in various tissues. Unesterified cholesterol, sphingomyelin, bis(monoacylglycerol)-phosphate, glyco sphingolipids and sphingosine are stored in excess in the liver and spleen, while levels of glucosylceramide, lactosylceramide and, above all, GM2 and GM3 gangliosides are markedly increased in the brain [116].

NP-C has an extremely heterogeneous clinical presentation characterized by a wide range of symptoms that are not specific to the disease, and which arise and progress over varied periods of time [113,117]. This complicates diagnosis, and is likely an important factor in the under-detection of the NP-C and, in some cases, its mis-diagnosis. In the first decade of life, the most common presentations are neurological, although early-onset patients are often diagnosed based on isolated systemic manifestations (e.g. neonatal jaundice, splenomegaly). Many cases are also diagnosed in adulthood, sometimes even up to the seventh decade of life [118].

The age at onset of neurological symptoms has a major influence on disease progression; [119] if neurological symptoms arise early in life the rate of deterioration is generally faster and premature death occurs sooner. Patients with the perinatal-onset form present during the first 3 months of life with an enlarged liver and spleen, prolonged cholestasis, hydrops fetalis and/or respiratory failure [113,114], usually without presenting neurological signs. Infantile, juvenile and adolescent/adult forms usually present with neurological signs including progressive ataxia, dystonia, dysarthria, dysphagia, deafness, cataplexy or, more rarely, epilepsy. Most notably, vertical supranuclear gaze palsy (VSGP) – particularly paroxysms of down-gaze – is a highly specific and highly prevalent sign that may be present at an early stage of the disease [113,115]. VSGP or discrete slowing of saccades is present in almost all cases at some point during the disease course.

Diagnosis of NP-C requires a skin biopsy and a fibroblast culture in a specialized center, with the resulting cultured cells stained with filipin (which binds excess cholesterol) and tested for cholesterol esterification. However, data suggest that plasma oxysterol measurements may represent a simpler screening and/or diagnostic method in the coming years [120].

Therapy for NP-C has, until recently, been limited to supportive measures, including pharmacotherapy to alleviate neurological and psychiatric symptoms [113,115,121]. Miglustat, an iminosugar compound that reversibly inhibits glucosylceramide synthetase and thus inhibits the formation of excess gangliosides, is a substrate-reduction therapy that has been shown to stabilize neurological manifestations in children and adults [122-124].

Psychiatric signs
Numerous cases of NP-C presenting with schizophrenia-like symptoms have been reported in adolescent and adult patients, and nine case series and reports were identified and included in this literature analysis [125-133]. Definitive diagnoses are commonly delayed in patients with adult psychiatric presentations of NP-C, sometimes by up to 10 years [134].

Psychotic presentations among children and adolescents with NP-C have been reported, and may be comorbid with a pervasive developmental disorder (PDD). Sandu et al. reported a case of an 8-year-old with PDD who presented with auditory hallucinations and 7 years later developed a typical paranoid schizophrenic illness that was partially responsive to risperidone [132]. One notable report described two siblings with psychosis [131]. The male sibling presented at 16 years old with visual and auditory hallucinations, and later developed dysarthria and ataxia leading to a definitive diagnosis at the age of 24 years when vertical supranuclear ophthalmoplegia was discovered. His sister developed schizophrenia-like symptoms a decade later, but diagnosis was made rapidly when she was examined for vertical supranuclear ophthalmoplegia based on the family history. Notably, her later onset and lower antipsychotic dosage required to effect symptom resolution mirrored the gender dimorphism seen in typical schizophrenia, which raises the possibility of a gender effect in presentation and progression of NP-C [131].

The onset of developmental delay is commonly seen between 6 and 15 years of age in NP-C, and may result in a learning disorder and/or impaired school performance [117,135,136]. Patients commonly display cognitive impairments involving logical thinking and abstraction, impaired attentional processes, poor working memory, word retrieval difficulties, and a lack of interpersonal ‘distance’ [121,136]. The typical cognitive profile in adult patients is one of significant executive dysfunction and impaired working memory [115,136].

Discussion
This article is the first systematic review in this field. Widely unknown and neglected by psychiatrists, IEMs represent a growing field in research that interfaces with clinical psychiatry due to the fact that a number of disorders may initially present to psychiatrists. New treatments are available for a number of these diseases [137].

One key finding of this literature review is that the clinical signs of IEMs are poorly documented in terms of both quantity (only 63 articles with original data for seven different disorders) and quality (non-systematic clinical evaluations, lack of standardized clinical scales, sparse clinical description). A second clear finding is that many cases of WD, MTHFR-D and NP-C are strongly associated with psychotic illness.

It is not realistic, and probably unnecessary due to the rarity of the association, to consider IEMs in all psychiatric
patients. It is also not feasible to train psychiatrists to become metabolic specialists. However, it is crucial for all professionals working in psychiatry to be aware of the large variety of organic disorders that may be associated with psychiatric diseases, particularly treatable IEMs such as those addressed in this review, and to be aware of clinical features that may herald an underpinning organic disorder for the patient's psychiatric presentation.

One major difficulty in considering the association of IEMs with psychosis is in ascribing causality. If prevalence rates across a number of populations are higher than 0.8–1.0% (the general population prevalence for schizophrenia) [138,139] it may be difficult to consider an association with IEMs as significant as their prevalence is more likely around 1 in 10 000. In addition, when treatment of an organic disorder leads to an improvement in psychotic symptoms, this association is strengthened, and the Bradford-Hill criteria of strength, consistency and temporality are met [140]. These associations may also aid in shedding light on the potential neurobiological origins of schizophrenia. There is a wide consensus regarding the neurodevelopmental hypothesis of schizophrenia [141,142], as well as the role of complex genetic determinism and gene–environment interactions [143]. The historical association of a range of organic disorders with schizophrenia-like psychosis has shed light on the role that the medial temporal lobe and diencephalon play in the origin of psychotic symptoms [2], and similarly the recent advancement in our understanding of the neurobiology of various IEMs has shed light on the role of anatomical disconnection and disruption to a range of neurotransmitter systems in the genesis of psychotic illness [130].

The second major difficulty is to recognize IEMs and to think about an organic etiology in clinical practice. In order to help psychiatrists, it could be clinically useful to identify psychiatric features that may trigger for the search of organic disorder in patients with schizophrenia. Unfortunately, data regarding organic psychosis and its specific associated symptoms are scarce. One study, which was not specific for IEMs, analyzed the phenomenology of 74 patients with 'organic schizophrenia' compared with 'non-organic schizophrenia' [144]. Visual hallucinations and confusion were seen more often among patients with organic schizophrenia, and comparable features have been observed in elderly schizophrenia patients [146,146]. A handful of inborn errors of metabolism may cause elementary hallucination and visual hallucinations which are associated with various organic and psychiatric conditions [147]. Hallucinations are a core symptom of schizophrenia and are more often auditory or at least, auditory hallucinations are more important than visual hallucinations. We suggest therefore that predominant visual hallucinations are highly suggestive of organic disorders such as IEM. An acute onset of psychiatric symptoms may also raise suspicion of IEMs (e.g. UCDs, porphyria or homocysteinemia with CBS-D). It is also notable that data indicate a high degree of association of catatonia with organic disorders, especially if it occurs during childhood or adolescence [148]. An unusually high proportion of patients with organic disorders has been reported in large series of patients with early-onset schizophrenia, which suggests that an early-onset of schizophrenia-like symptoms is another indicator for possible organic origin of disease, especially if associated with progressive cognitive decline, which is a common feature in IEMs [149]. Finally, treatment resistance is frequently associated with IEMs [150], again suggesting its possible use as an indicator for possible organic disease. In summary, we may suggest six readily recognizable features that should trigger the suspicion of organicity associated with schizophrenia-like symptoms: 1) acute confusion; 2) visual hallucinations more important than auditory hallucinations; 3) catatonia; 4) progressive cognitive decline; 5) early or acute onset and; 6) treatment resistance (see Table 1). As the validity and specificity of these atypical psychiatric signs have not yet been evaluated, they are presented to raise awareness and suggest clinical and neurological exams prior to further progressive screening. Both atypical psychiatric signs and main clinical/biomarker features of IEM lead us to propose an algorithm (see Figure 2). This algorithm is based on clinical practice of OB, HK and MW and DC.

Table 1 Atypical psychiatric features which should trigger a search for inborn error of metabolism in patients with schizophrenia

<table>
<thead>
<tr>
<th>First level atypical feature (atypical on their own)</th>
<th>Second level atypical features (atypical when associated with first level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>Acute onset</td>
</tr>
<tr>
<td>Visual hallucinations more important than auditory hallucinations</td>
<td>Early onset</td>
</tr>
<tr>
<td>Catatonia</td>
<td>Intellectual Disability</td>
</tr>
<tr>
<td>Progressive cognitive decline</td>
<td>Unusual or severe side effects</td>
</tr>
<tr>
<td>Treatment resistance</td>
<td></td>
</tr>
<tr>
<td>Fluctuating schizophrenia core symptoms</td>
<td></td>
</tr>
</tbody>
</table>

As the validity and specificity of these atypical psychiatric signs have not yet been validated, they are presented to raise suspicion and suggest clinical and neurological exam prior to further progressive screening.
Figure 2: Diagnostic algorithm for diagnosing inborn errors of metabolism in patients with schizophrenia-like symptoms. Negative: If exams are negative and suspicion is high. Positive: Could lead to diagnoses or high suspicion of specific disease. MRI = magnetic resonance imaging, MTHFR-Cbs = methylenetetrahydrofolate reductase-cystathionine beta-synthase; NP-C = Niemann-Pick disease type C; UCDs = urea cycle disorders; WD = Wilson disease.

Table 2: Synthesis of main clinical, contextual, ophthalmologic symptoms associated with 7 treatable IEM associated with schizophrenia-like symptoms

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical signs</th>
<th>Context</th>
<th>Eye exam</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson disease (WD)</td>
<td>Tremor</td>
<td></td>
<td>Kayser-Fleischer ring</td>
<td>Ceruloplasmin</td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dystarhia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea cycle disorders (UCDs)</td>
<td>Confusion</td>
<td>Protein diet</td>
<td>–</td>
<td>Hyperammoniemia</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Post surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea/Vomiting</td>
<td>Drugs*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocysteinemia (MTHFR)</td>
<td>Ataxia</td>
<td>–</td>
<td>–</td>
<td>Homocysteinemia</td>
</tr>
<tr>
<td></td>
<td>Mental regression</td>
<td>–</td>
<td></td>
<td>Methioninemial</td>
</tr>
<tr>
<td>Homocysteinemia (CBS)</td>
<td>Thromboembolism</td>
<td>Protein diet</td>
<td>Severe myopia</td>
<td>Homocysteinemia</td>
</tr>
<tr>
<td></td>
<td>Scoliosis</td>
<td>Post surgery</td>
<td>Ectopic lens</td>
<td>Methioninemial</td>
</tr>
<tr>
<td></td>
<td>Marfan-like cerebellar signs</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niemann-Pick disease type C (NP-C)</td>
<td>Dystonia + ataxia Dysarthria</td>
<td>Neonatal icterus</td>
<td>Supranuclear vertical gaze palsy</td>
<td>Skin biopsy, Fillipin test, NPC1 and NPC2 gene test</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
<td>Slow progression</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Cerebrotonylous xanthomatosis (CTX)</td>
<td>Chronic diarrhea</td>
<td>–</td>
<td>Juvenile cataract</td>
<td>High cholesterol</td>
</tr>
<tr>
<td></td>
<td>Spastic paraparesis</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphyria (POR)</td>
<td>Black or red urine</td>
<td>Periodic</td>
<td>–</td>
<td>Porphobilinogens (URINE)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Abdominal pain</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Nausea/Vomiting</td>
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</tr>
</tbody>
</table>

*Example drugs: valproate/corticoids.
We plan to study his validity and reliance in further study in population of patients with psychiatric signs and IEM. Further research is needed to develop a real suspicion index from our group of atypical psychiatric signs associated with this algorithm.

Biological screening is not recommended for all patients but only in case of high suspicion. It is also important to know that the cost of screening for most of these disorders in standard metabolic reference laboratories is usually modest, generally consisting of serum or urine tests for various metabolites, comparable or less than the cost of basic neuroimaging. The costs of treating these IEMs varies widely; from B-vitamin replacement and/or dietary modification in a number of disorders, to more expensive long-term treatments in disorders such as NPC, and potential high-cost hospitalizations during metabolic crises in UCDs and porphyria. This should however be referenced against the cost of treating true schizophrenia, at a cost of at least SUS7 50000 per year [151], with at least one third of this borne in direct treatment.

Toward atypical psychiatric signs, IEMs presents specificities and Table 2 provides a summary that encompasses the main clinical signs of six treatable IEMs, and highlights the main clinical symptoms, biomarkers and context as well as ophthalmologic signs, which occur in at least four of the treatable IEMs.

It is important for psychiatrists and other associated professionals to be specifically aware of potential IEMs when patients present with such indicators (organic signs and atypical psychiatric symptoms) of possible organic psychosis.

Conclusions
Based on published evidence this review highlights the role of a range of IEMs as possible underlying organic causes of schizophrenia or schizophrenia-like syndromes. It is important to identify such cases as some IEMs are treatable (sometimes simply with vitamin replacement or supplementation) and new treatments continue to appear. Clinical studies suggest that some IEM-specific treatments may be most effective during the early stages of disease when psychiatric symptoms may be evident. Efficient recognition and identification of the underlying organic disease could therefore allow earlier initiation of specific therapy and, possibly, improve outcomes.

Although the literature base from which to draw conclusions is limited, clinicians managing patients presenting with new-onset psychosis should pay particular attention to IEMs as a possible underlying cause in patients with atypical symptoms, and in the presence of specific clinical contexts. It is hoped that this review summarizing six easily assessed features that might trigger suspicion of organicity in patients with psychosis will help to detect patients with treatable IEMs as early as possible during their disease course. While not intended to replace specialized psychiatric or neurological examination and measurements, our proposed algorithm (Figure 2) is a pragmatic tool that can be used to reduce the risk of mistaken diagnoses among patients with atypical psychiatric signs and treatable IEMs.

Competing interest
OB, WM, FS and HK declare past and present honorarium from Actelion Pharma. DC and ST have no competing interest.

Authors' contribution
OB wrote the first draft of the article which was reviewed by all authors.
ST, DC, WM and HK helped OB for response to reviewers. Regarding specific systematic review work, two groups worked separately in screening abstracts from relevant articles from the literature review (Group 1: WM and HK; Group 2: OB, DC, ST and FS). All authors read and approved the final manuscript.

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Niemann-Pick disease type C symptomatology: an expert-based clinical description

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Abstract
Niemann-Pick disease type C (NP-C) is a rare, progressive, irreversible disease leading to disabling neurological manifestations and premature death. The estimated disease incidence is 1:120,000 live births, but this likely represents an underestimate, as the disease may be under-diagnosed due to its highly heterogeneous presentation. NP-C is characterised by visceral, neurological and psychiatric manifestations that are not specific to the disease and that can be found in other conditions. The aim of this review is to provide non-specialists with an expert-based, detailed description of NP-C signs and symptoms, including how they present in patients and how they can be assessed. Early disease detection should rely on seeking a combination of signs and symptoms, rather than isolated findings. Examples of combinations which are strongly suggestive of NP-C include: splenomegaly and vertical supranuclear gaze palsy (VSGB); splenomegaly and clumsiness; splenomegaly and schizophrenia-like psychosis; psychotic symptoms and cognitive decline; and ataxia with dystonia, dysarthria/dysphagia and cognitive decline. VSGB is a hallmark of NP-C and becomes highly specific of the disease when it occurs in combination with other manifestations (e.g. splenomegaly, ataxia). In young infants (<2 years), abnormal saccades may first manifest as slowing and shortening of upward saccades, long before gaze palsy onset. While visceral manifestations tend to predominate during the perinatal and infantile period (2 months–6 years of age), neurological and psychiatric involvement is more prominent during the juvenile/adult period (>6 years of age). Psychosis in NP-C is atypical and variably responsive to treatment. Progressive cognitive decline, which always occurs in patients with NP-C, manifests as memory and executive impairment in juvenile/adult patients. Disease prognosis mainly correlates with the age at onset of the neurological signs, with early-onset forms progressing faster. Therefore, a detailed and descriptive picture of NP-C signs and symptoms may help improve disease detection and early diagnosis, so that therapy with miglustat (Zavesca®), the only available treatment approved to date, can be started as soon as neurological symptoms appear, in order to slow disease progression.

Keywords: Niemann-Pick disease type C, Lysosomal lipid storage disease, Splenomegaly, Ataxia, Dystonia, Vertical supranuclear gaze palsy, Gelastic cataplexy, Cognitive impairment, Diagnosis

Introduction
Niemann-Pick disease type C (NP-C) is a rare, progressive genetic lysosomal lipid storage disease caused by mutations in the NPC1 or NPC2 gene [1,2]. It is a highly heterogeneous disease, characterised by visceral, neurological and psychiatric manifestations that can present alone, or in specific or non-specific combinations. Moreover, age at onset and disease course vary greatly from one patient to another, including among siblings [1,2]. Patients often first present to general practitioners; due to its challenging presentation, especially for non-specialists, the disease often remains undetected for many years, with an average delay in diagnosis of 5–6 years from onset of neurological symptoms [3–6]). Early diagnosis is essential so that therapy with miglustat (Zavesca®), Actelion Pharmaceuticals Ltd, Allschwil, Switzerland), the only available disease-specific therapy approved for NP-C [7], can be initiated as soon as neurological
symptoms appear in order to slow the progression of neurological damage.

Individual NP-C manifestations are not specific to the disease, but the combination of multiple signs and symptoms shows more diagnostic specificity for NP-C, which may aid with disease detection. Therefore, understanding how and in which combination these manifestations present will help physicians identify possible suspected cases of NP-C.

This review provides an expert-based descriptive clinical picture of NP-C that goes beyond the scope of currently available information to practising clinicians, and includes details on specific signs and symptoms and how they present in individuals with NP-C. This qualitative description of NP-C signs and symptoms is not limited to published clinical study data, but also reflects experts' opinion drawn from clinical practice and personal experience. It aims to increase disease awareness among physicians in order to improve early diagnosis and timely referral to specialists of patients with suspected disease.

Disease description, epidemiology and aetiology

NP-C is a genetic, progressive, irreversible and chronically debilitating neurovisceral lysosomal lipid storage disease leading to premature death [1,2]. NP-C is generally panethnic, although some mutations may occur with higher incidence in defined ethnic groups [8,9]. The minimal estimated incidence of the disease is one case in every 120,000 live births [2], although this value is likely to represent an underestimation due to failure to reliably recognise the disease (see below).

NP-C is a genetic autosomal recessive disease caused by mutations in the genes NPC1 (~95% of cases), NPC2 (~4% of cases) and possibly other as yet unidentified genes (~1% of cases) [1,10,11]. As of November 2012, 252 gene sequence variants have been listed for NPC1 and 18 for NPC2, with a majority of point mutations [12]. Mutations in either gene lead to the same cellular deficits, including impaired cholesterol esterification [13] and intracellular lipid trafficking [14]. This results in intracellular accumulation of different lipids and altered sphingolipid metabolism leading to the pathophysiology of the disease. Putative functions of NPC1 and NPC2 and their role in the pathophysiology of NP-C have been described more comprehensively elsewhere [2,14,15]. Depending on whether the NPC1 or NPC2 gene carries mutations, the disease is sometimes referred to as NPC-1 or NPC-2, respectively. For certain gene mutations, there appears to be a correlation between genotype and the severity of the neurological course of the disease [16]. For a comprehensive definition of the disease, including its historical delineation, we refer the reader to a recent review [2].

Clinical description and differential diagnosis

NP-C is a complex disease that first of all affects the spleen, liver and brain, resulting in visceral abnormalities as well as neurological and psychiatric manifestations (Table 1). The combined presentation of visceral, neurological and psychiatric manifestations should therefore lead to the consideration of NP-C in the differential diagnosis of this symptomatology. Examples of combinations which are strongly suggestive of NP-C include: splenomegaly and vertical supranuclear gaze palsy (VSGP); splenomegaly and clumsiness; splenomegaly and schizophrenia-like psychosis; psychotic symptoms and cognitive decline; and ataxia with dystonia, dysarthria/dysphagia and cognitive decline [17] (Table 2).

The combination of cerebellar ataxia and dystonia of the hands and the face is one motor hallmark of NP-C. However, a combination of cerebellar ataxia and dystonia can also be found in other diseases, including mitochondrial disorders such as Leigh syndrome, GM2 gangliosidosis, ataxia with oculomotor apraxia type I, Gaucher disease type 3 (GID3), and spinocerebellar ataxia.

Table 1 Classification of signs and symptoms in NP-C

<table>
<thead>
<tr>
<th>Visceral</th>
<th>Neurological</th>
<th>Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated unexplained splenomegaly</td>
<td>Vertical supranuclear gaze palsy</td>
<td>Developmental delay and pre-senile cognitive decline</td>
</tr>
<tr>
<td>Hepatomegaly/Splenomegaly</td>
<td>Gelastic encephalopathy</td>
<td>Organic psychosis</td>
</tr>
<tr>
<td>Prolonged neonatal cholestatic jaundice</td>
<td>Ataxia</td>
<td>Disruptive/aggressive behaviour</td>
</tr>
<tr>
<td>Hydrops foetalis or foetal ascites</td>
<td>Dystonia</td>
<td>Progressive development of</td>
</tr>
<tr>
<td>Pneumopathologies (aspiration pneumonia,</td>
<td>Dysarthria</td>
<td>treatment-resistant psychiatric</td>
</tr>
<tr>
<td>alveolar lipoidosis, interstitial lung</td>
<td>Dysphagia</td>
<td>symptoms</td>
</tr>
<tr>
<td>involvement)</td>
<td>Hypotonia</td>
<td></td>
</tr>
<tr>
<td>Mild thrombocytopenia</td>
<td>Clumsiness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delayed developmental milestones</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hearing loss</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NP-C, Niemann-Pick disease type C.
Table 2: Signs and symptom combinations strongly suggestive of NP-C

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>NP-C Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical supranuclear gaze palsy</td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia-like psychosis</td>
<td></td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td></td>
</tr>
<tr>
<td>Dysarthria/dysphagia</td>
<td></td>
</tr>
<tr>
<td>Cognitive decline</td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
</tr>
<tr>
<td>Delayed developmental milestones</td>
<td></td>
</tr>
</tbody>
</table>

The combination of one or more of the symptoms on the left with at least one of those on the right is strongly suggestive of NP-C.

Abbreviation: NP-C, Niemann-Pick disease type C.

Therefore, even if this combination is highly suggestive of NP-C, it does not necessarily confirm a diagnosis of NP-C. NP-C presentations are often categorized based on the age at onset of the neurological symptoms: early infantile (2 months–2 years of age), late infantile (2–6 years of age), juvenile (6–12 years of age), adolescent/adult (>12 years of age). The perinatal form (up to the age of 2 months) is characterized by systemic symptoms only [1,2].

Visceral symptoms in NP-C

Isolated unexplained splenomegaly or without hepatomegaly

Historical or current isolated unexplained splenomegaly, with or without hepatomegaly, is observed in the majority of patients with NP-C [1] and is the strongest visceral indicator of the disease [18]. When present in combination with other neurological and/or psychiatric symptoms, including VS suggestive of NP-C type A and B [1]. Isolated unexplained splenomegaly should always lead to the inclusion of NP-C in the differential diagnosis, and hence trigger a search for other symptoms of the disease. Splenomegaly in NP-C presents along a continuum, ranging from slight to tremendous enlargement, even in young children. Importantly, the degree of splenomegaly does not correlate with neurological manifestations, disease severity or illness stage. Absence of splenomegaly should not lead to the exclusion of NP-C.

In young patients, splenomegaly can be assessed by turning the patient on the right side in order to have the spleen falling downwards. In this position, the spleen should not be palpable under normal conditions. A palpable spleen indicates that its size is increased by at least two-fold. In adolescent and adult patients, mild splenomegaly may only be detected by abdominal imaging such as ultrasound [1,3].

Unlike splenomegaly, hepatomegaly is less frequently observed in adult patients with NP-C [1,3]. Hepatomegaly presentation in NP-C is non-specific; it generally appears at the same age as splenomegaly, or in some cases may present without it, which is often attributed to a failure to clinically detect splenomegaly in the absence of an abdominal ultrasound. Hepatomegaly can be detected by palpation of the patient lying in a supine position, starting from the right flank and slowly moving upwards. A palpable lower edge of the liver indicates hepatomegaly. Upward palpation should also be started from the left flank, as occasionally only the left lobe of the liver is enlarged, crossing over the midline. While up to a two-fold increase in spleen size can remain palpable, liver enlargement as small as 1 cm can be readily felt. Notably, the degree of hepatomegaly and splenomegaly are not related, and unlike splenomegaly [2], hepatomegaly does not appear to resolve spontaneously.

Isolated spleno- or hepatosplenomegaly also occur in some other inherited metabolic diseases, such as mucopolysaccharidoses, glycogen storage disorders, Sandhoff disease, GD3, lysosomal acid lipase deficiency and Niemann-Pick disease type A and B [1].

Prolonged or unexplained neonatal cholestatic jaundice

Signs of perinatal liver involvement range from transient conjugated hyperbilirubinaemia to severe cholestatic hepatopathy leading to liver failure and death in the first year of life.

A history of prolonged or unexplained neonatal cholestatic jaundice is a strong visceral indicator of NP-C [18]. Generally defined as prolonged conjugated hyperbilirubinaemia that occurs in newborns, it is frequently observed in patients with early- and late-infantile disease onset [19-22]. In NP-C, jaundice always has a cholestatic origin and is defined by a conjugated bilirubin level >1.2 mg/dL and/or >50% of total bilirubin for a period of over 2 weeks [1].

Conjugated bilirubin levels and speed of symptom resolution are non-specific in NP-C. Acholic stools can be a characteristic of NP-C-related cholestatic jaundice. Since this condition does not require phototherapy (unlike unconjugated jaundice), its symptoms may often not be recalled by parents and hence may be missed when obtaining medical history.

Cholestasis should always lead to the consideration of NP-C in the differential diagnosis of neonatal jaundice. In neonates and young infants, NP-C should be differentiated from other causes of cholestatic jaundice, e.g. idiopathic neonatal hepatitis or biliary atresia [1]. The occurrence of isolated spleno- or hepatosplenomegaly is a helpful indicator and should raise suspicion of NP-C [18].

Hydrops foetalis or sibling with foetal ascites

The presence of perinatal hydrops foetalis or a sibling with foetal ascites occurs frequently in newborns with lysosomal storage diseases [23,24]. However, they are
considered ancillary indicators of NP-C as they are less frequent in patients with this disease [18,20,25]. In NP-C, hydrops foetalis has a non-immune origin and always presents with ascites, never as a classical hydrops foetalis. It is usually detected upon antenatal foetal ultrasonography scanning and presents as global swelling, with some fluid accumulating in the abdominal cavity or around the heart. Hydrops foetalis may be missed during the medical and family history, because the information is often held with obstetricians rather than paediatricians. Differential diagnosis for hydrops foetalis include chromosomal disorders, congenital heart malformations, infectious diseases and haemoglobin disorders.

Other symptomatology
Lung disease can occur in both NP-C1 and NP-C2 disease, and is usually associated with more severe types of the disease. In NP-C2, the clinical picture can be similar to that of chronic lung disease of the newborn in the absence of an evidence to support it. Helical computed tomography imaging of the chest may occasionally show classical interstitial lung disease. These features have been poorly described in the literature [26-28] but are often anecdotally reported by experts. There is no specific therapy for the pulmonary manifestations, although bone marrow transplantation may offer some resolution in NP-C2 [29].

Mild thrombocytopenia in newborns or toddlers with NP-C has been anecdotally reported, with limited evidence (II and C+H, personal communication). This finding is non-specific, as platelet abnormalities are common in cases of splenomegaly and have been described in other lysosomal storage diseases. Bone marrow infiltration with foam cells may cause platelet abnormalities in newborns, although this remains to be confirmed. Foamy cells can be detected by bone marrow aspiration. Usually, patients with classical foamy cells are the most severely affected and present with large splenomegaly, low platelet counts, bone infiltrates, and a most widespread presentation. It should be noted, however, that patients may rarely present with classical foamy cells and splenomegaly from an early age, yet remain asymptomatic for the neurological manifestations of the disease.

Neurological symptoms in NP-C
Vertical supranuclear gaze palsy
VSGP is characterised by impaired saccadic movements of the eyes in the vertical direction as a result of a supranuclear lesion [30]. Patients with VSGP exhibit a deficit in voluntary and reflexive vertical saccades, as well as in vestibulo-ocular nystagmus. Along with gelastic cataplexy, VSGP is the strongest neurological indicator of NP-C [18], and becomes highly predictive of NP-C when found in combination with other manifestations, such as splenomegaly, ataxia or psychosis. During later stages of the disease, horizontal saccades are also affected, reflecting progressive degeneration of neurons within the paramedian pontine reticular formation, which controls horizontal saccades [30-32]. Neuronal loss in the rostral interstitial nuclei of the medial longitudinal fasciculus results in a palsy of voluntary and reflexive vertical saccades, as well as of the quick phases of vertical nystagmus [1,30]. Importantly, the vestibulo-ocular reflex, which depends on the vestibular nuclei under the control of cerebellar projections, is often preserved until very late in the disease progression [1,3,32,33]. Slow and hypometric vertical saccades followed by compensating head movement may be the first sign in children and infants long before gaze palsy develops, and may start in infants below the age of 2 years. Children may fall as they become unable to adjust their vision for stairs or other obstacles. In cases where children are clumsy and fall often, but have not been diagnosed with VSGP, the initiation, velocity and amplitude of upward saccades should be assessed. Typically, children close their eyes when trying to look up and re-open them once they have reached their upward position; alternatively, they may blink when asked to look up. These are features that a physician should pay attention to when conducting a clinical examination. In older children, adolescents and adults, downward gaze appears to be affected first [3,30]; it can manifest as a tilt of the head for everyday tasks such as writing, driving, or using a cash machine, or as a difficulty when descending stairs [3].

During the neurological examination, it is important to assess voluntary vertical saccades, and not only eye pursuit movements (Figure 1) [30]. The examiner should require the subject to visually fixate on two separate objects, e.g. the examiner’s finger and a hatpin, which are displaced first horizontally and then vertically, but always within the subject’s visual field. The subject is then asked to look at each object alternately.

VSGP can be misdiagnosed as vertical ocular motor apraxia (OMA), both of which involve impaired vertical saccades. The two can be differentiated by assessing reflexive saccades, which are abnormal in VSGP but more prominently generated in OMA [30]. In addition, VSGP involves reduced saccadic velocity and range, whereas vertical OMA is typically characterised by a deficit in the initiation of voluntary vertical saccades, with normal vertical quick phases of nystagmus [30]. Reflexive saccades can be assessed by asking the patient to look at the examiner’s wiggling finger, which suddenly moves above or below the straight ahead position of the patient [30].

In children, OMA usually occurs in the horizontal plane; therefore, abnormal initiation and speed of vertical saccades makes OMA less likely and favours a VSGP diagnosis.
Other diseases and conditions associated with VSGP include, for example, progressive supranuclear palsy or other tauopathies, multiple system atrophy, dementia with Lewy bodies, spinocerebellar ataxia, Tay-Sachs disease, Wilson disease, vitamin B12 deficiency, Wernicke encephalopathy, Huntington’s disease and Creutzfeldt–Jakob disease [30]. As opposed to these disorders, VSGP development has an earlier onset in NP-C.

**Ataxia**

Ataxia, which is associated with early loss of Purkinje cells in the cerebellum [34,35], is a moderate indicator of NP-C [18]. In combination with dystonic manifestations of the hands and the face it becomes highly suggestive of NP-C.

In NP-C, ataxia presents as ‘slow’ ataxia, manifesting itself in quite slow movements, compared with other ataxic patients. Gait may appear normal in the early stages of the disease. Children with a mild form of NP-C may appear to be slow, for example, walking instead of running, or cautiously taking objects instead of rapidly grabbing them. Ataxia generally appears after dystonia, with the delay between the two symptoms dependent on disease progression, however, in a proportion of infantile and juvenile-onset cases, ataxia may present before dystonia is apparent. In cases where ataxia is the only presenting neurological symptom, it may be useful to wait and watch for additional signs before suspecting NP-C, as ataxia can have multiple aetiologies.

Clinical assessment of ataxia includes provocative tests, such as tandem gait, rapidly alternating movements, finger-to-nose or heel-to-shin tests. Patients with NP-C may be able to adequately perform these tests, but will exhibit slower movements to compensate for their ataxia. Ataxia can be further assessed based on standard scales, such as the International Cooperative Ataxia Rating Scale [36] and the Brief Ataxia Rating Scale [37], which may be more useful in the office setting.

NP-C is part of the expanding group of hereditary autosomal recessive cerebellar ataxias (ARCA) [38]. However, the following aspects may help distinguish NP-C from other ARCA: absence of retinal/macular degeneration; lack of peripheral neuropathy in adult patients; marked cerebellar atrophy is usually only observed in advanced stages of the disease; and the presence of VSGP, an almost constant feature which, in combination with splenomegaly, virtually defines the clinical diagnosis of NP-C.

**Gelastic cataplexy**

Gelastic cataplexy, characterised by episodes of sudden loss of muscle tone that can cause the patient to collapse or fall, is one of the strongest neurological indicators of NP-C [18]. Although relatively rare, it is a strong predictor of NP-C when it occurs in combination with other manifestations, such as VSGP. Gelastic cataplexy is not associated with loss of consciousness, abnormal vigilance or altered awareness. In NP-C, gelastic cataplexy presents along a continuum, from rubbery feeling in the legs and minor head-drops to full collapse of the entire body [1], and can appear as early as 2 years of age.
A history of drop attacks or loss of posture associated with emotional stimuli (e.g. laughing or crying) should raise the suspicion for gelastic cataplexy. This sign may be missed in children, as falls due to cataplexy may be often misinterpreted as secondary to cerebellar ataxia [1,39]. Gelastic cataplexy, characterised by a normal electroencephalogram (EEG), must be differentiated from gelastic seizures, which exhibit clinical features of epilepsy and usually abnormal EEG. As gelastic cataplexy can be part of the narcoleptic tetrad, which includes cataplexy, narcolepsy, sleep paralysis and hypnagogic hallucinations, it is important to exclude narcolepsy, which is not observed in patients with NP-C.

**Dystonia**

Dystonia is a neurological movement disorder characterised by excessive involuntary muscle contraction as a result of pathology in the basal ganglia and, to a lesser extent, the cerebellum [35,40]. This symptom is very common and, if present in patients with NP-C, occurs more frequently in the adolescent/adult onset form than in the juvenile form [2,39] and is a moderate indicator of the disease [18].

In NP-C, dystonia rarely presents in isolation but usually with ataxia, a combination highly specific for NP-C [17]. Occasionally, dystonia may present in isolation of ataxia, which can lead to misdiagnosis as genetic forms of primary dystonia, for example DYT1 and DYT6. In NP-C, dystonia affects the extremities and the face. During later stages of the disease, dystonia may also involve the neck and trunk, and as illness progresses it can also affect gait [41]. Typical dystonic features in NP-C include focal hand dystonia with wrist flexion, a forced (subtle) smile when speaking, resulting from dystonia of the jaw musculature and wrinkles on the forehead. Dystonia tends to worsen during intercurrent illnesses. Differential diagnosis of dystonia in inborn errors of metabolism include respiratory chain disorders, pyruvate dehydrogenase deficiency, glucose transporter 1 deficiency, vitamin E deficiency, organic acidemia, urea cycle disorders, homocystinuria and Wilson disease. Genetic forms of primary dystonia, such as DYT1 and DYT6, are not strictly neurodegenerative.

**Dysarthria/dysphagia**

Dysarthria results in slurred and irregular speech with impaired pronunciation, due to a lack of coordination of the motor-speech system [42]. It results from a combination of ataxia and dystonia and involves pathologies in the cerebellum and basal ganglia. Dysarthria is a moderate indicator of NP-C [18] which, in combination with other symptoms, increases the diagnostic likelihood of NP-C.

Dysphagia, or difficulty in swallowing, is associated with dysfunction not only in the brainstem (affecting motor and sensory functions of swallowing), but also in cortical areas in the frontal lobe (responsible for swallowing initiation as well as management and retention of safe swallowing strategies) [43,44]. This common symptom of NP-C may appear early or later in the disease course [1]. It is a moderate indicator of NP-C and its combination with other symptoms is specific to the disease [18]. Dysphagia represents a major problem as it correlates with aspiration pneumonia, one of the most common causes of death of NP-C [45,46]. Swallowing function can be assessed by standardised swallowing assessments of different substances, and via investigations such as video fluoroscopy and fiberoptic endoscopic evaluation of swallowing [47–49].

**Hypotonia**

Hypotonia, the first neurological signs of NP-C appearing in the second year of life, is a non-specific indicator of the disease, but early onset of hypotonia around or before the first birthday is associated with the more progressive infantile type of NP-C [18]. In toddlers, clumsiness results from a combination of hypotonia, beginning of ataxia and abnormal eye movements, which lead to stumbling over obstacles. In school children clumsiness is usually related to ataxia and may manifest as the deterioration of handwriting. This deterioration is related to the onset of dysmetria, a lack of movement coordination that can be detected using the Archimedes spiral test.

**Delayed developmental milestones**

Delays in the developmental milestones are an ancillary indicator of NP-C [18]. These include motor delays (e.g. slow movements while walking and transferring objects, clumsiness, poor head control), speech delay, vision/ocular-motor developmental delay, and social delay (e.g. interactive play). When associated with other manifestations such as isolated splenomegaly without hepatomegaly and VSGP, this sign becomes specific to NP-C. Virtually all children with NP-C exhibiting developmental delays have a history of splenomegaly. In practice, the range and extent of developmental delay can vary widely between patients, but can be very useful for early diagnosis in infant and juvenile patients. The majority of infants will typically fail to reach some, or all, of the following developmental milestones, in the following chronological order: delays in picking up and transferring small objects, lack of visual attention, delayed walking, frequent falls and a tendency to stand/hold onto parents/solid objects to aid balance. A common feature in juveniles is a delay in language, until 3–4 years old. However, this sign is not specific to NP-C as speech delay may have many causes, and other signs and symptoms should therefore be checked.

**Seizures**

Seizures are not specific to NP-C and are considered an ancillary indicator of the disease [18]. In NP-C, seizures can
be partial/focal, or generalised, myclonic or tonic-clonic, and can vary substantially in frequency and intensity [1]. In the differential diagnosis process, it is important to exclude other disease involving seizures, e.g. myclonic epilepsy or mitochondrial disease.

Hearing loss
High frequency sensorineural hearing loss has been reported in NP-C and can be light or severe [2,5]. It affects about 20% of the patients and appears to be more frequent in adults. Hearing ability can be tested by audiograms or auditory brainstem responses.

It is believed that cholesterol, whose trafficking is impaired in NP-C, plays a key role in auditory physiology [50,51]. Animal studies have shown that the cholesterol-chelating agent 2-hydroxypropyl-β-cyclodextrin, a promising experimental therapy for NP-C, may have deleterious effects on hearing impairment [52,53], emphasising the need for auditory testing in patients receiving this treatment.

Psychiatric symptoms in NP-C
Cognitive decline
Progressive cognitive decline affects all patients with NP-C and is a strong indicator of the disease [18]. In combination with VSGP, cognitive decline is strongly suggestive of NP-C.

In adult forms of NP-C, the typical profile is characterised by initial deficits in executive functioning, followed by memory impairment and cognitive slowing. In adult patients initial changes may be subtle. Executive impairment includes very early disinhibition, perseveration (i.e. inflexibility in thinking and inability to shift set), poor judgement, lack of insight, impaired ability for abstraction, attentional deficits, and cognitive slowing. Disinhibition is often the earliest sign, detected neuropsychologically by tools such as the Stroop colour-word test [28]. However, memory impairment can also manifest as an early feature.

Cognitive impairment in children manifests as a delay in normal cognitive development, or mental retardation. It is common that children reach a certain stage of development, stop progressing, and start showing cognitive decline associated with functional loss. Attention-deficit hyperactivity disorder may be present in childhood as a precursor to adolescent or adult development of NP-C.

Memory deficits, including impaired formation of new memories and disorientation, reflect hippocampal abnormalities [54,55]. Cognitive slowing may be due to changes in white matter causing disconnection of frontal-subcortical circuitry [56]. In addition, direct striatal pathology causes cognitive slowing through disruption of frontostriatal loops [57].

Cognitive impairment is commonly screened for by performing a Mini-Mental State Evaluation [58]. Although not sensitive in early stages of NP-C, it is useful for assessing cognitive function in patients with moderately severe NP-C in more advanced stages. Other traditional neuropsychological tests for global cognition and memory include the Wechsler Adult Intelligence Scale (WAIS) [59] and the Wechsler Memory Scale (WMS). Tests for executive dysfunction include the trail-making test and the Controlled Oral Word Association test [60]. Moreover, memory deficits can be assessed, for example, by the Rey Auditory Verbal Learning Test (RAVTL) [61].

In children, cognitive impairment may be monitored using the Bayley Scales for Infant Development [62], Vineland Adaptive Behaviour Scales [63], the Wechsler Intelligence Scale for Children [64], the Denver Developmental Screening Test [65] and the Griffiths Mental Development Scale [66].

NP-C should be differentiated from Alzheimer's disease (AD), also characterised by cognitive decline and short-term memory loss. Cognitive impairment in NP-C is characterised by a more pronounced prefrontal involvement, as opposed to the more generalised dementia and different degree of cognitive slowing observed in patients with AD. As a result, patients with NP-C mostly exhibit deficits in executive function and disinhibition. Whilst executive deficits in adult patients in NP-C are similar to those observed in patients with frontotemporal dementia [67], the presence of VSGP and motor signs such as ataxia and dystonia allows readily differentiating the two diseases.

Psychosis
Psychosis is characterised by hallucinations, delusions and/or thought disorder and is a moderate indicator of NP-C [18]. In NP-C, psychotic symptoms typically present in adolescence or early adulthood, may be treatment resistant and sensitive to neuroleptic side effects (particularly dystonia), and may be associated with secondary signs (visual hallucinations, catatonia and fluctuating symptoms) [68].

Disruptive or aggressive behaviour in adolescence and childhood
Disruptive or aggressive behaviour in adolescence and childhood is an ancillary indicator of NP-C [18]. In pubescent patients, it may present in addition to cognitive impairment and behavioural disinhibition.

Diagnosis and diagnostic methods
As described earlier, NP-C presents in a highly heterogeneous manner, sometimes with atypical phenotypes, which makes the disease difficult to detect.

An NP-C Suspicion Index (SI) tool was recently developed to aid clinicians identify patients with suspicion of
NP-C, for whom other common diseases have been ruled out [18]. This highly specific, sensitive, easy-to-use and reliable tool provides information about symptomatology and presentation patterns in NP-C [18].

The diagnostic process includes recording a full medical history and a comprehensive clinical and neurological examination to detect characteristic signs and symptoms, followed by a differential diagnostic procedure to exclude other possible causes and, finally, confirmation of NP-C diagnosis by biochemical (filipin staining) and genetic testing [1,69-71]. As part of genetic counselling, heterozygous carriers should always undergo genetic testing in order to reliably determine their genetic status, which is useful for family planning implications [1]. Oxysterols (cholesterol oxidation products) have recently been shown to be significantly elevated in the plasma of patients with NP-C1 [72,73], thus bearing the potential for being used as biomarkers for NP-C. Measurement of plasma oxysterol levels is recommended as a supplementary test for cases with unclear NP-C genetic mutations and biochemical phenotypes [1].

**Disease management and treatment**

Detailed guidelines have been recently published on disease management including treatment [1]. In the absence of a curative treatment, improving or maintaining patients’ quality of life and their neurological and mental functions is considered the best possible reasonable goal. Optimal disease management should rely on a multidisciplinary treatment approach, combining symptomatic treatment, close community support and disease-specific therapy. To date, miglustat is the only disease-specific approved therapy for the treatment of progressive neurological manifestations in paediatric and adult patients with NP-C [7]. Miglustat has been shown to improve or stabilise key parameters of neurological disease progression in children, and in juvenile and adult patients, both in clinical trials and in clinical practice settings [47,49,74-79].

In order to stabilise or slow the progression of irreversible neurological damage, disease-specific therapy with miglustat should be initiated at the earliest signs of neurological manifestations [1].

**Prognosis**

NP-C is a progressive, irreversible and chronically debilitating disease leading to premature death, usually between the ages of 10 and 25 years according to previous studies [70]. However, this figure may no longer be valid as more late-onset patients are now diagnosed in adulthood. Prognosis largely correlates with age at onset of neurological signs, whereby early-onset forms progress faster [1,2].

Dysphagia has been identified as a major risk factor for mortality in patients with NP-C [46]. In fact, impaired swallowing is associated with aspiration pneumonia, the most common cause of death in neurodegenerative disease including NP-C [45,46,80]. Improving swallowing function may therefore help increase patients’ life expectancy.

**Unresolved questions and future perspectives**

Despite increasing research in the field, open questions remain regarding the exact function of NPC1 and NPC2 proteins, as well as the precise role of sphingosine and other lipids in the pathogenesis of NP-C [14]. As such, further investigations are required to elucidate the biochemical and cellular mechanisms leading to the disease, in order to design new targeted therapies. Moreover, this may help understand the connection between a traffic lipid disorder and the various neurological phenotypes observed in patients.

The lack of a single, definitive diagnostic test for all populations means that NP-C remains largely under- or misdiagnosed. Currently available screening and diagnostic techniques are not straightforward and may contribute to delays in diagnosis. The advent of faster and cheaper genetic tests such as Next-Generation Sequencing, as well as the potential use of plasma oxysterols as biomarkers of NP-C [1,72,73], will likely have a great impact on future screening and diagnostic strategies for NP-C and other rare diseases. Establishment of a test to implement oxysterols for their potential use as screening and diagnostic biomarkers is currently under development. Furthermore, preliminary data indicate that levels of certain oxysterol species correlate with disease severity in patients with NP-C1 [73]. However, further data are required to determine whether oxysterols may be used as biomarkers for monitoring disease progression.

Walterfang et al. have recently shown that patients with NP-C exhibit alterations in brain morphology [35,81-83]. Preliminary data suggest that miglustat can maintain brain volume in treated patients compared with untreated control subjects. However, further evidence is required to establish whether miglustat has an effect on brain morphology and whether magnetic resonance imaging measures can be used to monitor disease progression (Walterfang, unpublished data).

**Conclusions**

Detection of NP-C remains challenging, due to the highly heterogeneous presentation of the disease, with manifestations occurring along a continuum. While individual signs and symptoms may not be specific to NP-C, their specific combinations can be an important indication of the disease [18]. Therefore, single findings are often insufficient and further investigations to identify any other symptom should always be performed when a diagnosis is lacking.

Correct assessment of different symptoms is crucial to identifying the disease. A combination of splenomegaly, VSGP and cognitive impairment, together with other,


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Dysphagia as a risk factor for mortality in Niemann-Pick disease type C: systematic literature review and evidence from studies with miglustat

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Abstract
Niemann-Pick disease type C (NP-C) is a rare neurovisceral disease characterised by progressive neurological deterioration and premature death, and has an estimated birth incidence of 1:120,000. Mutations in the NPC1 gene (in 95% of cases) and the NPC2 gene (in approximately 4% of cases) give rise to impaired intracellular lipid metabolism in a number of tissues, including the brain. Typical neurological manifestations include vertical supranuclear gaze palsy, saccadic eye movement abnormalities, cerebellar ataxia, dystonia, dysmetria, dysphagia and dysarthria. Oropharyngeal dysphagia can be particularly problematic as it can often lead to food or fluid aspiration and subsequent pneumonia. Epidemiological data suggest that bronchopneumonia subsequent to food or fluid aspiration is a major cause of mortality in NP-C and other neurodegenerative disorders. These findings indicate that a therapy capable of improving or stabilising swallowing function might reduce the risk of aspiration pneumonia, and could have a positive impact on patient survival. Miglustat, currently the only approved disease-specific therapy for NP-C in children and adults, has been shown to stabilise key neurological manifestations in NP-C, including dysphagia. In this article we present findings from a systematic literature review of published data on bronchopneumonia/aspiration pneumonia as a cause of death, and on the occurrence of dysphagia in NP-C and other neurodegenerative diseases. We then examine the potential links between dysphagia, aspiration, pneumonia and mortality with a view to assessing the possible effect of miglustat on patient lifespan.

Keywords: Niemann-Pick disease type C, Dysphagia, Mortality, Swallowing, Pneumonia, Aspiration, Miglustat.

Introduction
Niemann-Pick disease type C (NP-C) is a rare neurovisceral disease characterised by progressive neurological deterioration and premature death, and has an estimated birth incidence of 1:120,000 [1,2]. It is caused by the autosomal recessive inheritance of mutations in either of the two genes, NPC1 (in approximately 95% of cases) or NPC2 (in approximately 4% of cases) [3-5]. Mutations in either of these genes result in impaired metabolism of endocyted cholesterol and intracellular accumulation of a number of lipid moieties in various tissues, particularly in the brain [1,6].

Patients with NP-C usually present with one or more neurological signs during childhood [1], although an increasing number of patients with adult onset of neurological manifestations are being diagnosed based on late-onset neurological signs and psychiatric manifestations [7-9]. The age at onset of neurological manifestations has a major influence on the rate of disease progression and prognosis. In general, patients with neurological onset early in life deteriorate faster and have a shorter life expectancy than those with adult onset [10-14].

The clinical presentation of NP-C is extremely heterogeneous. Systemic symptoms such as neonatal jaundice and hepatosplenomegaly usually occur early in the course of the disease [1,15]. Typical neurological manifestations include vertical supranuclear gaze palsy (VSGP), saccadic eye movement (SEM) abnormalities, cerebellar ataxia, dystonia, dysmetria, dysarthria and dysphagia [1]. These neurological signs arise at different ages, but invariably progress over time [10,16].
Dysphagia occurs in most NP-C patients at some point in the disease course, ranging in severity from occasional swallowing difficulties to loss of swallowing function necessitating placement of a nasogastric tube or gastrostomy feeding [10]. Dysphagia of neurological origin arises primarily from impairment in the oral and pharyngeal phases as opposed to the later oesophageal phases of swallowing, and as such is defined as oropharyngeal dysphagia [17]. Oropharyngeal dysphagia disrupts feeding but, more significantly, it increases the risk of aspiration. In NP-C, it is contributed to by bulbar motor dysfunction, dystonia, and reduced sensation. Patients with more severe neurological involvement generally have more severe dysphagia, and worsening neurological involvement correlates with a higher risk of aspirating food or fluid [18]. It is therefore recommended that patients with impaired swallowing function be closely monitored to avoid serious lung infections secondary to aspiration [15] and to ensure adequate nutrition.

Data from epidemiological studies suggest that bronchopneumonia subsequent to food or fluid aspiration is a major cause of mortality in NP-C and other neurodegenerative disorders. While precise causes of death are not consistently reported in NP-C, two studies have identified bronchopneumonia as the leading cause of death in two separate NP-C patient cohorts, accounting for approximately two-thirds of patients [19,20]. Marik et al. recognised aspiration pneumonia as the leading cause of death among a range of neurodegenerative disorders [21]. Among factors known to contribute to the development of aspiration pneumonia (e.g., poor oral hygiene, sleep disorders, emesis), dysphagia is considered to contribute by far the greatest risk [22].

Substrate reduction therapy with miglustat (Zavesca®; Actelion Pharmaceuticals) was first approved for treatment of progressive neurological deterioration in children and adults with NP-C in Europe in 2009, and has since been approved in a number of other countries [23]. The primary therapeutic mode of action of miglustat in NP-C is thought to be the reduction of glucosylceramide-based glycosphingolipid synthesis in the CNS, through the reversible inhibition of glucosylceramide synthase [15,24]. In clinical studies miglustat therapy stabilised key neurological manifestations of the disease in adults and children [25–27]. While experience with the use of miglustat in clinical practice settings is increasing [11,18,28–31], published data on long-term clinical outcomes in NP-C patients receiving miglustat remain relatively scarce, owing to the rarity of the disease.

The progressive neurodegenerative nature of NP-C and its typically delayed diagnosis means that disease stabilisation, or a reduced rate of disease progression, are the best attainable goals for long-term disease-specific therapy, given that most patients have a substantial burden of disease by the time of diagnosis [15]. Published data suggest that therapies capable of stabilising/improving swallowing function can reduce the risk of aspiration pneumonia and, potentially, reduce mortality risk [32,33]. In this article we review published information on the most common reported causes of death in NP-C, and evaluate disease factors that might contribute to an increased risk of mortality. We then examine the impact of miglustat on these disease factors to gain insight into the potential effects of this drug on patient lifespan.

**Systematic review methodology**

**Epidemiological research**

A series of systematic epidemiological literature reviews was conducted using the Embase online database in March 2011, to investigate several disease-related factors. Owing to the rarity of the disease and to limited long-term outcome reporting in NP-C (such as precise causes of death), literature reviews examining disease factors specific to NP-C were conducted in parallel with searches on a range of other neurodegenerative diseases. We compared outcomes data in NP-C with those from disorders with similar motor manifestations (particularly dysphagia), and similar neurodegenerative courses [34,35]. Data from patients with acute stroke were also evaluated because of the frequency of dysphagia following stroke [36]. Searches were performed to investigate the following disease-related factors:

2. Causes of death in progressive neurodegenerative disease in general (key terms: mortality, neurodegenerative disease*)
3. The prevalence of dysphagia in neurodegenerative diseases including NP-C (key terms: swallowing, dysphagia, neurodegenerative disease*, NP-C)
4. The association between dysphagia and aspiration pneumonia (key terms: swallowing, dysphagia, aspiration pneumonia, neurodegenerative disease*, NP-C, stroke, traumatic brain injury)
5. The association between aspiration pneumonia and mortality (key terms: death, cause of death, mortality, aspiration pneumonia, neurodegenerative disease*, NP-C, stroke, traumatic brain injury)

*Neurodegenerative diseases included some or all of: Huntington's chorea, Parkinson's disease [PD], amyotrophic lateral sclerosis [ALS], multiple sclerosis [MS], Alzheimer's disease [AD], frontotemporal dementia [FTD], Wilson's disease, olivopontocerebellar atrophy [OPCA], progressive supranuclear palsy [PSP], neuroferritinopathy, motor neurone disease (MND), neuromuscular disease and epilepsy.
Literature data sets were fine-tuned using a standard set of inclusion and exclusion criteria. Only original research reports containing numerical data from clinical assessments were included. Non-English articles were excluded, as were reports based on preclinical data or any duplicate reports of previously published data sets.

Research on the effects of miglustat on dysphagia and outcomes in NP-C
Because NP-C is rare, we conducted broad literature searches to capture any randomised controlled trials comparing miglustat with standard (symptomatic) medical management, as well as evidence from non-randomised studies providing any additional data on miglustat treatment in patients with NP-C.

Initial searches of Medline, Embase, the Cochrane Central Register of Controlled Trials, the National Institutes of Health (NIH) clinical trials database (Clinicaltrials.gov) and the Australian Clinical Trials Registry (Anzctr.org.au) were conducted in January 2010. A further search was then repeated in March 2011 to identify any updated published information. In addition, manual searches were conducted using reference lists from all relevant articles identified in the automated database searches.

Literature review findings
Causes of death in NP-C
Out of 741 potentially relevant articles, seven were identified that specifically discussed cause(s) of death in patients with NP-C [8,19,20,37-40]. Additional studies were identified during the literature search, but no data on causes of death were reported. See Additional file 1: Table S1, for a full listing of literature search findings.

Overall, the identified studies included data from 82 patients with NP-C. While there was no specific reference to ‘aspiration pneumonia’ in the identified publications, the most frequent reported cause of death was bronchopneumonia, based mainly on a retrospective case study analysis in 43 UK patients [20] and a chart review of 20 patients in Nova Scotia [19]. While no actual numbers of deaths related to specific causes were reported in the UK-based study, the major cause of death was cited as bronchopulmonary failure with secondary infection [20]. In the Nova Scotia cohort, swallowing difficulties were reported in 100% of patients, and drooling in 95%; pneumonia was cited as the cause of death in 12/20 (60%) patients.

In the wider community, aspiration pneumonia occurs more frequently among individuals who are at risk of aspiration than is reported; in many cases, it goes unrecognised and is not recorded [22]. In the following discussions regarding these and other data, it is important to consider a number of factors that contribute to the under-reporting and/or under-recognition of the role of aspiration pneumonia as a cause of death.

Disease coding systems can complicate the accurate recording of precise causes of death in patients with neurodegenerative diseases. Some coding systems restrict physicians to recording progression of the underlying (primary) disease on death certificates [41,42]. Some physicians also prefer to record a cause of death as ‘pneumonia’ rather than ‘aspiration pneumonia’ [34]. In a large-scale study of dementia patients in England and Wales from 1979 to 2004 [41], only half of deaths that were attributed to ‘AD’ according to the ICD-10 classification would have been coded as such based on ICD-9 criteria, which allowed the specification of bronchopneumonia and dementia. Similar results were reported for PD patients [41].

There is currently a lack of specific or sensitive markers for aspiration, which limits the ability to discern aspiration pneumonia from other forms of pneumonia and results in deaths related to aspiration being recorded under the term ‘pneumonia’ [21,43,44]. Aspiration is considered the predominant mode of infection in nosocomial pneumonia, mostly among the elderly [34]. However, aspiration events are rarely witnessed in patients with aspiration pneumonia, where the clinical presentation typically matches that of community-acquired pneumonia [21]. This is particularly relevant in patients with ‘silent aspiration’, where aspiration occurs without obvious clinical signs of swallowing difficulty [45].

Because of the limited number of precise data on death in NP-C, it may be instructive to refer to data from other, more frequent neurodegenerative diseases that bear similarities to NP-C at the cellular and phenotypic level. For instance, there is a number of common aetiological factors between Huntington’s chorea and NP-C at the level of membrane trafficking [46], and patients with these two conditions share certain symptomatologic similarities such as dystonia, motoric difficulties that impair manual and oropharyngeal coordination, and impairments to memory and executive functioning that regulate feeding behaviour and the use/retention of safe swallowing strategies. Similarly, AD and NP-C share certain neurodegenerative pathways and neuropathological signs [47,48].

Causes of death in other neurodegenerative diseases
Data on causes of death in a variety of neurological diseases including Huntington’s chorea, amyotrophic lateral sclerosis (ALS), Alzheimer’s disease (AD), frontotemporal dementia (FTD), multiple sclerosis (MS), olivopontocerebellar atrophy (OPCA), Parkinson’s disease (PD), progressive supranuclear palsy (PSP) and Wilson’s disease are listed in Additional file 2: Table S2.
Cause-of-death data were available from 24 out of 1,180 potentially relevant articles. Across all the diseases studied, 20% of patients were classified as having died due to 'aspiration pneumonia'. Among patients with Huntington's chorea, which probably most resembles NP-C in terms of the profile of motor deficits seen, data from the automated literature search indicated that the overall proportion of deaths due to 'aspiration pneumonia' or 'pneumonia' was 37.5% (see Additional file 1: Tables S1, Additional file 2: Table S2, Additional file 3: Table S3, Additional file 4: Table S4 and Additional file 5: Table S5). A further two studies were identified during manual searching. In one study, 'pneumonia' was the reported cause of death in 55% of patients, among whom 89% died due to 'aspiration pneumonia' [44]. In the other study, 42% of deaths were recorded as being due to 'pneumonia' [49]. Surprisingly, 'aspiration pneumonia' or 'pneumonia' were only recorded as causes of death among 11% of ALS patients, despite that fact that most (if not all) ALS patients in the later stages of the disease show some degree of dysphagia [34].

In non-quantitative articles that were excluded from the numerical analysis, aspiration pneumonia was stated as a major cause of death in patients with neurodegenerative disorders, particularly in those with dysphagia due to neurological deterioration [21,22,35]. Precise causes of death were difficult to quantify due to inconsistent reporting, even in studies of more common dementias (where 'aspiration pneumonia'/pneumonia' caused 45% of deaths [50]) and PD (where aspiration pneumonia caused up to 48% of deaths).

**Dysphagia in NP-C and other neurodegenerative diseases**

Among 821 potentially relevant articles identified in the search designed to quantify the prevalence of dysphagia in NP-C and other neurodegenerative diseases, data from 52 studies were included for analysis (see Additional file 3: Table S3 for full data listing). Overall, 4,065 from a total of 14,664 patients (28%) had dysphagia. Figure 1 summarises the prevalence of dysphagia in each condition for which quantitative data were available.

The estimated incidence of dysphagia in a large study including PD patients was low at only 8% [51], bringing the unweighted average prevalence for PD down to 25%. However, this study relied on ICD-9 codes for dysphagia. The authors acknowledge that this figure is therefore likely an underestimate. When the results from this study are disregarded, the rate among PD patients becomes 43%, which is closer to other reported findings [52]. Further, the overall incidence for dysphagia among all patients with neurodegenerative diseases becomes 35%.

The incidence of dysphagia reported among ALS patients was surprisingly low (24%). However, the ALS data were strongly influenced by one large study in
3,428 patients that included a range of patients with different ages at onset, and therefore likely comprised a high proportion of patients with early-to-mid-stage disease [53]. Dysphagia was reported in 30–50% of patients among other ALS studies, and has been reported in most if not all late-stage ALS patients [34].

Among all neurodegenerative diseases PSP appeared to be associated with the greatest prevalence of dysphagia (85%), although these data were based on only one identified study with evaluable data. Patients with NP-C showed the second-highest prevalence (55%), which is substantially greater than the overall average prevalence among neurodegenerative disease patients. Further, this figure is likely an underestimate, as most patients included in NP-C studies were in the early stages of disease and were being treated with miglustat.

Association between dysphagia and aspiration pneumonia

Twelve out of 364 potentially relevant articles reported data on the association between dysphagia and aspiration pneumonia in patients with neurodegenerative disease, stroke or traumatic brain injury (see Additional file 4 for full data listing). Based on relative risk analyses, these published data consistently indicated an increased risk of aspiration pneumonia where dysphagia was present (Table 1). Relative risk values ranged from 1.6 (95% CI 0.1, 38.0) to 126 (95% CI 8, 2065).

Data from this literature search were combined for meta-analysis (Figure 2). After exclusion of one very large study [56], which included data from 77,540,204 general hospital patients resulting in unacceptably high weighting of the overall sample (accounting for 99.8% of all included patients), odds ratios indicated a highly significantly increased risk of aspiration pneumonia among patients with dysphagia. The overall odds ratio for developing pneumonia was 16.85 (95% CI 9.21, 30.83), with values ranging from 1.7 (95% CI 0.1, 42.4) to 174 (95% CI 10, 2,952). Analysis including data from the large general hospital population study confirmed this finding (odds ratio, 14.1 (95% CI 13.9, 14.3))

Association between aspiration pneumonia and mortality

Five of 243 potentially relevant articles were identified that reported data on both aspiration pneumonia and mortality outcomes in patients with PD, stroke or epilepsy (see Additional file 5: Table S5 for full data listing). One extra article was identified in an additional hand search of the literature that contained data from a mixed population of patients with PD, MND, AD or Huntington’s chorea [33]. No published articles were identified that reported data on both aspiration pneumonia and mortality in patients with NP-C.

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<tr>
<th>Table 1 Relative risk of aspiration pneumonia in patients with neurodegenerative disease or stroke and dysphagia</th>
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*Relative risk calculated using Mantel-Haenszel fixed effects method.

The relative risk (95% CI) of mortality among patients with aspiration pneumonia in the identified studies ranged from 1.51 (1.35,1.69) to 3.42 (0.82, 14.35) (Table 2). When data were combined in a meta-analysis to evaluate the relationship between these two outcomes, patients experiencing aspiration pneumonia were seen to have an increased risk of mortality (Figure 3). The overall odds ratio for mortality was 3.23 (95% CI 2.46, 4.25).

Epidemiological research: overall findings

The quantitative analysis of causes of death in NP-C patients is currently limited by the scarcity of relevant published studies, with few reports containing mortality data. There was limited but consistent reporting of bronchopneumonia as the most common cause of death in NP-C, accounting for over 60% of patients [19,20]. Supplemental analysis of data in other neurodegenerative diseases that feature dysphagia showed ‘aspiration pneumonia’ or ‘pneumonia’ reported as a cause of death in over 20% of patients. However, this is considered to be vastly underestimated due to a number of factors that contribute to under-reporting of aspiration pneumonia as cause of death.

The analysis of published data in NP-C and a range of other neurodegenerative diseases showed that dysphagia is a frequent symptom, particularly in NP-C and PSP. Further, relative risk data and meta-analyses provide clear evidence that patients with dysphagia are at an increased risk of developing aspiration pneumonia, and that there is a strong link between the occurrence of aspiration pneumonia and mortality risk. With these links now established, the following sections specifically examine the effects of miglustat therapy on dysphagia and mortality risk in NP-C.
Studies and methods assessing the effects of miglustat on dysphagia in NP-C

All published clinical studies providing data on swallowing function in miglustat-treated patients are summarised in Table 3.

Swallowing assessments based on clinical judgment

Swallowing function data were available from a 12-month randomised, controlled trial that assessed the efficacy, safety and tolerability of miglustat 200 mg t.i.d. in juvenile and adult patients aged ≥12 years (n = 29), compared with standard care [25]. Findings were also reported from a parallel non-controlled sub-study of this trial, which assessed miglustat in children aged 4–11 years (n = 12) [25].

Long-term data from patients continuing miglustat therapy during 12-month open-label extensions of the main juvenile/adult study (n = 21) and the paediatric sub-study (n = 10) have since been published [26,27]. In each of these reports dysphagia was assessed based on standardised clinical assessments of the patients’ ability to swallow different foods (e.g. water, puree, soft pasta/noodles, a cookie), graded using a five-point categorical scale: ‘no problems swallowing,’ ‘mild problems,’ ‘moderate problems,’ ‘severe problems,’ or ‘could not swallow at all.’

Retrospective data on swallowing function were reported in an international, multicentre, observational cohort study that evaluated neurological disease progression in patients treated with miglustat in clinical practice settings (n = 66) [70]. Swallowing function was evaluated based on patients’ scores on the dysphagia subscale of a modified, disease-specific disability scale [12]. Using this subscale the degree of dysphagia before miglustat therapy, at treatment initiation, and after therapy was rated as ‘normal’ (score = 0), ‘occasional dysphagia’ (score = 0.33), ‘daily dysphagia’ (score = 0.66), or ‘nasogastric tube or gastric button feeding’ (score = 1) [70]. Data then underwent categorical analysis for ‘improvement,’ ‘stabilisation’ or ‘worsening’ of swallowing function.

Swallowing assessments based on instrumental methods

Findings from instrumental, quantitative assessments of swallowing have been reported from two studies [18,29]. Both reports were based on longitudinal case analyses incorporating videofluoroscopic studies (VFSS), which are considered the gold standard method for studying oropharyngeal swallowing function. VFSS allow an in-depth evaluation of all phases of the swallowing motion, enabling clear distinctions between oral-phase and pharyngeal phase dysfunction [71].

Fecarotta et al. reported findings from detailed serial studies of swallowing function in three female patients
with late-infantile or juvenile-onset NPC1 and one male patient with severe early-infantile onset NPC2 [18]. These patients received miglustat therapy, dosed according to BSA for between 3 and 4 years. The severity of dysphagia was evaluated at 2–6 monthly intervals based on an adapted version of the 6-point Dysphagia Severity Score (DSS) [71], which ranges from normal swallowing (score = 0) to severe dysphagia with potential for aspiration (score = 5). A 7-point Penetration-Aspiration Score (PAS) was also applied at each VFSS assessment to quantify penetration/aspiration in the airways according to published methods [71]; again, higher scores on this scale indicated more severe impairment. VFSS were also conducted in parallel with NP-C disability scale assessments to assess correlations between swallowing function, overall neurological deterioration (based on composite disability scores [70]) and the dysphagia subscale scores.

Chien et al. reported data from two young symptomatic male patients with juvenile-onset NPC-NP-C who completed 1 year of miglustat therapy, dosed according to body surface area. One patient had severely impaired swallowing function, and the second displayed normal swallowing but impaired language and speaking ability prior to miglustat therapy [29]. Videotapes of VFSS of liquid barium swallowing were analysed by a single radiologist based on the Fan functional dysphagia scale [72]. Scores were assigned to 11 variables that covered the ‘entire swallowing cycle’ or ‘all aspects of the oropharyngeal swallow’. Individual scores assessing each of these variables were summed to provide a total functional dysphagia score ranging from 0 (no impairment) to 100 (severe impairment).

**Results from studies of the effects of miglustat on dysphagia in NP-C**

**Categorical data findings**

Based on clinical judgment, miglustat was reported to stabilise or improve swallowing function in a substantial proportion of patients with NP-C.

In the randomised controlled trial, improvements were seen in the ability to swallow water for six patients (30%), puree for three patients (15%), soft lumps for three patients (15%), and a third of a cookie for seven patients (35%) after 12 months of therapy [25]. The proportions of miglustat-treated juvenile/adult patients reporting no difficulty swallowing water, puree and one-third of a cookie after 12 months of miglustat therapy increased from baseline by 10–25% (Figure 4). In contrast, the proportions of juvenile/adult patients on standard care who showed no difficulty swallowing were either equal to or lower than baseline at 12 months.

In the non-controlled extension study [27], swallowing was improved or stable (versus baseline) in 86% of all juvenile/adult patients who completed 12 months of miglustat therapy (n = 21), and in 79–93% of those completing 24 months on miglustat (n = 15), depending on the substance assessed.

Swallowing difficulties were less common in the paediatric sub-study population (recorded in only 33% of patients at baseline) [25]. Over 80% of children swallowed all four test substances easily before treatment was started. It was therefore anticipated that improvements in swallowing were not likely. A worsening in the ability to swallow water, puree, soft lumps and one-third of a cookie was noted after 12 months of therapy in three patients (27%), two patients (18%), one patient (9%) and two patients (18%), respectively. However, among 10 paediatric patients who participated in and completed extension treatment, only one showed deterioration in the ability to swallow one-third of a cookie after 24 months of therapy. All other patients showed no change in swallowing function from baseline.

Dysphagia assessments in NP-C patients included in the retrospective observational NP-C cohort indicated similar findings among patients treated outside the context of clinical trials [70]. The retrospective cohort comprised 66 patients with a mean (SD) age at diagnosis of 9.7 (7.6) years; the mean (SD) age at treatment start was 12.5 (9.5) years. On average, patients had been under...