, in tissue remodeling and cell migration, as well as during atherogenesis. Plasma ChT is considered a useful surrogate marker in the lysosomal work-up of GD and NP-C patients with organomegaly, as it is relatively inexpensive and is easily assayed [12]. However, the use of plasma ChT as a marker of disease progression can be problematic in some patients who have no ChT activity due to possession of a 24-base pair (bp) duplication in the ChTF gene; this mutation is inherited as an autosomal recessive trait [11]. Nevertheless, plasma ChT is considered also to be of possible use as a screening marker in pediatric patients [12].

Currently, there is no cure for NP-C, although palliative therapy can alleviate some symptoms of the disease [13]. Miglustat (N-butyloxyxynorfinnycin; NB-DN; OGT-918) is a small iminosugar molecule that reversibly inhibits glucosylceramidase, the enzyme that catalyses the first committed step in glycosphingolipid synthesis [14]. The ability of miglustat to cross the blood-brain barrier indicated its potential use as a therapy for lysosomal storage diseases affecting the central nervous system. In animal NP-C models, miglustat delayed the onset of neurological symptoms and increased life span [15]. Evidence suggests that miglustat might also have beneficial effects on pathogenic NPC cellular pathways associated with calcium homeostasis [16]. Based on findings from a randomized, controlled clinical trial and a prospective observational cohort study [17,18], miglustat was approved in the European Union for the treatment of progressive neurological manifestations in adult patients and pediatric patients with NP-C in January 2009.

We report an evaluation of 17 patients with NP-C (16 symptomatic and one neurologically asymptomatic) from Spain and Portugal who were treated with miglustat for up to 4 years. We applied a standardized clinical, biochemical and neuroimaging protocol in order to establish the effect of miglustat on several markers of NP-C severity.

Clinical records for all patients were collected by a single investigator, and clinical NPC1 phenotypes were categorized according to age at onset of neurological symptoms. All 16 symptomatic patients received miglustat at doses based on body surface area (BSA) (BSA patient (m²) × adult dose (200 mg t.i.d.), the neurologically asymptomatic patient, who was diagnosed at 8 months of age due to splenomegaly, was not receiving miglustat and was included as a control at 8 years old, following all the protocol.

Clinical assessments

A standard assessment protocol was applied to all patients, including: clinical assessment (neurological examination, modified functional disability scale and cognitive development evaluation), biochemical analyses (plasma ChT and CCL18 activities), and imaging studies (abdominal ultrasound and cerebral positron emission tomography [PET] with radiolabelled [18F]-2-fluoro-deoxy-o-glucose). The full assessment battery was applied at baseline (treatment start), 6 months, 12 months and every year thereafter. Neurological examinations and biochemical analyses were also performed at screening and Months 4 and 8. Disability scale assessments were performed every 4 months. In addition, all treatment-emergent adverse events were recorded at each post-screening visit.

The modified disability scale, assessing four key functional domains (ambulation, manipulation, language and swallowing) relating to disease severity, was calculated as reported previously [8]. We modified our disability scale with the following scores: ambulation score ranged from 0 (clumsiness) to 5 (wheelchair-bound); manipulation ranged from 1 (mild tremor) to 4 (severe dysmetria/dystonia); language ranged from 1 (delayed acquisitions) to 5 (absence of communication); swallowing ranged from 1 (abnormal chewing) to 4 (nasogastric/gastric button feeding); epilepsy ranged from 1 (occasional seizures) to 5 (seizures resistant to antiepileptic drugs); ocular movements ranged from 1 (slow ocular pursuit) to 3 (complete opthalmoplegia) (Table 1). Scores on each of these domains were used to calculate an overall (composite) disability score, which are referred to simply as "disability scale scores throughout the remainder of this report.

The Denver developmental screening test (DDST) and Wechsler intelligence scale for children (WISC-R) were used to assess cognitive development and function. Cranial PET was used to assess brain metabolism in affected cerebral areas including the frontal and temporal-parietal regions, as well as in the thalamus, basal ganglia and cerebellum. Impaired brain function was rated according to scores ranging from 1 (mild) to 5 (severe).

Written informed consent for participation in this study was obtained from all parents or their legal representatives.

ChT studies

Plasma ChT activity was measured using the fluorogenic substrate, 4-methylumbelliferyl-β-D-N-acetyl-α-triacetylatedridioside (4-MU-chitotrioside; Sigma Chemical Co, St Louis, MO, USA), as described previously by Holak et al. [19]. Samples with high ChT activities were diluted to bring them into the linear range of the assay. Measured enzyme activities were doublet in patients carrying the mutated ChT gene.

A 24-bp duplication polymorphism in the ChT gene in some patients leads to a null allele, producing a defective protein product and a subsequent inherited deficiency in ChT activity. DNA analysis of ChT gene polymorphisms was undertaken in all but one patient using PCR followed by agarose gel electrophoresis of the amplified fragment as described previously [20].
Table 1
Modified disability scale for patients NP-C.

<table>
<thead>
<tr>
<th>Ambulation</th>
<th>Score</th>
<th>Language</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clumsiness</td>
<td>1</td>
<td>Delayed acquisitions</td>
<td></td>
</tr>
<tr>
<td>Autonomic ataxia gait</td>
<td>2</td>
<td>Mild dysarthria (understandable language)</td>
<td></td>
</tr>
<tr>
<td>Outdoor assisted ambulation</td>
<td>3</td>
<td>Severe dysarthria (only understood by some members of the family)</td>
<td></td>
</tr>
<tr>
<td>Indoor assisted ambulation</td>
<td>4</td>
<td>Non-verbal communication</td>
<td>4</td>
</tr>
<tr>
<td>Wheelchair-bound</td>
<td>5</td>
<td>Absence of communication</td>
<td>5</td>
</tr>
<tr>
<td>Manipulation</td>
<td></td>
<td>Aspiration</td>
<td></td>
</tr>
<tr>
<td>Swallowing</td>
<td></td>
<td>Altered swallowing</td>
<td></td>
</tr>
<tr>
<td>Speech</td>
<td></td>
<td>Speech disturbance</td>
<td></td>
</tr>
<tr>
<td>Novolons</td>
<td></td>
<td>Novolons</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>Seizures resistent to antiepileptic drugs</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>2</td>
<td>Seizures resistent to antiepileptic drugs</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>3</td>
<td>Seizures resistent to antiepileptic drugs</td>
<td></td>
</tr>
</tbody>
</table>

CCL18 protein assay

CCL18 protein assays were conducted using a CCL18-specific, enzyme-linked immunosorbent assay (ELISA) system according to the manufacturer’s instructions (CytoSet, Biosource International, Camarillo, CA). Dilution series of recombinant human CCL18 protein (Biosource International, Camarillo, CA) were used as controls to produce standard curves.

Results

Patients and disposition

A total of 17 NP-C patients (9 male and 8 female) were included. No patients had a family history of NP-C, but all had a confirmed diagnosis. Among all 17 patients, 16 showed mutations in the NPC1 gene (data not shown and partially published [21,22]). Table 2 summarizes patient baseline characteristics. Categorization of patients on clinical grounds according to age at onset of neurological symptoms identified five patients with the E1 form of the disease, four patients with the Li form, and seven patients with the juvenile form. The duration of migratory treatment ranged between 6 months and 4 years. Therapy was initiated at different patient ages, depending on the clinical form.

Discontinuations due to death were reported in the following patients: patient 2 (at 6 months of treatment), patient 5 (at 14 months of treatment due to respiratory infection as a complication of immunosuppressive therapy following liver transplantation) and patient 6 (at 2 years and 7 months of treatment, due to disease progression). Discontinuations due to financial decisions were reported in two patients: patient 7 after 2 years of treatment and patient 10 after 3 years of treatment.

Splenomegaly

Splenomegaly showed a high degree of variability in patients with E1 NP-C and in the neurologically asymptomatic patient. The median spleen volume ranged from 140 to 200 mm (normal spleen size, 100 mm). Patients with Li and juvenile NP-C showed relatively stable spleen size throughout treatment.

Disability scale scores

In the E1 patient subgroup (Fig. 1a), patients 1 and 4, who started treatment at the youngest ages, showed lower baseline disability scores than patients 2, 3 and 5. Patient 4 had the lowest disability score throughout treatment, possibly due to early diagnosis of the disease due to splenomegaly investigations. The disability score of patient 1 increased over a period of approximately 2 years, but remained stable thereafter. Patient 5 had the highest disability score at the onset of treatment, and died at 14 months of age.

In the Li patient subgroup (Fig. 1b), patient 7, who started treatment at 2 years and 7 months of age, showed a low initial degree of disability and slow disease progression during 2 years of follow-up. Patient 6, who started treatment later than other patients (at 8 years and 7 months of age), died after 2 years and 7 months on treatment.

In the juvenile patient subgroup (Fig. 1c), an initial decrease in disability score was observed in patients 10 and 11. The disability score for patient 10 started to increase at 32 weeks, which coincided with the onset of epilepsy that continued between Months 33 and 36; the patient discontinued treatment after this, and his disability score increased further, up to Month 44. In contrast, while patient 11 commenced treatment with the highest disability score, he showed stable disease throughout 3 years of treatment.

PET studies

In the E1 patient subgroup, cranial PET studies in patient 1 showed normal metabolism in the cerebellum, thalamus and basal ganglia throughout 2 years of treatment, but there were notable changes in frontal and temporo-parietal cerebral metabolism (Fig. 2a). Substantial and generalized effects on cerebral metabolism were also seen in Patient 2 at baseline, but no follow-up cranial PET assessments could be performed because the patient died 6 months after the baseline assessment. Patient 4 showed mild disruption of thalamic metabolism at baseline, which progressed to “moderate” at 1-year follow-up; this condition appeared stabilized at 2-year follow-up, with slight cerebellar hypometabolism. Patient 5 showed frontal-region impairment at baseline, which appeared stabilized at 1-year follow-up.

In the Li patient subgroup, cranial PET showed an increased degree of hypometabolism in the frontal and temporo-parietal regions as well as in the thalamus and basal ganglia at 1 year of treatment in patient 6, but cerebellar function remained stable (Fig. 2b). This condition was unchanged at 2-year follow-up. Patient 8 showed progressive increases in thalamic hypometabolism during the first and second years of treatment, and cerebellar changes also became apparent at 2-year follow-up. Patient 9, who had the highest disability score at baseline and throughout treatment in the Li subgroup, showed improved frontal and temporo-parietal metabolism at 1-year follow-up.
Table 2
Patient characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>CHI genotype</th>
<th>NPC1 genotype</th>
<th>Age at treatment start</th>
<th>Treatment duration</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-infantile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>Male</td>
<td>(dup/wt)</td>
<td>NPC49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 Years 6 months</td>
<td>4 Years</td>
<td>100 mg b.i.d.</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Female</td>
<td>(wt/wt)</td>
<td>NPC17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 Years 6 months</td>
<td>6 Months</td>
<td>200 mg b.i.d.</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Female</td>
<td>n.d.</td>
<td>NPC31&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 Years 1 month</td>
<td>1 Year</td>
<td>50 mg t.i.d.</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Female</td>
<td>(wt/wt)</td>
<td>NPC43&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 Year 4 months</td>
<td>2 Years</td>
<td>50 mg t.i.d.</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Male</td>
<td>(wt/wt)</td>
<td>NPC5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 Years</td>
<td>1 Year 2 months</td>
<td>30 mg t.i.d.</td>
</tr>
<tr>
<td>Late-infantile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 6</td>
<td>Female</td>
<td>(wt/wt)</td>
<td>NPC22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 Years 7 months</td>
<td>2 Years 7 months</td>
<td>200 mg b.i.d.</td>
</tr>
<tr>
<td>Patient 7</td>
<td>Male</td>
<td>(wt/wt)</td>
<td>NPC31&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 Years 7 months</td>
<td>2 Years</td>
<td>50 mg b.i.d.</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Female</td>
<td>(dup/wt)</td>
<td>NPC36&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 Years 7 months</td>
<td>4 Years</td>
<td>100 mg t.i.d.</td>
</tr>
<tr>
<td>Patient 9</td>
<td>Male</td>
<td>(wt/wt)</td>
<td>NPC2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 Years 2 months</td>
<td>2 Years</td>
<td>100 mg b.i.d.</td>
</tr>
<tr>
<td>Juvenile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 10</td>
<td>Male</td>
<td>(wt/wt)</td>
<td>NPC34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 Years 7 months</td>
<td>3 Years</td>
<td>200 mg t.i.d.</td>
</tr>
<tr>
<td>Patient 11</td>
<td>Male</td>
<td>(dup/wt)</td>
<td>NPC32&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 Years 1 month</td>
<td>4 Years</td>
<td>200 mg b.i.d.</td>
</tr>
<tr>
<td>Patient 12</td>
<td>Female</td>
<td>dup/16E10 + 43</td>
<td>NPC32&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11 Years</td>
<td>4 Years</td>
<td>100 mg t.i.d.</td>
</tr>
<tr>
<td>Patient 13</td>
<td>Male</td>
<td>(dup/wt)</td>
<td>NPC3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 Years</td>
<td>3 Years</td>
<td>200 mg b.i.d.</td>
</tr>
<tr>
<td>Patient 14</td>
<td>Male</td>
<td>(dup/wt)</td>
<td>NPC3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13 Years 10 months</td>
<td>21 Months</td>
<td>200 mg t.i.d.</td>
</tr>
<tr>
<td>Patient 15</td>
<td>Female</td>
<td>(wt/wt)</td>
<td>NPC3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 Years</td>
<td>1 Year</td>
<td>100 mg t.i.d.</td>
</tr>
<tr>
<td>Patient 16</td>
<td>Male</td>
<td>(wt/wt)</td>
<td>NPC3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 Years</td>
<td>1 Year</td>
<td>100 mg b.i.d.</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Female</td>
<td>(dup/wt)</td>
<td>NPC24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No treatment</td>
<td>No treatment</td>
<td>No treatment</td>
</tr>
</tbody>
</table>

<sup>a</sup> wt, wild-type allele; (dup/wt), 24-bp duplication in one allele; wt/wt, no duplication.
<sup>b</sup> Treatment duration at observation cut-off; CHI, chitotriosidase; n.d., not determined.
<sup>c</sup> Ref. [31].
<sup>d</sup> Ref. [32].
<sup>e</sup> Publication in draft.

![Graphs](https://via.placeholder.com/150)

**Fig. 1.** Composite disability score in (a) EI patients, (b) LI patients, and (c) juvenile patients with NP-C.
In the juvenile patient subgroup, cranial PET indicated stabilization throughout 3 years of treatment in patient 10 (Fig. 2c). Patient 11, who had the highest disability score in this subgroup, showed a generalized hypometabolism in all cerebral and cerebellar regions at baseline, which remained stable during 3 years of treatment. Patient 14 showed no changes on PET during 2 years of follow up, which appears in agreement with a lack of change in this patient’s disability score throughout observation. Brain metabolism was affected in the thalamic and cerebellar regions and in the basal ganglia in Patient 13 at baseline and follow up at 2 years. There was slight hypometabolism in the temporo-parietal cerebrum at 2 years, whereas there had been none at baseline or 1-year follow up.

Findings from cranial PET assessments in the asymptomatic patient showed stable cerebral, thalamic and cerebellar function throughout 4 years of follow up (data not shown).
Cognitive development and function

In the EI patient subgroup, patient 1 experienced substantial worsening of developmental cognitive function during follow up, which paralleled increases in his disability scores; his IQ score was 71 at baseline, which fell to 20 at both 1 and 2 years of treatment. Patient 4 showed stable developmental cognitive function at 2 years of treatment, with very slight retardation. No follow-up information on cognitive function was available for patients 2 and 5, as both patients died. It was not possible to evaluate cognitive development and function in patient 3 due to progressive neurological manifestations of the disease. Cognitive development and function data were not available from patients 9, 15 and 16.

In the Li patient subgroup, patients 6, 7 and 8 experienced progressive reductions in cognitive function during 2 years of treatment. It was not possible to evaluate cognition beyond 2 years due to progressive cognitive impairment (IQ < 20) and the evolution of physical conditions of the disease.

In the juvenile patient subgroup, patient 11 showed worsening of cognitive function between baseline (IQ score 78) and 1-year follow up (IQ score 55), but cognition has since remained stable throughout years 2 and 3. Cognitive function decreased during the first year of treatment in patient 11 (IQ score 35 at baseline and 20 at 1-year follow up), which reflected a parallel increase in disability scale score. Patients 10, 12 and 14 showed stable cognitive function (IQ score 40–50) during the first year of treatment. IQ scores for patient 10 ranged from 50 at 2 years of treatment to 40 at 3 years. Patient 14 had an IQ score < 40 at 2 years of treatment.

Cognitive function has remained stable in the asymptomatic patient throughout 4 years of follow up. IQ scores ranged between 70 and 80 throughout the observation period.

Plasma CHIT and CCL18 activities

Genotyping analyses for the 24-bp duplication polymorphism in the CHIT gene was conducted in 16/17 patients. Plasma CHIT "pseudo-deficiency" was confirmed for seven patients (i.e., those with the 24-bp duplication in one CHIT gene allele); patients 1, 8, 11, 12, 13, 14 and 17. Overall, plasma CHIT activity was lower in the juvenile patient subgroup (value range: 52–474 nmol/ml h) than in the EI (value range: 316–3245 nmol/ml h) and Li subgroups (value range: 323–2744 nmol/ml h) (Fig. 3), and was increased in patients who discontinued treatment (e.g., patients 3 and 10, who both discontinued based on family decisions). The asymptomatic patient showed the lowest plasma CHIT activity during 4 years of follow up (values range: 60–47 nmol/ml h).

Similar to findings with plasma CHIT (overall value range: 52–3245 nmol/ml h), patients in the EI (value range: 851–1691 ng/ml) and Li subgroups (value range: 176–950 ng/ml) had higher plasma CCL18 activities compared with both the juvenile patient subgroup (value range: 112–874 ng/ml) and the asymptomatic patient (value range: 213–423 ng/ml) (Fig. 4).

**Fig. 3.** Plasma CHIT activity in (a) EI patients, (b) Li patients, and (c) juvenile patients with NP-C. Pseudo-deficiency patients, possessing 24-bp duplication in one CHIT gene allele; CHIT, chitotriosidase. Note: plasma CHIT activity in normal, healthy subjects is ≤ 50 nmol/ml h. Data not available for patient 2 and patient 15.
Tolerability and safety

Miglustat was well tolerated, and no serious adverse events were recorded. The most frequently occurring adverse events were diarrhea and flatulence, which were managed satisfactorily using proper dietary and nutritional care such as the 'bland diet', an oral re-hydration solution, and loperamide. No patients showed clinically significant weight loss during the observation period.

Discussion

There are limited published case reports regarding the use of miglustat to treat pediatric patients with NP-C. Our case series assessed the effects of miglustat on disease progression in pediatric patients with different clinical forms of the disease. Our patients were classified on clinical grounds according to the age at onset of neurological symptoms. Splenomegaly did not appear to be a good marker of response to treatment, as there was no apparent effect of miglustat on spleen size; splenomegaly may be best considered as a disease hallmark for diagnosis. The disease-specific functional disability scale was a practical tool that provided valuable information from clinical assessments conducted according to a standard protocol. We modified our previous disability scale by adding epilepsy, which is a severe symptom that worsens the disease, and ocular movements, as it is a hallmark of the disease. PET is expensive and is unlikely to be of practical use for routine clinical monitoring, but it has the potential to be used as a quantitative and objective marker of treatment efficacy in the early stages of disease. Further PET data on untreated patients would be valuable. Plasma ChT and CCL18 activities may serve as biochemical markers of therapeutic response in NP-C, although possible genetic deficiency should be taken into account in the case of ChT. However, ChT and CCL18 do not necessarily reflect the evolution of neurological disease.

Our findings regarding changes in neurological symptom progression, brain metabolism, cognitive status and plasma disease markers add to existing published data on the efficacy of miglustat from previous clinical trials and case reports. Pivotal efficacy data were reported from a 12-month randomized, controlled, clinical trial involving 29 juvenile and adult patients, and a parallel, non-controlled sub-study, involving 12 patients aged 4–12 years [17]. The primary study end point – horizontal saccadic eye movement velocity (HSEM-α) – was improved with miglustat versus standard care in adult and juvenile patients; similar improvements were seen in children included in the pediatric sub-study [17]. Improved swallowing capacity, stable auditory acuity, and slower deterioration of ambulation were also seen in miglustat-treated patients aged over 12 years. Further data, indicating stabilization of key parameters of neurological disease progression in NP-C, were reported in a retrospective observational cohort study in 66 patients.
with a mean (standard deviation) age of 9.7 (7.6) years [18]. A published case series reported the efficacy of 24 months' miglustat therapy in three adult patients with NP-C, based on clinical evaluations and brain magnetic resonance spectroscopy (MRS) [23]. This study reported mild clinical improvement or stabilization in all patients. However, the findings were limited by the small number of patients and the choice of cerebral white matter to follow disease progression.

To date, cerebral PET scan data has not been reported from longitudinal follow up of patients with NP-C. Our PET imaging studies indicated that cerebral hypometabolism was stabilized in patients with juvenile-onset NP-C; miglustat appeared to slow progression of neurological symptoms. Patients with EI and LI forms of NP-C who started treatment in the advanced stages of the disease showed increased disability scores and progressive cerebral hypometabolism. Patient 9, who also had a high baseline disability score, showed an improvement on PET evaluation after 1 year of treatment. Control cranial PET and disability scale data indicated stable function over 4 years of follow up in the asymptomatic patient.

A published case series of two male Taiwanese patients with NP-C, who started miglustat therapy aged 14 and 9 years, reported substantial improvements in swallowing and ambulation by Month 8 of treatment, followed by stabilization of neurological symptoms between Months 6 and 12 [24]. Spleen size remained approximately stable throughout treatment in both patients and, predictably, there were no overt changes in plasma ChT activities. In our series, splenomegaly varied greatly between patients and over time, and did not appear related to treatment response or to neurological status. However, plasma CCL18 and ChT levels were higher in both the EI and LI patients compared with the juvenile group and the asymptomatic patient. Further, in patients with the EI and juvenile forms of NP-C, plasma ChT activities increased when patients discontinued therapy, suggesting that this marker is reflective of therapeutic response. The levels of plasma ChT and CCL18 indicated the presence of quantifiable, active disease in the asymptomatic patient.

Previous studies have demonstrated that both plasma ChT and CCL18 can serve as markers for the extent of pathological formation of lipid-laden macrophages in GD [10]. Further, reductions in plasma CCL18 levels have been shown able to reflect therapeutic corrections of the total-body burden of activated macrophages. It should also be noted that plasma CCL18 levels are affected by immune system activity, and it is possible that CCL18 levels might reflect specific immune processes during NP-C. Zimran et al. [25] characterized the inflammatory profile of patients with GD, and it might be that similar factors and processes are involved in the modulation of plasma CCL18 concentration in patients with NP-C.

Sapos et al. [26] studied the effects of miglustat treatment in a 4-year-old Brazilian patient, reporting a rapid and positive impact of therapy on cognitive function, ataxia, dysarthria and ophthalmoplegia. In addition, functional disability (assessed on the disability scale published by Iturria et al. [18]) was reduced from a pretreatment score of 15 down to a score of 8, after treatment. These findings are comparable with data from our series. Although disability scale scores increased in patients with EI disease (e.g. in patient 1 at 2-year follow up), progression was slow compared with the natural evolution of this clinical form. In addition, patient 4 remained stable throughout 2 years of treatment, and a decrease in disability scores was observed in patients with the juvenile form of the disease (although this trend reversed at the onset of epilepsy).

With regard to cognitive function and developmental level, the severity of cognitive impairment appears strongly related to the age at which treatment is commenced; in general, cognitive outcomes were worse in younger patients. There was a clear worsen-

ing of cognitive scores in patients with EI and LI disease during follow up, but scores appeared to remain stable in patients with juvenile-onset disease.

Miglustat was generally well tolerated in our patient series. Some patients experienced episodes of diarrhea and flatulence at the onset of treatment, but there was no weight loss during the observation period. There were no reports of insomnia, paresthesia or fine tremors, which have been described in previous studies with miglustat [17,24,26].

In summary, the patients in our series who showed deterioration during miglustat therapy were those who were at a more advanced stage of the disease. This seems in agreement with a previous case of a male patient aged 3 years, where limited therapeutic response was reported after 12 months' treatment with miglustat [27]. In general, patients with infantile NP-C generally exhibit greater symptom severity and more rapid disease progression than those with juvenile-onset disease [28], and therefore seem less likely to show appreciable therapeutic responses to miglustat therapy [9]. We consider that miglustat therapy should be commenced at or just before neurological signs start to appear. However, more data are necessary to define further the stages at which treatment is best initiated within the different clinical forms of NP-C.

Acknowledgments

Alpha-Plus Medical Communications Ltd provided medical writing assistance in the preparation of this report, paid for by Actelion Pharmaceuticals Ltd. The authors thank Dr. J.R. García Garzón, CETIR, PET Unit, Esplugues, Barcelona, who kindly performed the imaging studies, and are also grateful to the Spanish Niemann-Pick Foundation for providing research funding.

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Use of Miglustat in a Child With Late-infantile-onset Niemann-Pick Disease Type C and Frequent Seizures

A Case Report
Johannes Skorpen, Ingrid B Helland, Bjarne Tennesæ
J Med Case Reports. 2012;6(383)

Abstract and Introduction

Abstract

Introduction Niemann-Pick disease type C is a rare genetic lysosomal storage disease associated with impaired intracellular lipid trafficking and a range of progressive neurological manifestations. The influence of seizure activity on disease course and response to miglustat therapy is not currently clear.

Case presentation Niemann-Pick disease type C homozygous for NPC1 mutation p.S940L [c. 2819 C>T] was diagnosed in a four-and-a-half-year-old Norwegian Caucasian girl. The patient, who died at eight years and seven months of age, had a history of prolonged neonatal jaundice and subsequently displayed progressive neurological manifestations that started with delayed speech, ataxia, and gelastic cataplexy. A regimen of 100mg of miglustat three times a day was initiated when she was four years and 11 months old. She showed decreased neurological deterioration during about three and a half years of treatment. However, she displayed periods of distinct worsening that coincided with frequent epileptic seizures. Anti-epileptic therapy reduced seizure frequency and severity and allowed re-stabilization of her neurological function. Prior to her death, which was possibly due to acute cardiac arrest, seizure activity was well controlled.

Conclusions Miglustat delayed the expected deterioration of neurological function in this patient with p.S940L-homozygous late-infantile-onset Niemann-Pick disease type C and provided important quality-of-life benefits. This case demonstrates the importance of effective seizure control therapy in achieving and maintaining neurological stabilization in Niemann-Pick disease type C.

Introduction

Niemann-Pick disease type C (NP-C) is a potentially devastating progressive neurodegenerative disease currently estimated to occur in 1:100,000 to 1:120,000 live births.[1] NP-C is caused by autosomal recessive mutations in both alleles of either the NPC1 gene, which is detected in 95% of cases, or the NPC2 gene.[2] These mutations give rise to impaired intracellular lipid trafficking and subsequent accumulation of unesterified cholesterol, sphingosine, and a range of glycosphingolipids in various tissues, including the brain.[1]

NP-C has an extremely heterogeneous clinical presentation characterized by a wide range of systemic, neurological, and psychiatric symptoms, many of which are not specific to the disease.[3] This makes it difficult to establish an early diagnosis. Patients may present during infancy, but many cases present during adolescence or adulthood.[1,3] Clinical NP-C phenotypes can be broadly defined on the basis of age at disease onset.[3]

Until recently, no disease-modifying therapy was available for NP-C. In 2009, miglustat (Zavesca, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland) was approved in Europe for the treatment of adults and children with NP-C on the basis of clinical trial data and a retrospective observational cohort study showing improvements or stabilization of neurological disease manifestations.[4-7]

To date, no published reports have assessed the influence of seizure activity on disease course in NP-C or the possible impact of seizures on patient responses to miglustat therapy. We report the case of a young patient who had late-infantile NP-C and significant seizure activity and was treated with miglustat and anti-epileptic therapy.

Case Presentation

The patient was a girl born to Norwegian Caucasian parents following a normal pregnancy and birth; her birth weight was 3.44kg. As a neonate, she had jaundice that persisted for three months and that was considered to be due to breast feeding/breast milk icterus. No clinical signs of hepatomegaly or splenomegaly were noted, and further investigations, including abdominal
ultrasound, were not performed. After an initial assessment, she showed normal healthy psychomotor development and was walking independently at 12 months of age.

Follow-up was initiated locally when she was about two and a half years old because her speech development was delayed. When referred to the pediatric department at the age of two years and 11 months, she showed slowing of motor development, impaired balance and coordination, episodes of gelastic cataplexy, and arrested language and psychomotor development. Findings from brain magnetic resonance imaging (MRI), electroencephalogram, urine/plasma metabolic screens, and cerebrospinal fluid analyses were all normal. Clinical examination revealed no signs of hepatosplenomegaly.

She developed swallowing difficulties at three years and four months, at which time her fine motor skills had deteriorated further and included visible tremor. Vertical gaze palsy and ataxia were detected two months later, and her cataplectic episodes continued. Language testing showed pronounced deficits in speech. By the age of four years, her swallowing difficulties had noticeably worsened and she was losing further fine and gross motor skills, commencing the use of a walker to ambulate indoors and a wheelchair for outdoor ambulation. Her cognitive function was also significantly impaired, and repeat language testing indicated ongoing deterioration in speech. MRI analysis at the age of four years and seven months showed deep bilateral cerebral white-matter signal hyperintensities—a leukodystrophy-like pathology.

The rapidly deteriorating disease prompted a search for a specific diagnosis. The combination of cataplectic episodes, progressive ataxia, and a notable vertical gaze palsy ultimately provoked suspicion of possible late-infantile NP-C. When she was four years and eight months old, a diagnosis of NP-C was confirmed on the basis of filipin staining and cholesterol esterification assay findings. Genetic analysis later that year showed homozygous p.S940L (c. 2819 C>T) mutations in the NPC1 gene. Both parents were heterozygous for this mutant allele.

A regimen of 100mg of miglustat three times a day was commenced when our patient was four years and 11 months old, and regular follow-up was conducted until her death at the age of eight years and seven months; the total treatment period was three years and eight months. Before initiation of miglustat, a low-carbohydrate diet was implemented to reduce potential gastrointestinal disturbances. This diet was gradually phased out after four months of therapy. No gastrointestinal disturbances have been reported during miglustat therapy, possibly because of the early implementation of this low-carbohydrate diet.

At follow-up after one month on miglustat, our patient, who was five years old, showed continued deterioration in motor function in comparison with findings six months earlier. She was increasingly tired, and signs of spasticity were developing in her lower extremities. However, she displayed a noticeable improvement in chewing and swallowing function, and her overall awareness and concentration were improved.

Follow-up after six months on miglustat detected a general improvement in motor function. At 13-month follow-up, when she was six years old, her sitting balance and posture and both indoor and outdoor assisted ambulation were improved. Her gaze was also more stable, and she was continent for both urine and feces—a new skill. She no longer coughed or choked while drinking water. However, she showed gradually less interest in food, and it was decided that a gastrostomy tube should be established.

A general loss of energy and overall function that coincided with an increased frequency of epileptic attacks was observed about two and a half years ago. Concerted anti-epileptic treatment, which is described in detail below, significantly reduced the number of epileptic episodes, and she gradually improved to become medically stable. Although her functional abilities were variable, she was generally continent and was eating, drinking, sitting, and ambulating well. Two years ago, when she was seven years old, she experienced another period of frequent epileptic attacks and concurrent breathing difficulties with massive overproduction of mucus. As a result, she was temporarily hospitalized and during that time she again displayed a generalized deterioration in function. Control of her seizures was re-established about two months later, and anti-asthmatic therapy was reinforced. Within a short time, she showed signs of recovery and had retained her cognitive function.

Her function across four key parameters of neurological disease progression in NP-C—ambulation, manipulation, language, and swallowing—was assessed by using a published disease-specific disability scale modified to rate function across each domain from zero, indicating the best, to one, indicating the worst.17 Disability assessments were undertaken at planned visits approximately every six months from the time of our first data collection two years ago and retrospectively at time points before that. Overall, data from disability scale assessments were available between the ages of three years and eight and a half years for a total follow-up period of five and a half years and reflected the changes recorded on the basis of empirical clinical observations (Figure 1).
Composite Niemann-Pick disease type C disability scale score during about five and a half years of follow-up. Composite scores on the modified Niemann-Pick disease type C disability scale [7] are rated from zero, indicating the best, to one, indicating the worst. Disability scale assessments were performed by the author together with a child physiotherapist during planned follow-up visits at hospital from when the patient was six years and nine months old, to when she was eight years and five months old. Disability scores before age six years and nine months were evaluated retrospectively on the basis of patient records. FEA: frequent epileptic attacks.

Composite disability scores indicated sequential worsening during the 17 months before initiation of miglustat therapy, increasing from 0.13 when our patient was 36 months old to 0.65 at the last pretreatment assessment, when she was about four and a half years old. After miglustat was started, scores leveled off for about 17 months, remaining at 0.63 when she was five years old up to the first period of frequent epileptic attacks, when she was about six and a half years old, after which there was some worsening (Figure 1). Assessment four months later indicated a return toward stable disease, with a score of 0.71. Overall, these changes were dictated mainly by ambulation, manipulation, and swallowing function; speech had reached the near-maximal degree of impairment measurable before miglustat was started. During the second period of increased epileptic activity, when she was seven years old (Figure 1), her composite disability score increased to the maximum level of 1, indicating severe disability across all subscores. Her ambulation and language scores fell back to 0.88 when her epileptic episodes were once again under control three months later, but her manipulation and swallowing disabilities remained at 1, indicating permanent losses of function. Her remaining swallowing function was used only for tasting of food, not for feeding. There was no change in disability scale scores during follow-up clinical assessments afterward.
During the last clinical assessment before her death, she was awake and alert and interested in her surroundings, family members, teachers, and friends. Her disability scale score remained stable. While her ambulation and non-verbal communication were less frequent, she still conducted these activities in a purposeful manner. She also retained some function in terms of simple manipulation movements such as touching and reaching, raising arms, and assisting in feeding. On two separate occasions, seven weeks and three weeks prior to her death, she was hospitalized because of acute lung infections, which were resolved with treatment. Her precise cause of death is not known. She had no prevailing breathing difficulties or mucus overproduction and no signs of ongoing infection. An acute cardiac arrest cannot be ruled out.

Throughout her care, a rigorous approach was required to control her cataplexy and seizure activity. Initial treatment of her cataplexy with a daily dose of 5mg of fluoxetine when she was four years and nine months old reduced the frequency and severity of episodes by about 70%. However, fluoxetine was stopped when anti-epileptic treatment with 0.125mg of clonazepam three times a day was commenced following the onset of epilepsy with a long-lasting generalized tonic-clonic seizure. After two months, clonazepam was replaced by levetiracetam at doses gradually increased from 200mg twice a day to 450mg twice a day, which provided adequate seizure control for about six months until the first period of frequent epileptic attacks about two and a half years ago. Control was re-established initially by using 3.75mg of oral nitrazepam per day followed by maintenance therapy with a combination of levetiracetam and 7.5 to 10mg of clonazepam per day. After the second period of frequent epileptic attacks two years ago, control was re-established by adding 250mg of valproic acid twice a day to her existing combination therapy. After this, she was clinically seizure-free for more than a year. During the months prior to her death she had four to six seizures each week, lasting 10 to 30 seconds. But it was not considered that this activity required any alteration to her anti-epileptic therapy.

Discussion

This case report concerns the first known patient diagnosed as being homozygous for the NPC1 gene mutation, p.S940L. To the best of our knowledge, the clinical phenotype for homozygous p.S940L NP-C has not been described before. The course of progressive neurological symptoms in our patient, preceded by an initial isolated neonatal jaundice, is in agreement with previous data on the natural history of late-infantile-onset NP-C. However, the absence of hepatomegaly or splenomegaly in a patient with late-infantile onset is unusual. Although no specific ultrasound examinations were performed to assess the liver or spleen before diagnosis, repeated abdominal assessments since diagnosis showed only mildly increased spleen size. It cannot be stated for sure whether the absence of organomegaly represents a feature specific to homozygous p.S940L NP-C or whether the time window during which it was clinically measurable was missed.

In line with published data in childhood-onset NP-C, miglustat appeared effective in stabilizing neurological disease in our patient. During about three and a half years on miglustat, her rate of neurological deterioration was notably slower compared with the steady progression observed before therapy. While her epilepsy and occasional serious respiratory infections led to periods of deterioration, she regained a number of her previous levels of function a number of times.

Disease stabilization is widely viewed as an important therapeutic outcome in NP-C and was well represented in our patient on the basis of the disability scale assessments. However, even though the disability scale used here is based on empirical multidisciplinary clinical observations, due caution should always be adopted in assessing the clinical meaning of such retrospective analyses—prospective assessments offer much greater objectivity.

The age of this patient and the timescale of follow-up assessments largely precluded a quantitative, objective longitudinal analysis of her cognitive function. However, while she displayed early signs of serious cognitive impairment before therapy, her concentration and responsiveness improved after starting miglustat, and her overall cognitive function appeared intact even after periods of frequent epileptic episodes. The observed effects of miglustat on neurological and cognitive function were of great importance to her parents and other caregivers.

It seems clear that intercurrent illnesses require rigorous treatment in parallel with disease-specific therapy in order to maintain quality of life in patients with late-infantile-onset NP-C. Our patient’s repeated respiratory infections and ensuing breathing difficulties had an important impact on her everyday well-being. She also experienced pronounced overproduction of mucus, which was successfully alleviated using scooproamine skin patches together with saline inhalations and anti-asthmatic therapy.

Seizures are common among patients with late-infantile- and juvenile-onset NPC, but the type, progression, and response to therapy vary considerably. It is important to distinguish between cataplectic and epileptic episodes in order to define the most appropriate therapy. The recurrent bouts of seizure activity in our patient were believed to contribute strongly to significant losses of function during the periods of frequent epileptic attacks.

The precise processes underlying disease progression in NP-C are not yet entirely clear, and it is beyond the scope of this article to assess possible relationships between seizure pathology and NP-C severity. We believe that changes in seizure activity in this case were the result of NP-C disease progression. Seizures numbering more than 50 per day in one period and culminating in full status epilepticus in another had a devastating impact on her overall function and NP-C disability scale score. The successful control of our patient's seizures by using anti-epileptic therapy resulted in a significant improvement and a return to a level of function that, in our opinion, reflected the true deterioration related to the NP-C disease process. The triple regimen of anti-epileptic therapy that we applied appeared to provide satisfactory and prolonged seizure control. Given this case experience, the control of seizure activity appears vital for the maintenance of overall health and function in NP-C and should be a key focus in clinical management.

Conclusions

Miglustat appears to have provided distinct therapeutic benefits and improved quality of life in this patient with late-infantile-onset NPC. The effect of miglustat on neurological function and cognition was also vital for the family's quality of life, as expressed by her parents. This patient's history highlights the challenges posed by serious epileptic seizure activity and respiratory disease in the clinical management of NP-C. In particular, it is important to effectively control seizures in order to achieve and maintain neurological stabilization during miglustat therapy.

Consent

Written informed consent was obtained from the parents of the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References


Abbreviations

MRI: Magnetic resonance imaging; NP-C: Niemann-Pick disease type C.

Authors’ contributions

As coordinating study investigator and lead author, JS was involved with all stages of the patient's treatment and the writing of the manuscript. IBH conducted repeated clinical assessments of the patient at Oslo University Hospital, Norway. BT, also in Oslo, contributed repeated MRI analyses and diagnostic advice. Both co-authors contributed to the written content of the manuscript during draft stages. All authors read and approved the final manuscript.

Acknowledgments

We would like to thank the parents of our patient, who encouraged the publication of this case report. We are grateful to Jan-Eric Månsson and Marie-Thérèse Vanier for the confirmatory biochemical and genetic tests for NP-C and to Anita Sandanger for physiotherapy support and functional disability evaluations. Matthew Reilly, associated with InTouch Medical Ltd (Henri Hempstead, UK), provided medical writing assistance paid for by Actelion Pharmaceuticals Ltd.

J Med Case Reports. 2012;6(383) © 2012 BioMed Central, Ltd.
INTRODUCTION

- Niemann-Pick Type C (NPC) disease is a fatal neurological disorder linked to dysfunction in lipid trafficking.
- No treatment exists for this disease aside from palliative care.
- Clinical features include pulmonary infiltrates and liver disease in infancy, and progressive neurodegeneration in later childhood.
- The disease is characterized by accumulation of unesterified cholesterol and ganglioside (GM2) in the lysosomal compartments of many tissues.
- The abnormal storage of GSLs is associated with extracellular deposits and membrane formation that can affect characteristic features of NPC.
- MGLU8 (Zar8np) is a small lysosomal enzyme that can reversibly inhibit glucosylceramidase synthase, the enzyme that catalyzes the first committed step in GSL synthesis.
- Physico-chemical properties allow miglustat to cross the blood-brain barrier. As such, it may have potential as a therapeutic agent for NPC disease, including the neurological symptoms.

OBJECTIVES

- This study aims to evaluate the safety and efficacy of miglustat as a treatment for NPC disease.

PATIENTS & METHODS

- The study included 10 juvenile/adult patients randomized to receive either miglustat or standard care.
- In the placebo-controlled study, 12 patients received miglustat.
- The study cohort comprised male or female patients with NPC (confirmed by abnormal cholesteryl esterification and abnormal lipoprotein staining), with normal renal function, who were able to ingest a capsule, and who did not suffer from clinically significant diarrhoea.
- Patients >4 years of age and those with medical conditions or who were on concomitant medications that would render them unsuitable for the study were excluded.
- Patients were assessed for the primary endpoint, horizontal sacbé eye movement (HSEM), during the screening period and at Month 12. On each occasion, assessments of eye movement velocity were performed twice within 24 hours.
- Swallowing ability was assessed at screening, Months 6 and 12.
- Neurological examinations and quality of life assessments for (juvenile/adults) were performed at screening, Months 3, 6, 9, and 12, and at follow-up.
- Swallowing assessments were performed at screening, every 3 months, and at follow-up. Adverse events (AEs) were recorded as soon as possible.
- Measurements obtained in the figures were taken at baseline and at Month 12 (last value).
- The two treatment groups (miglustat vs. standard care) were compared using an analysis of variance (ANOVA).

RESULTS

- The demographics and characteristics of the juvenile/adult and paediatric patients at baseline are summarised in Table 1.
- At baseline, all patients suffered from various neurological manifestations, including vertical supranuclear gaze palsy, cognitive impairment, ataxia, dysarthria, and swallowing difficulties.
- The proportion of patients from each treatment group manifesting these neurological symptoms at baseline is summarised in Table 2.
- In paediatric patients, an improvement in HSEM was seen after 12 months of miglustat treatment (P<0.05).
- This result was comparable to that of the juvenile/adult patients.

CONCLUSIONS

- Miglustat treatment was noted to be well tolerated. No serious adverse events were reported in the study.
- Miglustat had a positive effect on swallowing capacity and swallowing ability of patients treated with miglustat compared to standard care in adult patients.
- Swallowing function was assessed in miglustat-treated juvenile/adult patients (untested patients showed a greater worsening).
- Miglustat had a positive effect on swallowing function of juvenile/adult patients treated with miglustat compared to standard care.
- No unexpected toxicity was found.
- Miglustat is a potential treatment option for patients with NPC, a disease with unmet medical needs.

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Recommendations for the diagnosis and management of Niemann-Pick disease type C: An update

Marc C. Patterson a,b, Christian J. Hendrikz b, Mark Walterfang c, Frederic Sedel d, Marie T. Vanier e, Frits Wijburg f on behalf of the NP-C Guidelines Working Group

a Mayo Clinic, Rochester, MN, USA
b Birmingham Children’s Hospital, Birmingham, USA
c Royal Melbourne Hospital, Melbourne, Australia
d Pitie Salpetriere Hospital, Paris, France
e INSERM Unit 880, Lyon, France
f Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 5 February 2012
Received in revised form 16 March 2012
Accepted 16 March 2012
Available online xxx

Keywords:
Niemann–Pick disease type C
Diagnosis
Screening
Treatment
Guidelines

ABSTRACT

Niemann–Pick disease type C (NP-C) is a rare inherited neurovisceral disease caused by mutations in either the NPC1 (in 93% of cases) or the NPC2 gene (in about 5% of cases), which lead to impaired intracellular lipid trafficking and accumulation of cholesterol and glycosphingolipids in the brain and other tissues. Characteristic neurological manifestations of NP-C include saccadic eye movement (SEM) abnormalities or vertical supranuclear gaze palsy (VSGP), cerebellar signs (ataxia, dystonia/dysmetria, dysarthria and dysphagia) and gelastic cataplexy. Epileptic seizures are also common in affected patients. Typically, neurological disease onset occurs during childhood, although an increasing number of cases are being detected and diagnosed during adulthood based on late-onset neurological signs and psychiatric manifestations. Categorization of patients according to age at onset of neurological manifestations (i.e. early-infantile, late-infantile, juvenile and adolescent/adult-onset) can be useful for the evaluation of disease course and treatment responses. The first international guidelines for the clinical management of NP-C in children and adults were published in 2009. Since that time a significant amount of data regarding the epidemiology, detection/diagnosis, and treatment of NP-C has been published. Here, we report points of consensus among experts in the diagnosis and treatment of NP-C based on a follow-up meeting in Paris, France in September 2011. This article serves as an update to the current guidelines providing, among other things, further information on detection/diagnostic methods, potential new methods of monitoring disease progression, and therapy. Treatment goals and the application of disease-specific therapy with miglustat are also re-evaluated.

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1. Introduction

Niemann–Pick disease type C (NP-C) is a rare inherited neurovisceral disease characterized by progressive, disabling neurological symptoms and premature death in most patients. Estimated to occur in 1 case in every 120,000 live births [1–5], NP-C generally arises sporadically in a panethnic pattern, although genetic isolates have been identified that show a higher than average incidence of the disease [6,7].

NP-C is caused by autosomal recessive inheritance of mutations in either of two genes, NPC1 (in 95% of cases) or NPC2 (in approximately 4% of cases) [5,8–11]. Mutations in either causal gene result in impaired processing and utilization of endocytosed cholesterol, with subsequent intracellular accumulation of unesterified cholesterol and alterations of sphingolipid metabolism [12–15].

Clinical presentations of NP-C are extremely heterogeneous, featuring a range of systemic and neurological signs that are not specific to the disease, arise at different ages, and progress at different rates [5,16–18]. As a result, the diagnosis of NP-C can be a prolonged and complicated process [19,20]. Patients typically present with one or more neurological signs during childhood [5,17,18], although very early-onset patients are often diagnosed based on isolated systemic manifestations [21,22]. An increasing number of cases are being detected and diagnosed during adulthood [5,16,23–24].

The age at onset of neurological manifestations has a major influence on disease progression and prognosis. In general, patients with neurological onset early in life deteriorate faster and die sooner [5,16–18,25]. Categorization of patients by age at onset of neurological manifestations in a number of studies has led to the definition of early-infantile, late-infantile, juvenile and adolescent/adult-onset disease forms [5,18,26]. These categories are useful for the evaluation of disease course and responses to therapy, and aid in clinical management and genetic counseling.

A variety of symptomatic treatments can alleviate neurological manifestations [27]. The appropriate application of such therapies can have an important influence on patient quality of life. Clinical experience with miglustat (Zavesca®; Actelion Pharmaceuticals), currently the only approved disease-specific therapy for children and adults with NP-C, is increasing. Miglustat was approved for the treatment of progressive neurological deterioration in children and adults with NP-C in Europe in 2009 [28], and has since been approved in a number of other countries [29–33]. Data on the use of miglustat in clinical practice settings has been published in a number of cohort studies and case reports/series [34–38].

The first international recommendations for the clinical management of NP-C were prepared in 2009 based on consensus among a panel of experts at a meeting in Paris [39]. The following article serves as an update, modifying the original recommendations with a comprehensive review after a second meeting of an NP-C Guidelines Working Group in September, 2011. New data on the epidemiology, differential diagnosis, and detection/screening of NP-C are presented, with updated recommendations for treatment initiation. Findings from further clinical experience with both symptomatic and disease-specific therapies, and information on potential new methods for monitoring disease progression and response to therapy are also included.

2. Disease nomenclature

- NP-C, in which the primary biochemical defect is impaired intracellular transport of endocytosed cholesterol, is caused by mutations in both alleles of either one of the two genes, NPC1 or NPC2.
- NP-C is distinct and separate from Niemann–Pick disease types A and B (NP-A and NP-B), where the underlying defect is primary acid sphingomyelinase (ASM) deficiency due to mutations in the SMPD3 gene. NP-A, NP-B and intermediate types are now more accurately termed ASM-deficient Niemann–Pick disease [40].
- Niemann–Pick disease type D (NP-D), which originally distinguished a genetic isolate from Nova Scotia, should no longer be used as it describes a group of patients with a common founder mutation in the NPC1 gene [41].
- Several terms have been used to describe what is now known to be NP-C, including juvenile dystonic lipodystrophy, DAF (downregulate paralysis, ataxia, foam cells) syndrome, neurovisceral storage disease with supranuclear gaze palsy, Neve–Lake disease and Niemann–Pick disease type II, type E or type F. We suggest using the term NP-C in preference to any of these alternatives, which are considered to be confusing. More recently, some lay groups have advocated the use of the term ‘childhood Alzheimer’s disease’. Although NP-C is a secondary tauopathy with some pathological features that overlap with Alzheimer’s disease, it is a distinct clinical, pathological and genetic entity, and we discourage the use of this misleading term.

3. Clinical 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.
- Broadly accepted age-at-onset subgroups are: pre/peri-natal (onset at age <3 months), early-infantile (at age 3 months to <2 years), late-infantile (at age 2 to <6 years), juvenile (at age 6–15 years), and adolescent/adult (at age >15 years) [28].
- Fig. 1 is a graphical representation of the occurrence of clinical manifestations by age [5]. The neurological manifestations of NP-C occur along a continuous spectrum, and there is considerable overlap between the age-at-onset forms.
- There is often significant discordance in the clinical course of NP-C between siblings, despite similar genotypes and biochemical phenotypes [5,42–44]. Patients born with the severe peri-natal form can have siblings with infantile- or juvenile-onset neurological disease [42].

3.1. Neurological manifestations

- The occurrence and natural history of neurological manifestations per age-at-onset group have been reviewed in French, Spanish and UK NP-C patient cohorts [5,17,18,23,24,45].
- The onset of neurological manifestations in NP-C is often insidious, with subtle signs such as low muscle tone (central hypotonia) or with frequent falls and clumsiness in late-infantile onset cases.
- Delayed or arrested speech development with or without global cognitive and/or motor developmental delay is common in early- and late-infantile onset cases.
- One or more cerebellar signs are often visible from the late-infantile period onwards. Typical signs include impaired gait, cerebellar ataxia, dysmetria, distal ataxiokinesias, dystarthritis and dysphagia. Their appearance reflects prominent Purkinje cell loss [46,47].
- Cerebellar ataxia is a common presentation in adult-onset cases [24].
- Dystonia correlates with pathology in the striatum, and is often manifest as focal dystonia affecting the hands and face; it may also affect gait [48]. Acute myoclonus or myoclonic tremor may develop as the disease advances, or sometimes arise at early stages, possibly arising from the cortex [49,50]; subcortical generators may also play a role.
- Dysphagia may be present early in the disease course, or may arise later, and presents a major problem in clinical management as it severely disrupts feeding at later stages, increasing the risk of aspiration and subsequent serious lung infections [36,39,51]. Dysphagia may start with simple choking or coughing during feeding, usually with fluids. Silent aspiration can often be detected using videofluoroscopy.
Ocular-motor abnormalities are the hallmark of NPC-1, seen in 81% of patients in one large-scale survey [16], and usually starting during the late-infantile period with impaired saccadic eye movements (SEM). SEM abnormalities may be missed when voluntary saccades are not assessed. This sign is detected in nearly all patients when examined properly, and published data likely underestimate its true prevalence [16,24].

Vertical SEM are affected first, followed by horizontal SEM reflecting progressive brainstem neurodegeneration [32,53]. At the start, only voluntary saccades are impaired, and slow eye pursuit may be normal. Over time these abnormalities progress to complete supranuclear gaze palsy, beginning with progressive reductions in saccadic velocity (while saccadic latencies remain normal), and leading to eventual complete saccadic paralysis [53-56]. The vestibulo-ocular reflex is often preserved until very late, indicating that the gaze palsy is truly supranuclear in nature.

Catalepsy is a relatively specific and common neurological sign of NPC-1, seen in over half of patients, overall [16]. It is uncommon in early-infantile patients, but frequently presents in late-infantile and juvenile-onset cases [5,7,17,57-60]. It manifests as sudden loss of muscle tone in the legs or sometimes the jaw or neck, and is triggered by emotions that cause laughter (gelastic catalepsy). This sign is easily overlooked and is often misinterpreted as falls secondary to ataxia or as tonic epileptic crises.

Epileptic seizures are less frequent in early-infantile or adult-onset patients than in late-infantile and juvenile-onset cases. NPC-1 patients can experience any type of seizure (partial/focal, generalized, absence, myoclonic, tonic-clonic); they vary markedly in intensity and frequency.

Sensorineural hearing loss is common in practice, but published reports on this finding are scarce [5,61,62].

Peripheral neuropathy is a rare complication in patients with NPC-1 that may be present in infantile forms [63]. It is never observed in juvenile- or adult-onset cases.

Example videos of characteristic neurological manifestations in NPC-1 can be found at: www.NPC-SC.com/symptoms/neurological.

3.2. Cognitive impairment

- Impaired cognitive function is observed in almost all adolescent/adult-onset NPC-1 patients at some point in the disease course [23,24,64], but is less commonly recognized early in childhood.
- Poor school performance and learning disabilities have been reported in late-infantile and juvenile-onset patients [5,17,18].
- Cognitive impairment in NPC-1 generally starts with frontal-subcortical deficits characterized by impairments in executive function, reduced processing speed and verbal memory impairment [24,64].
- As NPC-1 progresses patients experience a more general decline in cognitive function, leading in many cases to frank dementia with a prominent dysexecutive syndrome and memory impairment [65].

3.3. Psychiatric signs

- NPC-1 patients with adolescent/adult-onset disease often present with psychiatric illness [5,23,24,66], and juvenile-onset cases with a history of behavioral disturbance and other signs have been reported to present later on with a psychiatric disorder [67,68].
- In juvenile-onset patients, behavioral problems, impaired learning, expressive language disorder and attention deficit-hyperactivity disorder are often observed.
- Schizophrenia-like psychosis is a common presentation in adolescent/adult patients with NPC-1, reported in up to 25% of cases. Although clinical presentation is often indistinguishable from schizophrenia, with typical auditory hallucinations, delusions and disorganization of thought and behavior, there may be markers of organic psychosis including visual hallucinations, cognitive impairment and treatment resistance [43,49,66-72].
- Catatonia can also be seen, most frequently in younger-onset patients. It is often resistant to therapy, and can be considered as a sign of organic psychiatric disease.
- Other major psychiatric illnesses have been reported, including depression, bipolar disorder and obsessive-compulsive behavior [58,73-75].
3.4. Systemic symptoms

- The systemic symptoms of NP-C mainly comprise hepatosplenomegaly and associated symptoms. Pulmonary infiltration with foam cells is usually restricted to those with early-onset disease or those with severe NPC2 mutations [76,77].
- NP-C is recognized as a significant cause of liver disease in early life. Patients with the severe pre/perinatal form of NP-C exhibit one or more of fetal hydrops, ascites, neonatal cholestasis, hepatosplenomegaly and/or liver failure [5,16,17,45,78].
- A history of neonatal jaundice or persisting hepatosplenomegaly or isolated splenomegaly are common among patients with early- and late-infantile onset disease [17,18,21,22].
- Hepatosplenomegaly in older-onset patients, if present, is usually asymptomatic and is often unrecognized clinically, mandating abdominal ultrasound in suspected cases [24,79]. Data suggest that it is absent or minimal in approximately 15% of all patients, and almost half of adolescent/adult-onset patients [5]. Such published data likely underestimate the prevalence of hepatosplenomegaly because abdominal ultrasound is often not performed. When ultrasound was performed in one cohort the proportion of patients with splenomegaly (with or without hepatomegaly) was closer to 90%, even in adult-onset cases (unpublished observations; [24]).
- Although splenomegaly is almost invariably seen in NP-C, hepatomegaly is less frequent in adults [24]. In a patient with a neurodegenerative or psychiatric disorder, the existence of isolated splenomegaly in the absence of liver disease is strongly suggestive of NP-C.
- Systemic disease, when present, always precedes the onset of neurological signs [5]. Further, the age of onset of the systemic symptoms is not related to that of the neurological manifestations; neurological disease can start many years or even decades after the appearance of systemic symptoms [580].
- Retinal pigment abnormalities, which can be present in certain lysosomal storage disorders, do not occur in NP-C. In particular, macular halos or cherry-red maculae are not associated with NP-C, while they can occur in ASM-deficient Niemann-Pick disease [81–83].

4. Prognosis

- All patients with NP-C die prematurely, although rates of disease progression and life expectancy vary greatly. The majority of patients die between 10 and 25 years of age [5]. In very rare cases, patients can survive into the sixth or even seventh decade of life [73], some of whom have not exhibited neurological abnormalities at the time of their evaluation [7,84,85].
- In general, patients with onset of neurological manifestations in early childhood deteriorate faster, and death occurs sooner, compared with juvenile- or adolescent/adult-onset patients [5,16–18,25].
- Fig. 2 shows data from 97 untreated NP-C patients, illustrating that a greater number of patients who remained free of neurological signs up to 5 years of age remained alive beyond 10 years of age [5].
- Aside from a small subset of patients who die at or within 6 months of birth due to hepatic or respiratory failure, and exceptional adult cases, almost all patients develop progressive neurological disease that ultimately proves fatal.
- Published information on precise causes of death in NP-C are scarce, but historical data indicate that in the majority of patients death is often related to bronchopneumonia, most likely due to repeated aspiration following progressive dysphagia [21,86].

5. Differential diagnosis and initial detection methods

- Patients with NP-C may present many clinical practice settings, but should always be referred to regional or national care centers specializing in inherited metabolic disorders [26].
- General physicians should be aware that neurological onset in NP-C is insidious, often starting with subtle findings ranging from clumsiness and poor school performance to psychological disturbances.
- Delays between initial appearance of possible neurological dysfunction and further investigations, or referral to expert centers, should be minimized.
- As an example, patients presenting with any atypical psychiatric disorder or any progressive neurological syndrome including ataxia, early onset dementia or dystonia in addition to isolated splenomegaly and/or SEM abnormalities should be referred for possible NP-C (see Section 5.2).

5.1. The NP-C suspicion index

- The NP-C suspicion index is a new tool developed to enhance the detection of NP-C among patients suspected as having the disease, with a view to establishiing better and earlier diagnosis (www.NPC-Sl.com) [87].
- This index comprises ranked assessments of visceral, neurological and psychiatric signs and symptoms that are specific to NP-C, taking family history into account, to provide an NP-C risk prediction score (Fig. 3).
- Patients scoring ≥70 should be referred to an NP-C center for immediate testing, and scores from 40 to 69 indicate that further follow-up is required (and an NP-C center contacted for discussion).
- Scores <40 indicate a low likelihood of NP-C.
- The sensitivity and specificity of this tool for predicting the presence of NP-C were evaluated in a study of confirmed cases of
**5.2. Differential diagnosis**

- The common systemic symptoms (neonatal jaundice, isolated splenomegaly or hepatosplenomegaly) and neurological signs (e.g., loss or delay of motor skills, cerebellar signs) in NP-C arise in some other inborn errors of metabolism, including Sandhoff disease, Gaucher disease type 3 (GD3) and ASM-deficient Niemann-Pick disease.
- In Wilson's disease and some other metal storage disorders, liver cirrhosis may be associated with late-onset neurodegeneration, but such patients do not have splenomegaly unless portal hypertension is present.
- In neonates and young infants, the systemic symptoms of NP-C must be differentiated from idiopathic neonatal hepatitis and other causes of cholestatic jaundice.
- Early-onset NP-C can resemble ASM deficiency in a number of respects, particularly ASM deficiency type B based on early splenomegaly/hepatosplenomegaly. However, leucocyte enzyme analysis provides a simple and effective means of discounting ASM deficiency (see Section 5.3.8).
- NP-C patients frequently present during adolescence or early adulthood with psychosis, bipolar disorder, depression, atypical schizophreniform disorders and/or other psychiatric signs including attention deficit disorder, Asperger-like presentations and a dysexecutive syndrome [23,24,43,66–71,74].
- Organomegaly, slow-onset dystonia, ataxia and/or dysarthria are other useful, characteristic signs that can indicate possible NP-C in older patients with psychiatric disorders.
- It should be borne in mind that the signs and symptoms of NP-C vary with age at disease onset.
- Table 1 summarizes key identifiers for a number of metabolic disorders that can also be associated with psychosis; characteristic clinical signs, particularly SEM abnormalities (or full vertical supranuclear gaze palsy [VSGP]) and movement disorders in the case of NP-C, can be key in determining possible underlying organic disease [66].
- Cognitive decline, ataxia, movement disorders and VSGP can be seen in adult-onset neurodegenerative disorders such as Huntington's disease (HD), Gerstmann–Sträussler–Scheinker syndrome or progressive supranuclear gaze palsy (PSP). However, HD and GSS are transmitted as autosomal dominant traits, and PSP usually starts in the fifth to seventh decade of life. None of these disorders are associated with organomegaly.

**5.3. Detection methods**

### 5.3.1. Medical history and general physical examination

- Patients with suspected NP-C should undergo a comprehensive medical history assessment, with particular attention to neonatal jaundice, isolated splenomegaly or hepatosplenomegaly, seizures,
cataplexy and impaired academic or work performance, specifically for evidence of loss of skills.
- Vital signs, body weight, height and head circumference should all be recorded at initial assessment and at follow up.
- The date at which neurological signs first appeared should be ascertained as accurately as possible, and recorded.

5.3.2. Eye movement abnormalities
- The assessment of abnormalities in voluntary SEM is a vital part of diagnostic workup in NP-C as they are often the earliest visible neurological sign [52,56]. However, these signs can be overlooked without thorough assessment.
- Vertical SEM are affected first during the disease course; downward gaze is more affected than upward gaze. Horizontal SEM are generally preserved until later in the course of the illness [53,88].
- In all patients, saccadic, pursuit and vergence movements should be examined in both vertical and horizontal planes. In younger children use of novel visual stimuli such as toys and flashing lights presented in different locations in the visual fields may be helpful in eliciting saccades. Both large- and small-amplitude saccades should be tested.
- Typical images/videos from eye examinations for SEM abnormalities and VSGP can be found at: [www.NPC-SL.com/syndrome/neurological](http://www.NPC-SL.com/syndrome/neurological).

5.3.3. Assessments of hepatosplenomegaly
- Jaundice is not always visible in very young patients, so in those aged <1 year both total and conjugated bilirubin should be measured, with jaundice defined as a conjugated bilirubin level >1.2 mg/dL and >30% of total bilirubin for a period of over 2 weeks.
- In patients with later-onset neurological manifestations, visceromegaly often goes undetected. As a result, medical histories often reveal unexplained, isolated, non-progressive splenomegaly or hepatosplenomegaly [79].
- Organomegaly may be palpable, but abdominal ultrasound should be conducted in all patients (particularly adults) with suspected NP-C.

5.3.4. Neurological assessments
- A comprehensive neurological examination should always be conducted, including examinations of cranial nerves, muscle bulk, tone, power and stretch reflexes, gait, cerebellar and extrapyramidal function, and swallowing.
- Neurological evaluation in children under 4 years should include assessments of development with particular attention to arrested or delayed speech development, which is a frequent early neurological finding in NP-C.
- Gait can be assessed using the 10-m or timed walk test; tandem gait should be included. Patients may exhibit varying combinations of ataxia, dystonia and spasticity.
- Ataxia can be further assessed on established scales such as the International Cooperative Ataxia Rating Scale (ICARS) [89]. The Brief Ataxia Rating Scale (BARS), which was adapted from the ICARS, may be more useful in the office setting [90].
- Seizures should be characterized according to their semiology [91], ideally with EEG confirmation; EEG is also useful in differentiating epilepsy from cataplexy (e.g. in patients with tonic epileptic seizures).
- Cataplexy in NP-C ranges in severity from subtle signs (minor head-drop or falls, often confused with seizures) to full collapse in response to humorous stimuli; cataplexy occurs both with and without narcolepsy [5,57,58,92].
- Audiolingual and/or brainstem evoked potentials should be used to confirm clinical suspicion of impaired hearing and to track progress over time [93].
5.3.5. Psychiatric assessments

- Formal psychiatric assessment of mood and psychotic symptoms can be conducted using established rating scales such as the Brief Psychiatric Rating Scale (BPRS) [94].
- The Neuropsychiatric Inventory (NPI) can be useful for assessing the degree of behavioral disturbance, particularly in juvenile adolescent/ adult-onset patients [95].
- Patients presenting with psychiatric disorders, particularly those with older-onset disease, often receive drug therapies (e.g. antidepressants) that can affect both physical function (e.g. drug-induced dystonia) and psychological aspects (e.g. blunted affect). It is important to differentiate between drug effects and those due to the disease.

5.3.6. Cognitive assessments

- A variety of validated clinical tools are available to monitor cognition, although none are specific for NP-C.
- The Mini-Mental State Examination (MMSE) [96] is a generic measure of cognition that has previously been applied in NP-C patients [32,56]. While the MMSE has been validated for use in children [97,98], it does not assess executive functioning, which may be the critical domain of cognitive functioning to be impaired in adult patients, and may be insensitive to initial changes due to a ceiling effect in early-onset patients.
- The Addenbrooke's Cognitive Examination (ACE) [99], and the Neuropsychiatry Unit Cognitive assessment tool (NUCOT) [100] can be considered in order to evaluate executive functioning. Specific tests such as the trail-making test, the Stroop Task for disinhibition and verbal fluency assessments may also be of use.
- The Frontal Assessment Battery (FAB) evaluates executive functioning and may be particularly useful in patients with later-onset disease who present with predominantly executive impairment [101].
- More detailed neuropsychological assessments such as the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scale (WMS) can be also be used in older patients, particularly for assessing change over time [102].
- Frequently used tools to study cognition in children include the Bayley Scales for Infant Development (BSID) [103], Vineland Adaptive Behavior Scales (VABS; [104]), the Wechsler Intelligence Scale for Children (WISC) [105], the Denver Developmental Screening Test (DDST) [106] and the Griffiths Mental Development Scale (GMDS) [107]. These tests can provide objective longitudinal data if used in the correct age groups.

5.3.7. Laboratory analyses

5.3.7.1. Chitotriosidase

- Plasma chitotriosidase is useful as a screening marker in Gaucher disease (GD) and can also be useful in NP-C, but it has a relatively low sensitivity and specificity [108–109].
- Chitotriosidase activity is generally more elevated in very young patients compared with juveniles and adolescents/adults [35].
- A raised chitotriosidase activity in a child with isolated hepatosplenomegaly and any of the neurological symptoms listed in Section 3 should be considered as indicating an increased likelihood of NP-C.
- It should be borne in mind that around 6% of the general population is chitotriosidase-negative [111].

5.3.7.2. CCL18/PARC

- Chemokine (C-C motif) ligand 18 (CCL18), otherwise known as pulmonary- and activation-regulated chemokine (PARC) has also been evaluated as a potential disease marker in both GD and NP-C patients [112].
- Levels of CCL18/PARC have also been shown to be raised in young NP-C patients, and may serve as an alternative marker in patients who do not express chitotriosidase [35]. However, the sensitivity and specificity of this potential marker in NP-C have yet to be fully defined.

5.3.7.3. Oxytetracyclines

- Data on levels of cholesterol oxidation products (oxytetracyclines) in animals and humans with NPC1 mutations have recently been reported, indicating that they are sensitive and specific markers for NP-C screening [113,114].
- Initial cross-sectional data indicate that levels of certain oxytetracyclines correlate with disease severity as well as age at neurological disease onset in NP-C [114], but further longitudinal data are required to determine the clinical utility of these potential new markers.

5.3.7.4. Lysotracker

- The Lysotracker® assay has been used to follow the response to treatment (based on reduced lysosomal storage in stained B-lymphocytes) in one patient with NP-C [115]. There are no other clinical data on the use of this assay in NP-C, and we do not recommend this as a routine clinical assay.

5.3.8. Non-specific laboratory analyses

- Results from routine laboratory tests including standard ‘metabolic screens’, blood biochemistry and unconjugated bilirubin assays are generally normal in NP-C patients, but can still be informative in ruling out other diagnostic possibilities. Mild thrombocytopenia and elevations of transaminases (ASAT and ALAT) are frequent.
- ASM activities in NP-C have been reported as being normal or slightly elevated in leukocytes, which is at variance with the very low levels found in ASM deficiencies (formerly NP-A and NP-B) [116]. In cultured skin fibroblasts, ASM activities are typically reduced (but not absent), although normal activities have also been reported in a number of cases, with a correlation between the degree of cellular cholesteryl storage and the level of ASM activity [42,44,116,117]. More recent studies have provided important information regarding the cholesterol-ASM interaction in NP-C cells [118,119].
- Of note, decreased plasma LDL- and HDL-cholesterol and increased plasma triglycerides have been reported in NP-C patients [120]. HDL-cholesterol levels were suggested to be inversely correlated with the severity of NP-C biochemical phenotype in one study.
- Changes in plasma lipid levels are non-specific to NP-C patients, which precludes their use as screening biomarkers. Further data are required to verify the potential of plasma lipid changes as markers for disease severity in patients with confirmed NP-C.

5.3.10. Histology

- Filipin staining of bone marrow smears may provide a rapid screening test for NP-C [121], but should not be considered as a definitive assessment.
- Light microscopy can identify characteristic foam cells in various tissues, but findings are not specific to NP-C; false negatives may occur owing to sampling error [122,123].
- Electron microscopy of skin or liver biopsies can be diagnostic in the hands of experienced neuropathologists, but requires experience and is technically demanding [7,122].