<table>
<thead>
<tr>
<th>Trial ID [reference]</th>
<th>Design</th>
<th>Treatment</th>
<th>Patients</th>
<th>Swallowing function</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGT-918-007 [25]</td>
<td>12-month randomised, controlled Phase II study comparing miglustat with standard (symptomatic) therapy</td>
<td>Main study: miglustat 200 mg t.i.d. (n = 20) vs standard care (n = 9)</td>
<td>Main study: male and female adults and juveniles (aged ≥12 years)</td>
<td>Ability to swallow different foods (5 mL of water, 1 teaspoon of puree, 1 teaspoon of soft lumps, or a third of a cookie)</td>
<td>Improved ability to swallow water in 6 patients (30%), puree in 3 patients (15%), soft lumps in 3 patients (15%), and a third of a cookie in 7 patients (35%) after 12 months of miglustat therapy</td>
</tr>
<tr>
<td></td>
<td>Sub-study: miglustat 200 mg t.i.d. adjusted for BSA (n = 12)</td>
<td>Sub study: male and female children aged 4-11 years</td>
<td>Assessed at 6 and 12 months or withdrawal/follow-up</td>
<td>Over 80% of children had normal swallowing at baseline</td>
<td></td>
</tr>
<tr>
<td>OGT-918-007 ex (a) [27]</td>
<td>Prospective, non-controlled, 12-month extension to OGT-918-007</td>
<td>Miglustat 200 mg t.i.d.</td>
<td>Male and female adults and juveniles (aged ≥12 years) who received miglustat (n = 17) or standard care (n = 8) for 12 months</td>
<td>Swallowing assessment (as above) at 12 and 24 months and last visit</td>
<td>Swallowing improved/stable (vs. baseline) in 80% of patients completing 12 months, and 79-99% of those completing 24 months on miglustat</td>
</tr>
<tr>
<td>OGT-918-007 ex (b) [26]</td>
<td>Prospective, non-controlled, 12-month extension to OGT-918-007 sub-study</td>
<td>Miglustat 200 mg t.i.d. adjusted for BSA</td>
<td>Male and female children aged 4-11 years who underwent 12 months of miglustat therapy (n = 10)</td>
<td>Swallowing assessment (as above) at 12 and 24 months and last visit</td>
<td>Nine patients (90%) had normal swallowing function at both baseline and Month 24</td>
</tr>
<tr>
<td>NP/C retrospective Stage 1 survey [70]</td>
<td>Retrospective, multicentre observational cohort study</td>
<td>Adults ≥18 years (n = 14); miglustat 200 mg t.i.d.</td>
<td>Patients previously or currently treated with miglustat in clinical practice settings</td>
<td>Dysphagia subscale of NP/C disability scale [12]</td>
<td>Continuous deterioration prior to initiation of miglustat therapy</td>
</tr>
<tr>
<td></td>
<td>Juveniles 12-17 years (n = 13); miglustat 200 mg t.i.d.</td>
<td></td>
<td></td>
<td>Similar proportions of patients in each swallowing disability category at treatment start and last post-treatment assessment (stabilisation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paediatrics ≤12 years (n = 34); miglustat adjusted for BSA</td>
<td></td>
<td></td>
<td>Stable neurological manifestations (including swallowing) in juvenile-onset patients</td>
<td></td>
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<tr>
<td></td>
<td>Symptomatic therapy in 1 asymptomatic patient</td>
<td></td>
<td></td>
<td>Improved swallowing in patients with dysphagia/aspiration at baseline (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Italian case series [18]</td>
<td>Longitudinal case series of Italian patients</td>
<td>Miglustat 250-300 mg/mq/day in three divided doses for up to 4 years</td>
<td>Male and female patients treated for ≥3 years, with swallowing function assessed by VFSS (n = 4)</td>
<td>No deterioration in the patient with normal swallowing at baseline</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 Summary of randomised and non-randomised studies with information on the effects of miglustat on dysphagia (Continued)

| Taiwanese data [29] | Longitudinal case reports | Miglustat 200 mg q.d. adjusted for BSA for 1 year | Young male patient, 1 with severe swallowing impairment and 1 with impaired language/speech, who underwent serial VFSS | VFSS | Patient 1; substantially improved swallowing function after 6 months | Patient 2; normal swallowing before and throughout therapy |

BSA = body surface area; VFSS = videofluoroscopic studies.

observation for a mean (SD) period of 3.1 (3.4) years between diagnosis and initiation of miglustat therapy.

In line with other data on the natural history of NP-C [10,16], composite NP-C disability scale scores indicated marked neurological deterioration before the initiation of miglustat therapy [70]. On the dysphagia subscale, while 95% of patients had normal swallowing function or occasional dysphagia at diagnosis, this had dropped to 66% by the end of the pre-treatment observation period. In contrast, the proportion of patients with normal swallowing or occasional dysphagia after a median (range) of 1.5 (0.1–4.5) years’ miglustat treatment was almost identical to that at the start of therapy (67%). Overall, 51/63 (81.0%) patients showed a stable/
improved score on the dysphagia subscale during treatment.

Instrumental assessments of swallowing
Findings from direct instrumental assessments of the effects of miglustat on swallowing function, based on VFSS [18,29], support categorical data based on clinical observation of dysphagia [25–27,70].

In the Italian case series, where serial VFSS were conducted to quantify changes in swallowing function during 36–48 months of miglustat therapy, all three patients with dysphagia at treatment start showed early improvements in swallowing ability (DSS scores), and one patient who did not exhibit dysphagia before therapy showed stable swallowing function throughout treatment [18]. Improvements in swallowing ability, particularly in terms of pharyngeal phase function, occurred in parallel with improvements or stabilisation of overall neurological manifestations assessed by composite NP-C disability scores. These apparent long-term beneficial effects of miglustat on swallowing function were associated with sustained reductions in penetration/aspiration (based on PAS scores) in all patients who showed severe swallowing impairment and aspiration prior to treatment.

Impairments of pharyngeal swallowing function tended to occur later in the course of NP-C than oral-phase impairment, and more severe pharyngeal-phase involvement associated with penetration/aspiration of contrast agent in the airways was present in patients with the most severe overall neurological impairment [18]. Further, in all patients in this case series, improvements in pharyngeal swallowing function during miglustat therapy were greater, and occurred earlier, than those in the oral phase. Modest impairment in the preparatory/oral phase persisted during follow up in two patients with severe swallowing impairment (and higher NP-C disability scale scores) at treatment start.

It can be speculated that the apparent difference in the effects of miglustat on pharyngeal versus oral-phase swallowing function might reflect selective therapeutic effects of miglustat on the neurological pathways that control them [18]. While the preparatory/oral phase is activated by peripheral receptors as well as through stimulation of sensory cortical neurones, the pharyngeal and oesophageal phases are mediated by involuntary reflexes dependent on brainstem neurones. Since greater therapeutic effects were noted for pharyngeal phase swallowing, it might be that miglustat affects autonomic, brainstem-based neuronal circuits before higher, cortical centres in NP-C. The significant effects of miglustat on saccadic eye movements (which are also modulated by pathways in the brainstem) during the randomised clinical trial would certainly seem to support this [25].

Data reported from two male Taiwanese patients support findings from the Italian cohort [29]. In the patient with pronounced swallowing impairment, who had displayed neurological manifestations since 5 years of age, VFSS identified severe oropharyngeal dysphagia and prominent aspiration before miglustat treatment was initiated at the age of 14 years. Distinct improvements in swallowing function were seen after 6 months of therapy, reflected by a 25% reduction in Han functional dysphagia scale score that was sustained through to Month 12. Similar to findings reported in the Italian case series [18], this patient's improved swallowing function occurred simultaneously with improvements in ambulation [29]. The second patient, who had displayed splenomegaly since birth and behavioural problems (Asperger-like syndrome) since the age of 8 years, did not display significant swallowing impairment either before treatment or during therapy, but did show improvements in communication, social interaction and cognitive function by Month 12 [29].

Data limitations
In assessing the available published data on the effects of miglustat on dysphagia in NP-C, a number of limitations should be taken into account. NP-C is markedly heterogeneous and different patient cohorts have limited comparability, particularly in terms of age at neurological disease onset [1,10]. Most published evidence related to changes in swallowing function during miglustat therapy stems from subjective assessments (i.e. clinical observation and disability scales) rather than direct, quantitative swallowing studies such as those employed in the Italian cohort and Taiwanese case reports [18,29]. Dysphagia in NP-C often has mixed motor and sensory components, and silent aspiration of small or trace amounts of food or fluid is not well diagnosed without direct VFSS. Finally, the inclusion in this analysis of the retrospective miglustat observational cohort study [70] introduces potential bias, so the contribution of these data, albeit based on an established disease-specific disability scale, should be considered with caution.

Longitudinal analysis of survival in miglustat-treated patients
Analysis methods
To identify the effect of miglustat on patient survival, longitudinal statistical analyses were conducted based on all available published data from miglustat-treated patients and from an untreated cohort. Patient age at onset of neurological manifestations has previously been shown to have a strong influence on the severity, progression and prognosis of NP-C [1,10,15,70]. An analysis of patient survival was therefore conducted based on
subgroups of patients, categorised by age at neurological onset, from the overall groups of untreated and treated patients identified during our analyses of published data. Patient survival was then compared between the overall treated and untreated patient groups.

Survival analyses were based on both univariate and multivariate methods. A univariate Kaplan-Meier analysis using the log-rank test evaluated survival over time, and multivariate Cox proportional hazards modelling was performed to provide estimates of overall mortality risk per treatment group and according to patient age.

Analyses in miglustat-treated patients were based on time from the start of therapy as ‘age at neurological disease onset’ data were not available for many patients. However, analyses in untreated patients were based on time from onset of neurological manifestations, as most patients had available data [1].

Results
The untreated group comprised patients from the French NP-C cohort [1]. This population provided longitudinal data from a total of 97 patients diagnosed in French hospitals (Table 4). Nineteen patients were excluded from this control cohort as they died during the first days or months of life, and would therefore not have been eligible to receive miglustat therapy (see Data limitations).

The treated group (N = 90) comprised patients from the randomised controlled trial (n = 25) [25], the Italian cohort (n = 4) [18], and the retrospective observational cohort (n = 61) (Table 4). A number of patients were excluded from this data set due to non-availability of data, or to avoid overlap between different publications based on the same patients. Seven patients from the randomised trial data set were excluded. Six of these cases did not have a time of neurological onset recorded at baseline, disallowing their inclusion in the analysis. The seventh patient only received miglustat for 71 days, which made it very unlikely that a visible therapeutic response could be expected. Taiwanese patients (n = 2) [29] and patients from a Spanish clinical experience cohort (n = 16) [11] were excluded as they formed part of the retrospective cohort.

Findings from Kaplan-Meier log-rank analysis in different age-at-onset subgroups of untreated patients were in line with previous data on the natural history of NP-C [10]. Untreated patients with neurological disease onset at <2 years of age showed the lowest survival rate over a 10-year period of follow up, while patients with onset aged 11+ years had the best survival rate (Figure 5).

Analyses of survival by age at neurological onset among miglustat-treated patients were limited by low patient numbers and relative lack of long-term follow up among the available published data. No Kaplan-Meier curve was possible for treated patients with disease onset at <2 years of age as there were no deaths in this subgroup. Likewise, no meaningful analysis was possible for treated patients with neurological onset at >11 years of age, as only one patient in this subgroup died (early during miglustat therapy). Kaplan-Meier analysis was only possible for the 2–11 year age at onset subgroup, and showed a numerically better survival rate (2 deaths among 57 patients) during approximately 2.5 years of follow up versus the equivalent age subgroup of untreated patients (40 deaths among 48 patients).

In the overall treated versus untreated group analysis, a total of 74 patients died in the untreated group compared with just three patients in the treated group, leading to a large numerical difference in the overall mortality rates between the two groups; 76% versus 3%, respectively. However, Cox proportional hazard modelling did not establish statistical significance for this difference after adjusting for age (p = 0.34; hazard ratio [95% CI] for treated vs. untreated, 0.56; 0.17, 1.86), likely due to the very low number of deaths and relatively short follow-up time in the treated group. Kaplan-Meier analysis with univariate log-rank testing identified a significant difference in mortality between the treated and untreated groups (p = 0.044) (Figure 6).

Patient age at treatment start (in treated patients) and age at neurological symptom onset (in untreated patients) were found to have a very significant influence on survival. Cox proportional hazard modelling showed that, among all patients (treated and untreated), patients aged <2 years had a significantly higher mortality rate (87%, p < 0.0001; hazard ratio [95% CI], 5.56 [3.08, 10.13]) compared with 49% in patients aged 2–10 years (the reference group). Conversely, patients aged >11 years had a significantly lower rate (11%, p = 0.0003; hazard ratio [95% CI], 11% [0.10, 0.51]) compared with the reference group.

Table 4 Mortality in untreated and miglustat-treated NP-C patients included in survival analysis by age at neurological disease onset

<table>
<thead>
<tr>
<th>Age category*</th>
<th>Mortality in untreated (N = 97)</th>
<th>Mortality in treated (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>74 (76)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>27 (100)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>2–11 years</td>
<td>48 (83)</td>
<td>37 (5)</td>
</tr>
<tr>
<td>&gt;11 years</td>
<td>22 (32)</td>
<td>49 (2)</td>
</tr>
</tbody>
</table>

*Age at neurological symptom onset in untreated patients, and age at treatment start in treated patients.
Data limitations
A number of data limitations should be acknowledged in considering the results of these survival analyses, which are chiefly related to the composition and nature of the treated cohort compared with the untreated cohort. The untreated patient data used in these statistical comparisons are derived solely from the French NP-C cohort, while data from miglustat-treated patients are derived from a multinational group of patients who were included in a number of different studies.

There were large differences in the length of follow-up in treated patients compared with untreated patients. Follow-up data were available from approximately 1 month to 5 years among patients included in the randomised controlled trial, retrospective cohort study and Italian cohort [25,70,73], compared with approximately 23 years in the untreated cohort [1]. More specifically, while the unavailability of data for age at onset of neurological manifestations for many of the treated patients necessitated a comparison of survival from treatment start (in treated patients) with survival from neurological disease onset (in untreated patients), such a comparison presents difficulties.

Published data indicate that substantial periods of time (and likely, significant disease progression) may
pass between neurological onset and initiation of miglustat treatment, due either to diagnostic delay or the date at which miglustat became available (or both) [11,70]. Thus, some patients in the treated group might have progressed significantly before treatment initiation, while in some treated patients miglustat therapy might have been initiated after a relatively short period of time after neurological disease onset. However, given the low numbers of patients available for this assessment, it is not possible to properly assess the influence of this difference.

The untreated patient data constitute an unmatched (and generally younger) control cohort compared with the treated patients in terms of age. The mean (SD) age at treatment start in the randomised controlled trial of miglustat was 25.4 (9.8) years in adolescent/adult patients (range 12–42 years; n = 20) and 7.2 (2.5) years in paediatric patients (range 4–11 years; n = 12) [25]. The mean (SD) age at treatment start in the retrospective NP-C cohort study was 12.8 (9.5) years (range 0.6–43 years; n = 66). The mean age at treatment start in the Italian case series was 8.0 (4.9) years (range 0.9–12 years; n = 4). In contrast, the patient age at neurological symptom onset ranged between approximately 6 months and 55 years; 50% of patients were aged <5 years at onset, and a further 25% were aged <10 years. While both the Kaplan-Meier and Cox proportional hazard modelling analyses of patient survival were controlled for patient age, it cannot be discounted that age-related disease natural history might still have had an influence on the apparent difference in patient survival between the treated and non-treated groups.

It is possible that differences in regional population characteristics (e.g. lifestyle, diet, symptomatic therapies) between the treated and untreated cohorts could have contributed to, or in some other way influenced, the apparent treatment difference. However, it should be remembered that NP-C is pan-ethnic and occurs sporadically across populations, regardless of race. Differences in race per se were not expected to affect the study results.

Finally, while each of the published studies assessing miglustat therapy that were identified in this analysis made efforts to minimise bias, a number of sources of potential bias were inherent following their inclusion in the overall treated group. In particular, while there was minimal selection bias in the randomised, controlled trial of miglustat in NP-C, neither severely affected patients nor symptom-free patients were included in the study [25]. The exclusion of severely affected patients may remove those who were unlikely to improve, resulting in a positive bias (i.e. inclusion of patients more likely to improve). Conversely, non-inclusion of asymptomatic patients might exclude those whose symptom onset may be significantly delayed, thus extending the apparent survival (negative bias).

Safety and tolerability of miglustat in NP-C
While miglustat has been shown to be generally well tolerated in patients with NP-C, the perceived safety and tolerability profile of any drug can affect treatment compliance and can thus impact on clinical efficacy. Similar to previous observations in patients with Gaucher disease type 1 [23,74-78], the principal adverse events observed during clinical studies with miglustat in patients NP-C were gastrointestinal in nature [11,23,25-27,79].

During clinical trials and subsequent clinical experience, diarrhoea, flatulence, bloating and abdominal pain/discomfort were the most commonly reported adverse events associated with miglustat, particularly during the initial weeks/months of therapy [79]. While frequently observed, these gastrointestinal disturbances are generally mild or moderate in severity and usually resolve spontaneously with time on continued therapy [79]. Where required, diarrhoea can effectively be controlled using anti-diarrhoeal medications, used according to the respective manufacturers’ prescribing information. Dietary modifications such as restriction of disaccharides or general, controlled reductions in overall carbohydrate intake can improve the gastrointestinal tolerability of miglustat, particularly if initiated before the start of therapy. Such dietary modifications should be undertaken over a course of weeks or months, with patients gradually being re-introduced to a normal diet dependent on tolerability [79,80].

Conclusions
Published data indicate that aspiration pneumonia is the most common cause of death in neurodegenerative diseases, including NP-C, and that dysphagia can reliably be considered as a risk factor for mortality as it is a frequent cause of aspiration pneumonia.

Miglustat has been shown to stabilise neurological manifestations of NP-C. Beneficial effects of miglustat on swallowing function have been reported in a number of previously published studies based on clinical judgment and quantitative, instrumental VFSSS.

Our findings based on systematic literature analyses and statistical survival evaluations suggest that NP-C patients receiving miglustat therapy may have a greater lifespan compared with untreated patients, and that this effect is likely related to a beneficial effect of miglustat on dysphagia. Because of the extremely variable nature of this disease and the limited published data, further, longer-term data are required to confirm this apparent effect.
Additional files

Additional file 1: Table S1. Results for literature search examining cause of death in patients with NPC-C.

Additional file 2: Table S2. Literature search results for the cause of death in neurodegenerative diseases (B1-102).

Additional file 3: Table S3. Results for literature search to determine the prevalence of dysphagia in neurodegenerative diseases including NPC-C (103-142).

Additional file 4: Table S4. Literature search results for the association between dysphagia and aspiration pneumonia.

Additional file 5: Table S5. Literature search results regarding the association between aspiration pneumonia and mortality.

Abbreviations

Competing interests
None of the authors received honoraria for their roles in the production of this article. MW has received travel expenses, research grant funds and consulting honoraria from Actelion Pharmaceuticals Ltd. YHC has received consultancy honoraria from Actelion Pharmaceuticals Ltd. BFF has received travel expenses and consultancy honoraria from Actelion Pharmaceuticals Ltd. Dr. BFF is an employee of Actelion Pharmaceuticals Ltd, Switzerland.

Authors' contributions
All authors have contributed to the manuscript and approved the final version for submission. All authors read and approved the final manuscript.

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Research

Miglustat therapy in the French cohort of paediatric patients with Niemann-Pick disease type C

Bénédicte Héron1,2*, Vassili Valayannopoulos3,4, Julien Baruteau3,4, Brigitte Chabrol5, Hélène Ogier26, Philippe Latour2,2, Dries Dobbelaere2,8, Didier Eyer9, François Labarthe10, Hélène Maurey11, Jean-Marie Cuisset12, Thierry Billette de Villemeur1,2,13, Frédéric Sede12,14 and Marie T Vanier2,7,15

Abstract

Background: Niemann-Pick disease type C (NP-C) is a rare neurovisceral lysosomal lipid storage disease characterized by progressive neurological deterioration. Published data on the use of miglustat in paediatric patients in clinical practice settings are limited. We report findings from a prospective open-label study in the French paediatric NP-C cohort.

Methods: Data on all paediatric NP-C patients treated with miglustat in France between October 2006 and December 2010 were compiled. All patients had a confirmed diagnosis of NP-C, and received miglustat therapy according to manufacturer's recommendations. Pre-treatment and follow-up assessments were conducted according to a standardized protocol.

Results: Twenty children were enrolled; 19 had NP1 gene mutations and 1 had NP2 gene mutations. The median age at diagnosis was 1.5 years, and the median age at miglustat initiation was 6.0 years. Eight NPC1 patients had the early-infantile, eight had the late-infantile, and three had the juvenile-onset forms of NP-C. A history of hepatosplenomegaly and/or other cholestatic symptoms was recorded in all 8 early-infantile onset patients, 3/8 late-infantile patients, and 1/3 juvenile onset patients. Brain imaging indicated white matter abnormalities in most patients. The median (range) duration of miglustat therapy was 1.3 (0.6–2.3) years in early-infantile, 1.0 (0.6–5.0) year in late-infantile, and 1.0 (0.6–2.5) year in juvenile onset patients. NP-C disability scale scores indicated either stabilization or improvement of neurological manifestations in 1/8, 6/8, and 1/3 NPC1 patients in these subgroups, respectively. There were no correlations between brain imaging findings and disease course. Mild-to-moderate gastrointestinal disturbances were frequent during the first 3 months of miglustat therapy, but were easily managed with dietary modifications and/or anti-propulsive medication.

Conclusions: Miglustat can improve or stabilize neurological manifestations in paediatric patients with the late-infantile and juvenile-onset forms of NP-C. Among early-infantile onset patients, a shorter delay between neurological disease onset and miglustat initiation was associated with an initial better therapeutic outcome in one patient, but miglustat did not seem to modify overall disease course in this subgroup. More experience is required with long-term miglustat therapy in early-infantile onset patients treated from the very beginning of neurological manifestations.

Keywords: Niemann-Pick disease type C, Paediatric, Miglustat

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Introduction
Niemann-Pick disease type C (NP-C) is a rare lysosomal lipid storage disease characterized by neurological deterioration [1,2] with constant progression over time [3-5]. NP-C is caused by autosomal recessive mutations in either one of the two genes, NPC1 or NPC2, which encode proteins involved in the regulation of normal intracellular lipid trafficking [1,6]. It is estimated to affect 1 case in every 100,000–120,000 live births [1,7].

In very rare cases of the severe perinatal (systemic) form of NP-C, patients typically die from liver failure within the first months of life [8,9]. However, NP-C most frequently presents during middle-to-late childhood, and an increasing number of cases are being detected among adolescents and adults [10]. The symptomatology and rate of disease progression of NP-C are strongly influenced by age at onset of neurological manifestations, and different clinical forms have been described on this basis [3,11]. The early-infantile form arises at <2 years of age, the late-infantile form at 2 to 5 years, the juvenile form at 6 to <15 years, and the adolescent/adult form at ≥15 years [2,6,11-13].

Paediatric forms of NP-C tend to feature initial hepato-splenomegaly; an episode of neonatal cholestatic icterus may have occurred [1,8,14]. Later on, neurological manifestations begin to overshadow systemic symptoms. Early delay in motor milestones is often seen in the early-infantile form. Signs of vertical supranuclear gaze palsy (VSGP) are frequent early neurological manifestations, but frequently go undetected until later. Patients may present with clumsiness and progressive cerebellar ataxia. Over time, progressive dysmetria, dystonia, pyramidal signs, dysphagia, dysarthria, ataxia, and/or epileptic seizures, and cognitive impairment often develop [1,2,13,15]. Typically, patients with early-onset neurological manifestations experience a more rapid decline and a lower life expectancy than those with later-onset manifestations [1,2].

Miglustat was approved in Europe for the treatment of progressive neurological manifestations in adult patients and paediatric patients with NP-C in January 2009, and has subsequently been approved in a number of other countries, based on data from preclinical studies [16] and clinical trials showing that it can stabilize neurological disease and/or slow its progression [17-21]. Data from a retrospective observational study of miglustat efficacy in a large cohort of NP-C patients aged between 0 and 32 years demonstrated greater beneficial effects of miglustat on neurological disease in adolescents and adults than those seen in children with the earliest forms of NP-C [4].

Data on the therapeutic effects of miglustat in paediatric patients in clinical practice settings are relatively limited [22-27], and evidence from patients with the early-infantile form are particularly scarce. There is therefore an ongoing need for further clinical experience data on the use of miglustat in children, particularly with regard to disease-specific disability assessments. In addition, there are few data on the response of specific neurological manifestations such as epileptic seizures and ataxia to miglustat therapy.

We report data from a prospective open-label cohort study evaluating disease progression and response to miglustat therapy among all treated paediatric patients with NP-C diagnosed in French hospitals. Findings based on NP-C disability scale assessments, brain imaging and other follow-up assessments conducted according to international disease management recommendations are presented [2].

Methods
Patients
Data on all paediatric NP-C patients treated in France with miglustat between October 2006 and December 2010 were compiled from a network of treatment centres co-ordinated by the French Committee for the Evaluation of Treatment for Niemann-Pick diseases (CETNP). Participating sites included six reference centres and three competence centres.

All index patients had a confirmed diagnosis of NP-C based on filipin staining and molecular genetic laboratory tests. Genetic analyses comprised exon and junction sequencing of the NPC1 and NPC2 genes, and in specific cases cDNA sequencing or multiplex ligation-dependent probe amplification (MLPA). Cases with a sibling history of proven NP-C were diagnosed by genetic analysis alone.

Treatment
All patients received miglustat therapy according to manufacturer’s recommendations based on body surface area (BSA) [20]. Doses were escalated up to full doses as per BSA over a period of 3 weeks to 3 months, based on tolerability.

Patients undertook a diet incorporating reduced disaccharide content (decreased saccharose and other carbohydrates) at or after the start of therapy, as advised by investigators according to clinical need. Patients who experienced gastrointestinal disturbances received temporary reductions in miglustat doses and/or symptomatic therapy.

Assessments
Patient pre-treatment and follow-up assessments were conducted according to a standardized protocol that was in accordance with defined international guidelines for disease monitoring in NP-C (Table 1) [2].
Table 1 Standard assessments at treatment start and during follow up

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment start</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete physical examination</td>
<td>✓</td>
<td>Every 3–6 months</td>
</tr>
<tr>
<td><strong>Clinical parameters of neurological disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP-C functional disability scale</td>
<td>✓</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>Video recording</td>
<td>✓</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td>✓</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>Narcolepsy/cataplexy</td>
<td>✓</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td><strong>Other measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychometric evaluations</td>
<td>✓</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>Hearing</td>
<td>✓</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>✓</td>
<td>Depending on initial findings</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>✓</td>
<td>Initial assessment and depending on clinical evolution</td>
</tr>
<tr>
<td><strong>Laboratory parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function</td>
<td>✓</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>Haematology (blood counts)</td>
<td>✓</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>Plasma chitotriosidase (optional)</td>
<td>✓</td>
<td>Initial assessment</td>
</tr>
<tr>
<td><strong>Cerebral imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI or MRS (magnetic resonance spectroscopy)*</td>
<td>✓</td>
<td>Every 12 months</td>
</tr>
</tbody>
</table>

* Determination of Cho/NAA ratio optional.

Pre-treatment assessments included medical histories of systemic and neurological manifestations, clinical examinations, abdominal ultrasound, chest X-ray, electromyography, and laboratory tests (including haematology, liver markers and optional plasma chitotriosidase activities). Specific examinations were video-recorded.

Regular assessments of seizures (with electro-encephalography (EEG)) and cataplexy were conducted, when required. Other evaluations for characteristic NP-C manifestations included psychometric testing of neuropsychological impairment, ophthalmological examination including saccadic eye movement (SEM) abnormalities, and changes in hearing based on brainstem auditory evoked potentials (BAEP).

Cerebral imaging was conducted based on magnetic resonance imaging (MRI) [28], which included T1, FLAIR and T2-weighted sequences. When possible, magnetic resonance spectroscopy (MRS) was also conducted (often under general anaesthesia) with a single voxel at long (TR 1500 ms/TE 135 or 144 ms) and short (TE 28 ms) echo times in the centrum semi-ovale. The surfaces of metabolite peaks (N-acetyl-aspartate [NAA], creatine [Cr] and choline [Cho]) were integrated, and the NAA/Cr, Cho/Cr and Cho/NAA ratios were calculated and compared with normal values in age-matched children.

Patient scores on a published NP-C specific disability scale [11], which assesses four key parameters of neurological disease progression (ambulation, manipulation, language, swallowing) were measured before treatment and at multiple time points during follow up. A modified version of the original scale was used, which assigns scores from 0 (best) to 1 unit (worst), with equal weighting for each parameter [4].

No statistical analyses were performed as this was an open-label study with no pre-defined hypotheses. Descriptive statistics were used to describe observed clinical changes. All results are stratified according to established forms of neurological disease in NP-C, based on age at neurological disease onset [2].

**Results**

**Patients**

A total of 20 children born between 1994 and 2010 were included in the study (11 females and 9 males), among whom 19 had mutations in the NPC1 gene and 1 had mutations in the NPC2 gene. Cases 12 and 13 are siblings.

All patients were fully genotyped (Table 2); in 17/19 families the genotypes of the patients’ parents were also characterised to establish segregation of alleles.

Among the NPC1 patients, eight were classified as having the early-infantile form, eight as having the late-infantile form, and three as the juvenile form, as defined by the age of neurological onset [12]. Overall, the
<table>
<thead>
<tr>
<th>Patient NP-C gene mutations</th>
<th>Gender</th>
<th>Visceral</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cholestasis</td>
<td>HSM</td>
</tr>
<tr>
<td>Perinatal visceral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#1 NPC2 C99R/C99R</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Early-infantile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#2 L850P/R858X</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>#3 C635S/C635S/C635S/C635S</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>#4 T1205R/T1205K</td>
<td>M</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>#5 IVS21-2delATGC/IVS21-2delATGC</td>
<td>M</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>#6 G1195W/G1195W</td>
<td>M</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>#7 P543L/IVS14+1G&gt;A</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>#8 P543L/T1205fs</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>#9 T1036M/T1036M</td>
<td>F</td>
<td>Yes (foetal)</td>
<td>Yes</td>
</tr>
<tr>
<td>Late-infantile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#10 Y509S/del exon4</td>
<td>F</td>
<td>No</td>
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</tr>
<tr>
<td>#11 I1061T/C242H</td>
<td>M</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>#12 P1007A/T1205K</td>
<td>M</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#13 P1007A/T1205K</td>
<td>F</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>#14 R518W/G992W</td>
<td>M</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#15 A470P+1837V/A470P+1837V</td>
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<td>Yes</td>
</tr>
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<td>#16 R518W/D9444N</td>
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<tr>
<td>#17 I1061T/R934X</td>
<td>M</td>
<td>No</td>
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</tr>
<tr>
<td>Juvenile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#18 I1061T/Q421X</td>
<td>M</td>
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<td>Yes</td>
</tr>
<tr>
<td>#19 Q691X/1005W/1143R</td>
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<td>Yes</td>
</tr>
<tr>
<td>#20 I1061T/I1051T</td>
<td>F</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Motor deficits (hypotonia and motor delay) in early-infantile onset patients; cognitive deficits (learning difficulties) in late-infantile and juvenile onset patients; 1 distal motor deficit in early-infantile patients due to peripheral neuropathy; and 'dystonia' in late-infantile and juvenile patients. HSM = hepatosplenomegaly; VSGP = vertical supranuclear gaze palsy.
median (range) age at neurological disease onset was 3.0 years (5 months to 7 years). The median (range) age at diagnosis was 1.5 years (prenatal to 14 years), and the median (range) age at start of miglustat therapy was 6.0 years (2 months to 14.8 years).

Pre-treatment disease history

Patient with perinatal visceral disease
Patient 1 developed cholestasis and hepatosplenomegaly at 1 month of age. This patient was homozygous for the well described NPC2 mutation, p.C99R, which has previously been associated with either a perinatal lethal disease or an early-infantile neurological form in the same sibship [29,30]. No disability scale or brain imaging assessments were performed in this child, but clinical examination revealed hypotonia, due either to the severity of his liver disease or to early cerebral disease. Haematopoietic stem cell transplantation was declined due to his poor general condition.

Patients with early-infantile neurological onset
All eight patients with early-infantile neurological disease onset had a history of hepatosplenomegaly, and all but one had prolonged neonatal cholestasis; liver biopsy revealed evidence of cirrhosis in two patients (Table 2). One patient (#7) had severe portal hypertension with oesophageal varices (but no digestive bleeding) at 5 months of age. Five patients had a history of pulmonary involvement, but only two (#4 and #5) had specific alveolar or interstitial pulmonary disease detected by chest X-ray at 6 months of age and confirmed by bronchoalveolar lavage revealing accumulation of foamy macrophages; patient 4 needed oxygen therapy up to 15 months of age, and currently has frequent pulmonary infections; patient 5 had frequent bronchitis with interstitial signs on chest X-ray around 6 months of age and then developed alveolar proteinosis with progressive respiratory failure. Patient 6 had repeated pulmonary infections from birth to 3 months of age. Patient 8 had subacute aspiration pneumonia at 2 years of age without specific biological signs on bronchoalveolar lavage. Patient 9 had bronchopulmonary dysplasia presumably due to prematurity, and which required non-invasive ventilation up to 6 months of age.

Neurological manifestations among early-infantile patients appeared between 5 and 12 months of age, and included initial hypotonia, delayed motor development and swallowing disorders. VSGP was observed at 9, 18, and 24 months of age in five patients, but no patients had cataplexy. One patient had pronounced dysphagia and subsequent feeding difficulties at 5 months of age, requiring enteral feeding with nasogastric tube followed by gastrostomy aged 9 months. Four patients exhibited clinical signs of peripheral neuropathy, which included distal motor deficit, dysesthesia and diminished osteotendinous reflexes. In each case a myelinic neuropathy was confirmed by electrodiagnostic testing.

Filipin staining, performed in fibroblasts from each patient, invariably showed a massive accumulation of unesterified cholesterol in perinuclear vesicles (classic phenotype). The NPC1 T mutation p.11061T was not observed in this age subgroup, in good accordance with our previous observations [6,30,31]. The p.P543L mutation (present in patients 7 and 8) has previously been reported to lead to an early-infantile form of NP-C [29]. Mutations p.G1195V and p.L830P were detected in one patient each; to our knowledge these mutations have not previously been reported.

Patients with late-infantile neurological onset
Three of the eight late-infantile onset patients had splenomegaly, among whom only one also had a history of neonatal cholestasis (#11 – his elder brother died from foetal hydrops due to NP-C). No patients in this subgroup exhibited pulmonary disease. Neurological manifestations appeared between 2 and 5 years of age, and included initial slow motor function and clumsiness or ataxia, delayed language development, and behavioural disturbances with relational troubles. All patients exhibited VSGP, and 5/8 patients had cataplexy and/or epilepsy. Because of pronounced dysphagia and related feeding difficulties, gastrostomy tube and discontinuous enteral feeding became mandatory before initiation of miglustat in patient 12 (at 12 years of age) and patient 17 (at 10 years of age). Another patient (#14) underwent gastrostomy a few weeks after miglustat initiation because he refused oral treatment due to its bitter taste.

A ‘classic’ filipin staining result was observed in fibroblasts from all cases except patient 16, including patient 12 who had one p.P1007A allele, which is usually associated with a ‘variant’ filipin staining pattern [31]. The p.1061 T mutation constituted 2/14 of the mutant alleles among 7 unrelated patients in this age subgroup. Mutations detected in patients 10 and 15 have not previously been described. Two patients (#14 and #16) were heterozygous for the p.R518W mutation, which in the homozygous state has previously been reported in adult-onset patients [10].

Patients with juvenile neurological onset
Only one juvenile-onset patient had visceral symptoms: enlarged spleen without a history of neonatal cholestasis. No patients in this subgroup exhibited pulmonary disease. Neurological manifestations started between 5 and 7 years of age in all three juvenile-onset patients, and included praxis disorders, a cerebellar-dystonic syndrome, cognitive decline and swallowing disorders (but no psychiatric signs). All patients had VSGP. Two
patients (#s 19 and 20) experienced epileptic seizures and cataleptic episodes before miglustat therapy, at the ages of 9 years and 12 years, respectively. At the age of 5 years, one patient (#18) diagnosed earlier based on visceral symptoms was found to have deafness, a probable early sign of the disease.

As regards biochemical phenotype and genotype, a ‘classic’ flamin pattern was found in all juvenile-onset patients. The p.1061 T mutation constituted 3/6 of the mutant alleles detected in this age subgroup.

Miglustat therapy and effects on neurological disease
Key age milestones (periods before and with neurological manifestations, age at diagnosis and duration of miglustat therapy) are summarized in Figure 1. Details of miglustat therapy and changes in neurological disease status are summarized in Table 3.

Patients with early-infantile neurological onset
The median (range) interval between the onset of neurological manifestations and initiation of miglustat therapy was 14 (4–34) months, and the median (range) age at miglustat start was 25 (9–43) months. Early-infantile patients received miglustat for a median (range) of 16 (8–27) months.

Based on disability scale assessments, key neurological parameters were stabilized in 1/8 (13%) patients (Figure 2a). Patient 6, who started miglustat aged 3.6 years, was essentially stabilized throughout 18 months on miglustat. In spite of showing initial neurological signs at 9 months of age, the evolution of disease before miglustat therapy in this patient was similar to that seen in the late-infantile onset form (i.e. a slower disease progression). Patient 2, who had the earliest neurologic onset in this group (at 5 months), started miglustat at the age of 9 months and showed consistent improvement throughout 15 months of therapy, but began to deteriorate after Month 18. By Month 22 of therapy her disability score was similar to that at initiation of miglustat.

During a mean treatment period of approximately 18 months, disability scale scores increased (indicating disease progression) in five patients in spite of slight improvements in interactions, tone and/or salivation. All but one exhibited pyramidal tract involvement. Three patients required discontinuous enteral feeding by nasogastric tube (#7, persistence of severe portal hypertension with oesophageal varices contra-indicated the gastrostomy) or by gastrostomy tube (#s 3 and 8) after 10 to 12 months of miglustat therapy, and one patient (#4) developed epilepsy at the age of 32 months. NP-C disability scale data were not obtained for patient 5, whose steady respiratory worsening was associated with neurological disease progression during a 13-month period of therapy; the severity of his respiratory condition precluded disability scale assessments.

Patients with late-infantile neurological onset
The median (range) interval between the onset of neurological manifestations and initiation of miglustat therapy was 4.2 (1.0–9.6) years, and the median (range) age at miglustat start was 8.0 (4.0–12.6) years. The median (range) treatment duration at last evaluation was 1.0 (0.8–5.0) years.

Disability scale scores indicated improvement/stabilization of neurological parameters in 6/8 (75%) patients in this subgroup (Figure 2b). Patients 11 and 17 both improved during 12 months of miglustat therapy. Patient 17, whose epilepsy was very active before miglustat, showed a global improvement and became free of seizures after months 5 on miglustat. Patient 16 showed initial
Table 3 Migiustat therapy and neurological evolution during follow up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset of neurological manifestations</th>
<th>Age at start of miglustat therapy</th>
<th>Miglustat dose (mg/day)</th>
<th>Duration of miglustat therapy</th>
<th>Disease evolution*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal visceral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#1</td>
<td>2 months</td>
<td>2 months</td>
<td>50</td>
<td>2 months</td>
<td>NA†</td>
</tr>
<tr>
<td>Early infantile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td>5 months</td>
<td>9 months</td>
<td>100–150–100</td>
<td>22 months</td>
<td>Initially improved then worsened</td>
</tr>
<tr>
<td>#3</td>
<td>6 months</td>
<td>2 years 1 month</td>
<td>200</td>
<td>18 months</td>
<td>Worsened</td>
</tr>
<tr>
<td>#4</td>
<td>7 months</td>
<td>2 years 3 months</td>
<td>150–300–150</td>
<td>27 months</td>
<td>Worsened</td>
</tr>
<tr>
<td>#5</td>
<td>9 months</td>
<td>20 months</td>
<td>200</td>
<td>13 months</td>
<td>Worsened†</td>
</tr>
<tr>
<td>#6</td>
<td>9 months</td>
<td>3 years 7 months</td>
<td>200–300–150</td>
<td>18 months</td>
<td>Stabilized</td>
</tr>
<tr>
<td>#7</td>
<td>10 months</td>
<td>2 years 2 months</td>
<td>200–150–200</td>
<td>12 months</td>
<td>Worsened</td>
</tr>
<tr>
<td>#8</td>
<td>12 months</td>
<td>2 years</td>
<td>50–100</td>
<td>12 months</td>
<td>Worsened</td>
</tr>
<tr>
<td>#9</td>
<td>12 months</td>
<td>2 years</td>
<td>100–200</td>
<td>8 months</td>
<td>Worsened</td>
</tr>
<tr>
<td>Late infantile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#10</td>
<td>2 years</td>
<td>4 years</td>
<td>250</td>
<td>60 months</td>
<td>Stabilized</td>
</tr>
<tr>
<td>#11</td>
<td>3 years</td>
<td>8 years</td>
<td>100–300</td>
<td>12 months</td>
<td>Improved</td>
</tr>
<tr>
<td>#12</td>
<td>3 years</td>
<td>12 years 7 months</td>
<td>600–400</td>
<td>12 months</td>
<td>Worsened†</td>
</tr>
<tr>
<td>#13</td>
<td>4 years 6 months</td>
<td>8 years</td>
<td>400</td>
<td>9 months</td>
<td>Worsened†</td>
</tr>
<tr>
<td>#14</td>
<td>5 years</td>
<td>6 years</td>
<td>150–250</td>
<td>36 months</td>
<td>Worsened transiently then stabilized</td>
</tr>
<tr>
<td>#15</td>
<td>5 years</td>
<td>7 years 9 months</td>
<td>200–300</td>
<td>12 months</td>
<td>Stabilized†</td>
</tr>
<tr>
<td>#16</td>
<td>5 years</td>
<td>9 years 10 months</td>
<td>400–200–400</td>
<td>9 months</td>
<td>Worsened transiently then improved</td>
</tr>
<tr>
<td>#17</td>
<td>5 years</td>
<td>10 years 3 months</td>
<td>300</td>
<td>12 months</td>
<td>Improved</td>
</tr>
<tr>
<td>Juvenile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#18</td>
<td>5–6 years</td>
<td>7 years</td>
<td>300</td>
<td>12 months</td>
<td>Worsened†</td>
</tr>
<tr>
<td>#19</td>
<td>5–6 years</td>
<td>9 years 9 months</td>
<td>400</td>
<td>7 months</td>
<td>Worsened then stable</td>
</tr>
<tr>
<td>#20</td>
<td>6–8 years</td>
<td>9 months 9 months</td>
<td>600</td>
<td>30 months</td>
<td>Improved then stable</td>
</tr>
</tbody>
</table>

*Patient 1 died aged 4 months, patient 5 died aged 2 years and 9 months, and patient 12 died aged 13 years 11 months; †disease evolution based on NPC disability scale [11] and global clinical judgment; NA: not applicable due to young age. Miglustat treatment was stopped in patient #13, 15 and 18 after 9, 12 and 12 months, respectively.

deterioration during the first month of treatment, and improved later on. Patient 15 showed stabilization during 12 months on miglustat before treatment was stopped because of adverse events. Two patients (#'s 10 and 14) showed overall improvement, but epileptic and cataplectic episodes started 44 months after and just after miglustat initiation, respectively. In patient 14, seizures and cataplectic episodes are controlled using symptomatic medications. In patient 10, neurological deterioration began when epilepsy became medication-resistant (persistence of one to three short tonic seizures per day despite antiepileptic polytherapy). Patient 12 exhibited pronounced worsening during the initial 6 months of treatment, but appeared stabilized (albeit at a high disability score) after 12 months. Patient 13 experienced difficulties to ingest miglustat powder due to its bitter taste and worsened during therapy, showing more active epilepsy; miglustat was discontinued after 9 months.

Patients with juvenile neurological onset
The median (range) interval between the onset of neurological manifestations and initiation of miglustat therapy was 4.3 (1.5–7.7) years, and the median (range) age at miglustat start was 9.8 (7.0–14.8) years. The median (range) treatment duration at last evaluation was 1.0 (0.6–2.5) years.

Disability scale scores indicated improvement of neurological manifestations in one of the three patients (Figure 2c). Patient 20 showed initial improvement then stabilized. Cataplectic episodes began in this patient at Month 22; her cataplectic episodes and epilepsy are currently controlled using symptomatic therapy. Patient 19 worsened during the first 3 months of miglustat therapy.
and then appeared stable between 4 and 7 months of treatment, showing less dystonia but more swallowing difficulties. This patient’s epilepsy became more active during miglustat treatment but was stabilized following alteration of antiepileptic therapy. Patient 18 displayed worsening of neurological manifestations during 12 months of miglustat therapy before treatment was stopped.

Electrophysiological findings

Patients with early-infantile neurological onset

Slight non-specific abnormalities such as bioccipital slow waves or slow background activity were identified in EEG analyses before and during miglustat therapy. Rare posterior spikes were observed in patient 4 when he developed epilepsy aged 32 months, after 5 months on miglustat therapy.

Hearing was normal in all patients in this subgroup, although BAEP showed prolonged latencies in two patients aged 2 and 3 years.

Pre-existing electromyographic signs of myelinic neuropathy in four patients did not worsen after 12–24 months in four patients. Clinical signs of myelinic neuropathy worsened in patient 2 after 22 months on miglustat, which correlated with viral infection and simultaneous losses in the ability to stand and language, as well as complete dysphagia. This worsening neuropathy is considered as being related to disease progression.

Patients with late-infantile neurological onset

Several non-specific signs were observed in EEG assessments. EEG findings were normal or showed slow waves or a slow background activity in two patients without epilepsy (#’s 11 and 15), and in two patients (#’s 10 and 14) before epilepsy. Various types of electro-clinic seizures were observed before miglustat start (patients 12, 13, 16 and 17), or during miglustat treatment (patients 10 and 14), including atypical or myoclonic absence, generalized tonic-clonic, and focal seizures. After the start of epilepsy, EEG abnormalities were more active, showing focal, multifocal or generalized interictal spikes or spike-waves.

Late-infantile onset patients did not develop hearing impairment, although BAEP showed prolonged latencies in four patients aged between 8 and 9.5 years (#’s 11, 13, 14 and 16). Findings were normal in the three other patients.
Patients with juvenile neurological onset
Juvenile-onset patients exhibited a similar profile of EEG abnormalities as that seen in patients with late-infantile onset. For one patient (#18), early-onset deafness at the age of 5 years was considered a sign of neurological disease onset, and required a hearing prosthesis. No hearing loss was observed in the other two juvenile patients.

Imaging findings
Findings from MRI and MRS assessments before therapy and at follow up are summarized in Table 4.

Patients with early-infantile neurological onset
The seven living early-infantile patients showed white-matter abnormalities indicative of delayed myelination or demyelination before miglustat therapy, with three showing atrophy in the periventricular or subcortical regions or the corpus callosum, and two also showing slight atrophy of the cerebellar vermis or peduncles (Table 4). Patient 9 had a normal MRI at 5 months of age before developmental delay was noted at 12 months. These white matter abnormalities remained stable in patients 8 and 9, but worsened slightly during miglustat treatment in the three other patients (#'s 3, 4 and 7), who experienced clinical worsening. The two patients who showed initial improvement (#2) or clinical stabilization (#6) had stable MRI abnormalities and normal MRS at pre-treatment assessment and at 12-month follow up. Patient 3, who showed clinical worsening, also had normal MRS findings at pre-treatment.

Pre-treatment MRS showed low NAA and high Cho peaks in 2/5 patients (#'s 4 and 9). Low NAA peaks were noted at Months 8–24 of miglustat therapy in four patients (#'s 4, 7, 8 and 9) who showed clinical worsening, with normal Cho peaks in patients 4 and 8.

Patients with late-infantile neurological onset
Before starting miglustat, three late-infantile onset patients (#'s 11, 14 and 17) had normal brain MRI findings at 6, 8 and 10 years of age, respectively. Five patients had slight periventricular or more generalized white matter abnormalities on MRI (#’s 10, 12, 13, 15, and 16), with cortical or slight cerebellar atrophy also seen in two patients (#’s 15 and 16).

Four patients developed cortical, subcortical or cerebellar signs of atrophy after the commencement of miglustat therapy, two of whom (#’s 10 and 14) experienced stabilization of neurological symptoms, while patients 12 and 13 worsened. Follow-up MRI findings are not yet available for four patients (#’s 11 and 17 who had normal findings before therapy, and #’s 15 and 16).

MRS findings were normal before treatment in patients 10, 12, 13, 14 and 16, and showed a low NAA peak in patient 15. At follow up, patient 10 showed a persistent low NAA peak. Patient 14 had a transient low NAA peak at Month 18 on miglustat, and MRS findings became normal at Month 24. A high Cho peak was also noted at Month 12 in patient 10 and at Month 18 in patient 14, which contrasted with a slight improvement of symptoms.

Patients with juvenile neurological onset
Magnetic resonance imaging analysis revealed slight periventricular white matter abnormalities in patient 18 before therapy and at Month 12 of follow up during miglustat therapy, but MRS findings were normal. Periventricular white matter abnormalities were associated with cortical atrophy in patient 19 before therapy, but no MRI follow-up is yet available for this patient, who has so far received 7 months of miglustat treatment. In patient 20, imaging findings were normal before miglustat at the age of 14 years and 9 months, but follow-up analysis showed slight cortical atrophy after 12 months of miglustat therapy and a high Cho/NAA ratio after 30 months, associated with clinical stabilization.

Safety and tolerability
Fifteen out of 20 patients (75%) in this paediatric cohort experienced adverse effects that were considered related to miglustat therapy, including diarrhoea, abdominal pain, anorexia and weight loss. Gastrointestinal adverse events occurred mostly during the first 3 months of miglustat therapy, and usually resolved during continued therapy at lower doses, following institution of a disaccharide-free diet and/or administration of symptomatic treatment (e.g. loperamide).

Most adverse events were mild or moderate in severity, except in three cases where adverse events led to discontinuation of miglustat therapy. Asthenia and/or persistent diarrhoea motivated a decision to stop miglustat therapy after 1 year in one late-infantile onset patient (#15) and one juvenile-onset patient (#18). These adverse events resolved without clinical sequelae after withdrawal of miglustat.

Patient 13 experienced persistent diarrhoea, but refused the recommended disaccharide-free diet and became anorectic; miglustat was subsequently discontinued after 9 months of therapy. One late-infantile onset patient (#14) refused to ingest oral miglustat powder due to its bitter taste, and a gastrostomy was conducted to enable drug administration. This patient subsequently received a normal oral diet and miglustat was well tolerated. Miglustat commercial 100-mg capsules were repackaged in smaller capsules of 50 mg to allow easier swallowing for patient 7. Patient 9 remains strongly constipated on miglustat treatment in spite of laxative medications. Patient 20 presented at the age of 16 years (1 year after starting miglustat therapy) with rectal fistula that persisted despite many
<table>
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<td>#13</td>
<td>Diffuse WMScA</td>
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<td>Periventricular WMScA, cortical and cerebellar atrophy</td>
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<td>ND</td>
<td>ND</td>
</tr>
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<td>Juvenile</td>
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<tr>
<td>#18</td>
<td>Periventricular WMScA</td>
<td>M12: stable</td>
<td>ND</td>
<td>M12: normal</td>
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<tr>
<td>#19</td>
<td>Posterior periventricular WMScA and slight cortical atrophy</td>
<td>ND</td>
<td>Normal</td>
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</tr>
<tr>
<td>#20</td>
<td>Normal</td>
<td>M18 and M30: slight cortical atrophy</td>
<td>M0: high myo-inositol</td>
<td>M18: high myo-inositol, M30: high Cho/NAA ratio</td>
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Cho = choline; M = month on miglustat therapy; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate; ND = not done; WMScA = white matter signal abnormalities.
treatments. She was later discovered to have Crohn’s disease, which was subsequently controlled with symptomatic therapy (mesalamine) to allow continued miglustat treatment.

Three patients died during follow up. The patient with perinatal visceral disease (i.e. NPC2; #1) developed cholestasis and hepatosplenomegaly at 1 month of age, and died aged 4 months (after 2 months of miglustat therapy) due to liver failure. One early-infantile onset patient (#5) died aged 2 years and 9 months due to respiratory failure with alveolar proteinosis, which was considered to be associated with neurological disease progression during the patient’s 13-month period of miglustat therapy. One late-infantile onset patient (#12) died aged 13 years and 11 months due to aspiration pneumonia.

Discussion
Assessments of key parameters of neurological disease progression based on the published NP-C disability scale indicated either stabilization or improvement of neurological manifestations in 1/8 early-infantile, 6/8 late-infantile, and 1/3 juvenile-onset NP-C patients who received miglustat in this multicentre, open-label cohort study. Beneficial therapeutic effects were seen more frequently in patients with late-infantile/juvenile neurological disease onset than in those with early-infantile onset.

In agreement with previous reports, visceral disease (prolonged neonatal cholestasis and/or hepatosplenomegaly) was more prevalent among early-infantile onset patients than in later-onset patients in this paediatric cohort [1,26]. Neonatal cholestasis healed in all NPC1 patients before miglustat therapy, but portal hypertension persisted in one patient during miglustat treatment. While visceral disease was not a focus of disease monitoring in this study, miglustat did not appear to have any effect on hepatosplenomegaly (data not shown) or pulmonary disease (patient 5 died from alveolo-intestinal complications after 13 months of miglustat treatment).

While the NPC2 patient had cholestasis and hepatosplenomegaly from 1 month of age (before initiation of miglustat), she developed hepatic failure during miglustat therapy. It is not possible to ascertain whether miglustat might have worsened the liver disease in this patient as a similar course of disease is quite common in NPC2 [29].

In general, our findings appear in line with those from previous clinical trial data [4,18,19] and case reports [23,25,27] on the effects of miglustat on neurological disease manifestations in paediatric NP-C patients. Based on clinical assessments in a 24-month study of miglustat in children aged 4–12 years, Patterson et al. reported stabilization of SEM, an accepted marker of early neurological deterioration in NP-C, in 67% of patients throughout therapy [18]. Ambulation (measured using the standard ambulation index) was stabilized in 80% of patients, and swallowing (patients’ ability to swallow various substances) remained stable in 90% [18]. Based on the same NP-C disability scale as that employed in the current study, a retrospective analysis of miglustat efficacy in 66 NP-C patients aged between 0 and 32 years (mean ± SD, 9.7 ± 7.5 years) showed that ambulation, manipulation, language and swallowing were stabilized or improved in 75% of patients during an average of 18 months of therapy [4]. Stratification of patients according to age indicated that beneficial effects were greater in juvenile, adolescent and adult patients than in those with disease onset before 6 years of age [4].

Pineda et al. reported clinical experience with the use of miglustat in a paediatric cohort of 16 Spanish NP-C patients, comprising five with the early-infantile form, four with the late-infantile form, and seven with the juvenile form [26]. As in the current study, efficacy assessments were based on an NP-C specific disability scale, albeit a modified version that included scores for the presence of epilepsy and ocular movements. Similar to our findings, the Spanish cohort study indicated that patients with the late-infantile and juvenile-onset forms were more likely to show improvements or stabilization of neurological disease during miglustat therapy compared with patients with severe, early-infantile onset [26]. However, Spanish early-infantile onset patients who showed deterioration during miglustat therapy were at an advanced stage of the disease before starting therapy, while those with a better evolution had started therapy at the youngest ages. Overall, the Spanish data suggested that better treatment effects might be expected when treatment was initiated early, before “irreversible neurological damage” [2,26].

In our cohort, there did not appear to be as strong a correlation between patients’ disability scale scores before treatment and subsequent changes during therapy. However, a short interval between neurological disease onset and the start of miglustat therapy and/or young age at treatment start was associated with a better initial therapeutic outcome in one early-infantile onset patient: in patient 2, who initially improved, the delay between neurological disease onset and initiation of miglustat was only 4 months, and miglustat was commenced at 9 months of age. Other early-infantile patients, four of whom worsened, had a mean (range) delay between neurological disease onset and start of treatment of 1.8 (0.9–2.8) years, and a mean (range) age at treatment start of 2.3 (range 1.7–3.6) years. In the late-infantile and juvenile-onset patients the mean (range) delay to therapy was 3.8 (1.0–7.8) years in patients who were stable or improved after treatment, and 4.8 (1.5–9.6)
years for those who worsened. These observations appear to support the argument for starting miglustat treatment earlier, as soon as possible after the onset of neurological symptoms and especially in the early-infantile onset patients.

Data from the current cohort are in line with previous data on the high prevalence of epilepsy and cataplexy in late-infantile and juvenile (but not early-infantile) onset patients [1,2]. Published data on the possible therapeutic effect of miglustat on cataplexy and epilepsy are very scarce. Zarowski et al. have previously reported a complete cessation of cataplectic activity in a young male patient with juvenile-onset NP-C [32]. In our study, miglustat did not appear to prevent the occurrence of, or to systematically improve, cataplexy or epilepsy among the small number of patients in the late-infantile and juvenile-onset subgroups. Limited data from the Spanish paediatric cohort study indicated that the onset of epilepsy and its resistance to symptomatic pharmacotherapy may result in worsening of patients’ scores on the NP-C disability scale [25]. In our series, the presence of pre-existing epilepsy, or its onset during miglustat therapy, did not appear to affect neurological outcome when seizures were stabilized using anti-epileptic therapies. Anti-epileptic drugs employed included sodium valproate, lamotrigine and levetiracetam. Carbamazepine, oxcarbazepine and vigabatrin were avoided as they could promote myclonias. Phenytoin was also not used in order to avoid possible cerebellar adverse effects.

Auditory acuity remained stable in this series, and no patient experienced worsening of electrical peripheral neuropathy during miglustat therapy.

Magnetic resonance imaging showed white matter abnormalities in NPC1 patients with each of the age-at-onset forms. In general, discrete posterior periventricular white matter abnormalities were followed by more diffuse changes resembling delayed myelination or demyelination among these patients. Cortical or subcortical atrophy tended to appear first in the infantile-onset forms (although it was also present in later-onset forms). Cerebellar atrophy was present in relatively few cases (two early-infantile and three late-infantile patients).

Magnetic resonance spectroscopy identified some abnormalities, including low NAA and/or high Cho with high Cho/NAA ratio. At short echo time, a high myoinositol peak was observed before therapy and at Month 18 of follow-up in patient 4 (worsened) and patient 20 (stabilized). It is known that progressive neurodegenerative diseases are associated with a decrease of the NAA peak, which is considered to be a marker of neuronal viability, and by an increase of the Cho peak, which is considered to be a marker of membrane destruction or gliosis. Nevertheless there was no consistent pattern of change over time or in response to miglustat in our series. A low NAA peak was associated with cerebral atrophy in 8/18 cases but not with clinical worsening in all of these. This contrasts with a previously published case series based on three adult NP-C patients treated with miglustat for 24 months, where mild clinical improvement or stabilization concurrent with sustained decreases in cerebral Cho/NAA ratio were observed [24].

While our imaging findings are of value in that they add to the relatively limited amount of published data from longitudinal imaging studies in paediatric NP-C patients, it is notable that there were no apparent correlations between MRI or MRS findings and clinical disease course during miglustat therapy. It is possible that methodological and data limitations in our cohort preclude a definitive conclusion on the utility of this imaging technique. MRS analyses for French paediatric patients were conducted at several different sites by several techniciens, and according to varied analysis protocols. MRS data follow up beyond 24 months were only available for 4/20 patients, which makes it difficult to assess long-term changes. However our findings do not favour the use of high Cho peak or Cho/NAA ratios as objective markers of therapeutic effect in paediatric patients, as has been proposed for adult patients [24].

A possible correlation between the evolution of neurological manifestations (based on changes in NP-C disability scores) and cerebral hypometabolism (measured using positron emission tomography [PET]) was previously reported based on data from Spanish juvenile- and infantile-onset patients treated with miglustat [26]. Cerebral hypometabolism was stabilized when miglustat appeared to slow the progression of neurological symptoms, and progressive hypometabolism correlated with increasing disability scores [26]. Nevertheless, PET is unlikely to be of practical use for routine clinical monitoring due to the limited availability of equipment.

Mild or moderate gastrointestinal disturbances were frequent during miglustat therapy, but usually resolved within the first 3 months of treatment. In addition, gastrointestinal adverse events were easily managed in most cases by the adoption of dietary alterations, by progressive initiation of miglustat treatment, or by the use of symptomatic therapy (e.g. loperamide). In particular, dietary modifications such as reduced consumption of dietary sucrose, maltose and lactose have been shown to improve the gastrointestinal tolerability of miglustat, and to reduce the magnitude of any changes in body weight, particularly if initiated at or before the start of therapy [33,34]. Finally, observed factors that appear to contribute to reduced treatment compliance among the youngest patients include the bitter taste of oral miglustat therapy, and the lack of a paediatric galenic form.
A decision to stop miglustat was taken for two late-infantile patients and one juvenile patient because of persistent adverse events (e.g. asthenia or anorexia) and clinical judgment of insufficient beneficial effects on disease progression. Such choices are made on a case-by-case basis with collaborative discussions between medical staff and parents, as well as detailed consideration of patients’ clinical evolution and quality of life, well in line with the updated recommendations from an expert panel [35].

In spite of the small number of patients and the relatively short period of follow up in the French paediatric NP-C cohort, and in recognition of the invariably progressive course of neurological deterioration in untreated patients [3,35], we conclude that miglustat can improve or stabilize neurological disease progression in paediatric patients with NP-C, particularly those with the late-infantile and juvenile-onset forms. Our data from early-infantile onset patients, who generally exhibit greater symptom severity and more rapid progression of neurological manifestations, indicate that commencement of miglustat at approximately 2 years of age has no sustained global effect on the natural course of the disease. A shorter delay between the onset of neurological manifestations and the start of miglustat therapy was associated with a better initial therapeutic outcome in one early-infantile-onset patient in this cohort. However, this patient later exhibited worsening of neurological disease after 2 years of age. More clinical experience in early-infantile onset patients treated at the very beginning of their neurological disease over a longer period is required to more fully assess the therapeutic effects of miglustat in this group.

Current guidelines for the clinical management of NP-C propose that miglustat treatment should be initiated at the onset of neurological signs [2,35]. However, among patients with early-infantile NP-C, the variable occurrence and high frequency of systemic symptoms particularly neonatal cholestasis and hepatosplenomegaly, often leads to a diagnosis before the appearance of neurologic signs or developmental delay. Regular and thorough clinical examination of these patients, if possible combined with cerebral MRI, could detect neurological problems at their very beginning, leading to earlier initiation of treatment with miglustat.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
MTV, FS, TBV, BH, BC and HO conceived the study and participated in its design. BH coordinated the study. BH, MTV and TBV drafted the manuscript. MTV and PL carried out the clinical and molecular genetic studies. All authors participated in collection of data, and have read and approved the final manuscript.

Disclosures
BH has received travel expenses, and been invited to meetings funded and organized by Actelion Pharmaceuticals Ltd, Storman, Genzyme Corporation and Shire HGT, and has received presentation honoraria from Actelion Pharmaceuticals Ltd. MTV has received travel expenses, carried out paid and unpaid consultancy work, and presentation honoraria from Actelion Pharmaceuticals Ltd, and has received travel expenses, presentation honoraria, and been invited to meetings funded and organized by Genzyme Corporation and Shire HGT. W has received travel expenses, research grants and presentation honoraria from Actelion Pharmaceuticals Ltd. FS has received travel expenses, carried out paid consultancy work, and received presentation honoraria from Actelion Pharmaceuticals Ltd. BC has received travel expenses and presentation honoraria from Actelion Pharmaceuticals Ltd. DD has received travel expenses and presentation honoraria from Actelion Pharmaceuticals Ltd. PL has received presentation honoraria from Actelion Pharmaceuticals France. FL has received travel expenses from Jinek Servano and Genzyme Corporation. TBV has received funds for an association (ASEP, for health and progress in paediatrics) from Shir HGT and Genzyme Corporation. DD, HO and HM declare that they have no competing interests.

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Niemann-Pick disease type C

Marie T Vanier

Abstract

Niemann-Pick C disease (NP-C) is a neurovisceral atypical lysosomal lipid storage disorder with an estimated minimal incidence of 1/120 000 live births. The broad clinical spectrum ranges from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. The neurological involvement defines the disease severity in most patients but is typically preceded by systemic signs (cholestatic jaundice in the neonatal period or isolated spleno- or hepatosplenomegaly in infancy or childhood). The first neurological symptoms vary with age of onset; delay in developmental motor milestones (early infantile period), gait problems, falls, clumsiness, cataplexy, school problems (late infantile and juvenile period), and ataxia not infrequently following initial psychiatric disturbances (adult form).

The most characteristic sign is vertical supranuclear gaze palsy. The neurological disorder consists mainly of cerebellar ataxia, dysarthria, dysphagia, and progressive dementia. Cataplexy, seizures and dystonia are other common features. NP-C is transmitted in an autosomal recessive manner and is caused by mutations of either the NPC1 (95% of families) or the NPC2 genes. The exact functions of the NPC1 and NPC2 proteins are still unclear. NP-C is currently described as a cellular cholesterol trafficking defect but in the brain, the prominently stored lipids are gangliosides. Clinical examination should include comprehensive neurological and ophthalmological evaluations. The primary laboratory diagnosis requires living skin fibroblasts to demonstrate accumulation of unesterified cholesterol in perinuclear vesicles (lysosomes) after staining with filipin. Pronounced abnormalities are observed in about 80% of the cases, mild to moderate alterations in the remainder (variant) biochemical phenotype. Genotyping of patients is useful to confirm the diagnosis in the latter patients and essential for future prenatal diagnosis. The differential diagnosis may include other lipidoses; idiopathic neonatal hepatitis and other causes of cholestatic icterus should be considered in neonates, and conditions with cerebellar ataxia, dystonia, cataplexy and supranuclear gaze palsy in older children and adults. Symptomatic management of patients is crucial. A first product, miglustat, has been granted marketing authorization in Europe and several other countries for specific treatment of the neurological manifestations. The prognosis largely correlates with the age at onset of the neurological manifestations.

Disease definition

Historical delineation

Coined in the late 1920's from the pioneering work of Albert Niemann and Ludwig Pick, the eponym "Niemann-Pick disease" has since been used to designate a heterogeneous group of autosomal recessive lysosomal lipid storage disorders, with common features of hepatosplenomegaly and sphingomyelin storage in reticuloendothelial and parenchymal tissues, with or without neurological involvement. In 1958, Crocker and Farber showed that there was a wide variability in age of onset and clinical expression, as well as in the level of sphingomyelin storage in tissues [1]. This led Crocker to propose a classification into four subgroups, A to D [2]. Type A was characterized by severe, early CNS deterioration and massive visceral and cerebral sphingomyelin storage. Type B showed a chronic course with marked visceral involvement but a sparing of the nervous system. Types C and D were characterized by a sub acute nervous system involvement with a moderate and slower course and a milder visceral storage. Type D patients were individualized essentially on their homogenous Nova Scotia Acanthic origin. In 1966, Brady and associates [3] demonstrated a severe deficiency in sphingomyelinase activity in tissues from patients with type A, a finding soon extended to type B, but not to types C and D, indicating that the two latter types constituted separate entities. From that time on, with a turn following seminal observations in a Balb/c murine model of the disorder [4], the concept of Niemann-Pick type C disease evolved...
from that of a sphingomyelin storage disorder to that of a cholesterol storage disorder [5]. This and later work led to the reclassification of type C as a cellular lipid trafficking disorder, involving more specially, but not only, endocytosed cholesterol.

**Definition of Niemann-Pick disease type C**

Today, by definition, "Niemann-Pick C disease" encompasses disorders characterized by unique abnormalities of intracellular transport of endocytosed cholesterol with sequestration of unesterified cholesterol in lysosomes and late endosomes [5-12]. Major advances have been the description of two genetic complementation groups [13,14] and the subsequent isolation of the two underlying genes [15,16]. NPC1 is involved in 95% of the families [14], including those with type D [17]. NPC2 is involved in rare families (about 50 are known to date). Although the precise functions of the NPC1 and NPC2 proteins are still elusive, current knowledge supports the idea that these proteins function in a coordinate fashion and that they are involved in the cellular postlysosomal/late endosomal transport of cholesterol and other molecules [10-12,18,19].

Niemann-Pick diseases thus oppose two clearly distinct groups: acid sphingomyelinase deficiencies (due to SMPDI mutations, including types A, B and intermediate forms,) and Niemann-Pick type C, with alterations in trafficking of endocytosed cholesterol (due to NPC1 or NPC2 mutations). Type D as a distinct entity is no longer justified. From a practical standpoint, no patient should today be longer qualified of suffering from "Niemann-Pick disease" without specification of the subgroup, either acid sphingomyelinase deficiency or type C.

**Disease name and synonyms**

"Niemann-Pick disease type C" (or "Niemann-Pick C disease"), often abbreviated as NP-C (or NPC), is currently the generic name widely used to designate the condition, irrespective of which gene, NPC1 or NPC2, is mutated. This term now encompasses the historical Niemann-Pick disease type D referring to the "Nova Scotia" isolate, later shown to be a genetic NPC1 variant [17]. Instead, a subdivision is sometimes made between Niemann-Pick C1 (NP-C1) or C2 (NP-C2), according to the gene involved. Patients with a retrospective diagnosis of Niemann-Pick C disease have also been described in the 1960s and 1970s as juvenile Niemann-Pick disease, juvenile dystonic lipidosis, atypical cerebral lipidosis, neurovisceral storage disease with vertical supranuclear ophthalmoplegia, maladie de Neville, DAF (down-gaze paresis, ataxia, foam cell) syndrome, adult dystonic lipidosis, adult neurovisceral lipidosis, giant cell hepatitis, and lactosylceramidosis [10,20].

**Epidemiology**

NP-C (either NP-C1 or NP-C2) shows autosomal recessive inheritance and is panethnic. The true prevalence of NP-C is difficult to assess, because of insufficient clinical awareness combined with the relative difficulty of biochemical testing. Estimates of birth prevalence ranging between 0.66 and 0.83 per 100,000 were proposed for France, the UK and Germany based on diagnoses made in the laboratory of the author over the period 1988-2002 [10,11]. However, very different figures of 0.47, 0.35 and 2.20 per 100,000, respectively, were reported in studies from Australia (20 cases between 1980-1996), The Netherlands (25 cases between 1970-1996) and Northern Portugal (9 cases 1985-2003) [21-23]. The low incidence found for Australia and the Netherlands might be explained by a non-exhaustivity of the diagnoses in the years of birth of many patients. The wide clinical spectrum of NP-C was not recognized until the early 1990s, especially regarding rapidly fatal infantile cases, and no specific laboratory testing was available until the mid-1980s. For this review, an updated incidence of 0.82/100,000 was calculated for France, considering the total number of cases (n = 63) diagnosed for French hospitals during the 2000-2009 period vs. the number of births during the same period, a possibly more appropriate way of calculation. This value should be considered as a minimal estimate, since atypical phenotypes may not be suspected clinically or may be missed by the diagnostic laboratory. Including prenatal cases from terminated pregnancies during the same period (n = 11) increased the incidence to 0.96 per 100,000.

Most families (about 95%) belong to the NP-C1 group. Two NP-C1 isolates have been described. The first one, in French Acadians originating from Normandy and originally established in Nova Scotia, was initially described as Niemann-Pick disease type D, it is characterized by the NPC1 p.G992W mutation [1,17, and 24]. Another isolate was described in Hispanics from southern Colorado and New Mexico with their roots in the Upper Rio Grande valley of the USA, carrying the NPC1 p.11061T mutation [25,26].

**Clinical Description**

The clinical presentation of NP-C is extremely heterogeneous, with an age of onset ranging from the perinatal period until well into adult age (as late as the seventh decade of life). Similarly, the lifespan of the patients varies between a few days until over 60 years of age, although a majority of cases die between 10 and 25 years of age [10,11,27-30]. The clinical spectrum discussed below has been analyzed from several large surveys [28-35].

NP-C is classically a neurovisceral condition. Importantly, visceral involvement (of liver, spleen, and sometimes lung) and neurologic or psychiatric manifestations