TABLE II. Dysphagia Severity Rating Scale and Penetration-Aspiration Score

A: Dysphagia Severity Rating Scale (DSS) [adapted from Gates et al., 2006]

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal swallowing</td>
</tr>
<tr>
<td>1</td>
<td>Minimal dysphagia [VFSS shows a slight deviation from a normal swallow;</td>
</tr>
<tr>
<td></td>
<td>impairment limited to oral stage]</td>
</tr>
<tr>
<td>2</td>
<td>Mild dysphagia [presence of oro-pharyngeal dysphagia; can be treated by</td>
</tr>
<tr>
<td></td>
<td>means of specific swallowing suggestions]</td>
</tr>
<tr>
<td>3</td>
<td>Mild to moderate dysphagia [presence of oro-pharyngeal dysphagia; potential</td>
</tr>
<tr>
<td></td>
<td>for aspiration exists but it can be diminished by specific swallowing</td>
</tr>
<tr>
<td></td>
<td>techniques]</td>
</tr>
<tr>
<td>4</td>
<td>Moderate dysphagia [presence of oro-pharyngeal dysphagia; potential for</td>
</tr>
<tr>
<td></td>
<td>aspiration exists; trace aspiration may be seen at VFSS]</td>
</tr>
<tr>
<td>5</td>
<td>Severe dysphagia [presence of aspiration; nothing by mouth is recommended]</td>
</tr>
</tbody>
</table>

B: Penetration-Aspiration Score (PAS) [according to Gates et al., 2006]

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Contrast agent does not enter the airway</td>
</tr>
<tr>
<td>1</td>
<td>Contrast agent enters the airway, but remains above the vocal folds; no</td>
</tr>
<tr>
<td></td>
<td>residue</td>
</tr>
<tr>
<td>2</td>
<td>Contrast agent remains above the vocal folds; visible residue</td>
</tr>
<tr>
<td>3</td>
<td>Contrast agent contacts the vocal folds; no residue</td>
</tr>
<tr>
<td>4</td>
<td>Contrast agent contacts the vocal folds; visible residue</td>
</tr>
<tr>
<td>5</td>
<td>Contrast agent passes the glottis; no subglottic residue</td>
</tr>
<tr>
<td>6</td>
<td>Contrast agent passes the glottis; visible subglottic residue</td>
</tr>
<tr>
<td>7</td>
<td>Contrast agent passes the glottis; visible subglottic residue absent</td>
</tr>
</tbody>
</table>

The severity of clinical conditions and neurological involvement was assessed according to an original severity scale, later adapted to the NPC disability scale (DS) proposed in the literature [Iturriaga et al., 2006; Wraith et al., 2009]; the total score and the partial scores for ambulation, manipulation, language and swallowing have been summarized at different time points for each patient.

RESULTS

Table III summarizes the descriptions of the swallowing stage impairment (oral and/or pharyngeal), the severity scores of dysphagia and the penetration/aspiration scores. It also summarizes the total and partial scores for disability scale to compare the results in swallowing ability before and after treatment with the changes in clinical conditions at each time point.

Patient 1 showed a mild dysfunction of oro-pharyngeal phase at baseline, but absence of penetration/aspiration. At that time the clinical assessment revealed some difficulties to swallow liquids, coughing during or after swallowing. After 6 months of miglustat treatment the patient experienced a transient worsening of swallowing ability in combination with the onset of epilepsy and presence of uncontrolled seizures. Moderate to severe dysphagia with aspiration of contrast agent was detected after 6 and 9 months of miglustat treatment (Fig. 1) and a percutaneous gastrostomy tube was needed to feed her and to administer drugs. After the control of seizures was reached with appropriate anticonvulsant drugs a sudden improvement of swallowing was detected in combination with improvement of neurological status; deglutition was normal after 14 months of treatment (Fig. 2) and improvement was sustained up to 48 months of miglustat therapy, making the gastrostomy tube unnecessary.

Patient 2 is the younger sister of Patient 1. She had almost normal clinical conditions at start of treatment with miglustat, showing a minimal neurological involvement and a normal swallowing. A sustained normal ability of swallowing was detected by VFSS up to 40 months of miglustat treatment.

Patient 3 showed severely compromised neurological status at start of treatment.

The VFSS performed at baseline showed severe dysphagia, including dysfunction of both oral and pharyngeal stages and aspiration of barium. After 6 months of treatment a clear-cut improvement was detected, with normalization of pharyngeal phase impairment and absence of aspiration. A minimal dysfunction, exclusively of the oral phase, was sustained up to 36 months of treatment.

Patient 4 was a 1-year-old child who showed severely compromised clinical conditions at baseline, including neurological, visceral and respiratory involvement. Severe dysphagia was clinically evident at baseline in combination with a severe secondary malnutrition. The VFSS evaluation at baseline has been performed with patient’s mother holding her child in her arms in a semisupine position, as the patient was unable to sit independently and only the starting dose of thin liquid barium was administered. The VFSS showed absence of oral phase and severe pharyngeal phase dysfunction with prominent aspiration of barium. A dramatic improvement of patient’s swallowing ability was shown 6 months later, when an isolated oral phase dysfunction, normal pharyngeal stage and absence of penetration/aspiration were detected. In parallel with improvement of swallowing the child showed a catch-up growth with normalization of all auxological parameters and a notable progressive and sustained improvement of
### TABLE III. Description of Swallowing Stages Impairment (SSI), Dysphagia Severity Score (DSS), and Penetration/Aspiration Score (PAS) in Four NPC Patients on Miglustat Treatment

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<tbody>
<tr>
<td></td>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
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<tr>
<td>Patient 2</td>
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<td>[A3M1L1S1]</td>
<td>[A3M1L1S1]</td>
</tr>
</tbody>
</table>

Comparison with the overall clinical disability scale (DS) total score, according to Iwuraga et al. [2006]. Partial scores for ambulation, manipulation, language and swallowing are shown in parentheses.

- A, ambulation; Normal, 0; 1: autonomous electric chair; 2: indoor assistance ambulation; 3: wheelchair bound, 4.
- S, language; Normal, 0; 1: mild dysarthria; 2: severe dysarthria; 3: non-verbal communication; 4: absence of communication, 5.
- L, swallowing; Normal, 0; 1: occasional dysphagia; 2: daily dysphagia; 3: N6 tube or 6-button feedings, 4.

*The DS total score could not be calculated as ambulation and language could not be assessed, due to the young age of patient (11 months).*
neurological status. The presence of a minimal dysfunction of the oral phase was sustained up to the last evaluation at month 36 of treatment, which was performed for the first time with the patient being unsupported in a sitting position.

Overall our data showed that all patients with abnormalities at baseline showed early improvements in swallowing ability after treatment and that the patient who did not show any swallowing abnormality at baseline remained stable. We also observed that improvement of swallowing coordination occur in parallel with improvement or stabilization of neurological conditions.

Our data showed that patients with more severe swallowing abnormalities, including involvement of the pharyngeal phase were those with the more severe neurological involvement, as confirmed by a higher total score at DS evaluation. In addition our data suggest that the pharyngeal phase of swallowing deteriorate later than the oral phase in the course of the disease and that worsening of overall neurological involvement as assessed by the DS correlate with worsening of swallowing ability, involvement of pharyngeal phase abnormalities and risk of aspiration, as detected by VFSS.

After treatment with miglustat we observed an improvement of the pharyngeal phase impairment more evident and earlier than the oral phase in all patients with abnormalities at baseline. In fact a minimal defect of the preparatory/oral phase persisted in two patients having the more severe swallowing impairment and the higher disability score at baseline (Patients 3 and 4) and it was sometimes detected in the course of follow-up in the patient with a mild swallowing defect at baseline and a moderate neurological involvement (Patient 1). Absence of progression for both oral and pharyngeal stages has been shown in the pre-symptomatic patient (Patient 2).

Our data also demonstrated that the long term improvement of coordination of the pharyngeal and oral stages of swallowing after miglustat treatment determines the sustained absence of aspiration of barium in the airways in all patients who showed severe impairment of swallowing and penetration/aspiration of the contrast agent.

DISCUSSION

This observational study reports on the use of miglustat in four pediatric patients with NPC, focusing on the efficacy of treatment on dysphagia. Miglustat has been suggested as a potential treatment for NPC disease, but little information about the effects of this drug is currently available in the literature.

Previous results from a controlled clinical trial in adult and juvenile patients with NPC [Patterson et al., 2007] and the pediatric subgroup [Patterson et al., 2010], data from a retrospective clinical study [Pineda et al., 2009] and also from single additional patients on miglustat treatment [Chien et al., 2007; Paciorekowsi et al., 2008; Santos et al., 2008; Galanaud et al., 2009] indicated the beneficial effect of miglustat on the progression of neurological manifestations, including dysphagia, although data on improvement of swallowing impairment were limited.

In the above cited studies the evaluation of dysphagia progression was based on the clinical assessment of the patient’s swallowing ability in the clinical trial, while history-based data were collected in the retrospective cohort study. Dysphagia is caused by progressive neurological involvement in NPC patients and it could be considered as one of the markers of disease progression. Progressive swallowing deterioration with subsequent complica-
tions as malnutrition and aspiration is a typical feature in NPC disease.

Our results of VFSS in four pediatric patients on long-term miglustat treatment confirm the efficacy of miglustat to either prevent or improve dysphagia in NPC patients in agreement with previous findings, and provide additional information on patterns of impairment of swallowing mechanisms. Actually, we observed improvement of dysphagia in all patients with abnormalities at start of treatment and absence of progression in the patient with normal swallowing at baseline. The use of VFSS to assess dysphagia provided original data about the effects of treatment on the different stages of swallowing and on aspiration in patients with severe dysphagia that, with a single exception [Chien et al., 2007], have not been studied to date.

The act of swallowing is a highly regulated activity, having voluntary and involuntary components that coordinate the sequence of three successive stages. The network of neurons responsible for coordinating the oral stage has a highly complex connectivity that overlaps only in some aspects with neuron subcircuits thought to control the subsequent parts of the deglutitive sequence [Bieger and Neuhuber, 2006]. Actually, while the preparatory/oral phase includes conscious effort to ingest food, being activated by peripheral receptors and also by stimulation of certain cortical neurons, the pharyngeal and esophageal stages are mediated by an involuntary reflex that involves a swallowing pattern generator in the brainstem [Goyal and Mashimo, 2006].

Using VFSS in our study we observed that the more severe swallowing abnormalities, including involvement of the pharyngeal phase and penetration/aspiration of barium in the airways, were present in patients with the more severe neurological conditions. In addition our data suggest that pharyngeal phase impairment occurs later than oral phase in the course of the disease, in parallel with worsening of neurological status and, also, that abnormalities in pharyngeal stage may show an earlier and sustained improvement in comparison with oral stage abnormalities after treatment with miglustat. As a whole these observations may suggest a greater effect of the treatment on selected neurons or subcircuits in the brainstem (which control the autonomics phases of swallowing), in comparison to neurons responsible of coordinating the oral stage (mainly neurons in the primary sensory cortex which are responsible for initiating the swallowing response). The hypothesis of a selective efficacy of miglustat on some neurons, mainly in the brainstem, is consistent with different results from the literature, such as the significant improvement of the saccadic eye movements in miglustat-treated patients, considering that saccades are under the control of neuron systems in the brainstem.

Alternatively, based on data suggesting that impairment of the pharyngeal phase of swallowing occurs later in the course of the disease, we hypothesize a more recent injury of the neuronal subcircuits which are mainly responsible of the control of the pharyngeal phase in the brainstem, in comparison to that controlling the coordination of oral stage. It is therefore reasonable to suppose a more evident effect of the treatment just on the more recently damaged brainstem subcircuits, that might consist of dysfunctional but yet surviving neurons.

Finally our VFSS data show that the long-term improvement of swallowing coordination after miglustat treatment determines the sustained absence of aspiration of barium in the airways in patients with severe dysphagia.

In conclusion our results confirm by instrumental evaluation the clinical evidence of the efficacy of miglustat on dysphagia progression in NPC patients on a long-term observation. This might represent a major clinical benefit for NPC patients as an improvement or stabilization of the swallowing ability may have immediate effects on the quality of life and can contribute to ameliorate the general status of the affected patients, mainly decreasing the risk of aspiration with a consequent longer survival.

Due to the information provided and the correlation of the results with the severity of the clinical involvement, we suggest that VFSS should be routinely used to monitor the effects of treatment on swallowing ability using a defined scoring system to assess all stages of the swallowing motion.

Finally, consistent with the ability of miglustat to cross the blood–brain barrier, our data can support the evidence that the substrate reduction have some efficacy in modifying the natural course of neurological manifestations in NPC disease, in agreement with the data reported in literature. Furthermore, we hypothesize that the therapeutic approach with miglustat could prevent neurological regression and disability and lead to improvement of the quality of life in NPC patients who start therapy before significant damage has occurred, as suggested by the data obtained in the pre-symptomatic patient, who showed the absence of deterioration over 3 years of follow-up, after the onset of minimal neurological signs, in contrast with the expected linear clinical progression of the disease [Yaujanju et al., 2009; Wraith et al., 2009].

Further follow-up is crucial to define the long-term maintenance of these effects.

ACKNOWLEDGMENTS

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stat: Initial responses and maintenance of effects over 1 year. J Inherit Metab Dis 36:326.


Case Report

Early Miglustat Therapy in Infantile Niemann-Pick Disease Type C

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ABSTRACT

Niemann-Pick disease type C is a rare inherited cholesterol trafficking disorder, where impaired intracellular lipid transport leads to storage of unesterified cholesterol and glycosphingolipids in many tissues, including the brain. Substrate reduction therapy with miglustat, an iminosugar that inhibits glycosphingolipid synthesis, was proposed to treat Niemann-Pick disease type C, based on evidence of slower disease progression and prolonged survival in animal models. Miglustat was subsequently approved in Europe to treat progressive neurologic manifestations in both children and adults in early 2009, based on clinical study data. We report on the early treatment of two pediatric Niemann-Pick type C patients with miglustat. Patient 1, a 7.5-year-old girl with early-infantile onset, began receiving miglustat at age 7 months. Patient 2, the brother of a girl diagnosed with late-infantile onset Niemann-Pick type C, began receiving miglustat at age 19 months, when he was asymptomatic for neurologic disease. After 7 and 5 years of miglustat therapy, respectively, both patients remain free of neurologic manifestations. These findings suggest that miglustat may be more effective if used to prevent, rather than treat, neurologic manifestations in infantile-onset Niemann-Pick type C.

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Introduction

Niemann-Pick disease type C is a rare autosomal recessive inherited disorder of cholesterol trafficking, where impaired intracellular lipid transport leads to the storage of unesterified cholesterol and glycosphingolipids in many tissues, including the brain [1]. Different clinical phenotypes of Niemann-Pick disease type C can be distinguished according to the patient’s age at onset of neurologic signs [2]. Early-infantile Niemann-Pick disease type C is characterized by early-onset hepatosplenomegaly and liver disease, and by hypotonia and psychomotor regression that typically appear by age 12–24 months, and which are often followed by progressive neurodegenerative disease and death by around age 5 years [1]. Late-infantile Niemann-Pick disease type C presents between ages 2 and 6 years, and is characterized by ataxia, supranuclear gaze palsy, dysarthria, dysphagia, dystonia, seizures, and progressive dementia [1,2]. Hepatomegaly and splenomegaly are frequently but not invariably evident at age 2–6 years, and death most often occurs at age 7–12 years [1,2]. The juvenile and adult forms are characterized by later-onset psychiatric and neurologic signs (e.g., cataplexy, clumsiness, cognitive decline, and seizures), but organomegaly is not a constant finding [3,4]. Intermediate forms have been reported, and Niemann-Pick disease type C phenotypes were proposed to fit with a continuous spectrum ranging from early-infantile through adult forms [1].

Substrate reduction therapy with miglustat, an iminosugar that inhibits glycosphingolipid synthesis, was first proposed for the treatment of Niemann-Pick disease type C, based on evidence of slower disease progression and prolonged survival in animal models [5]. Subsequent clinical studies demonstrated the stabilization of neurologic disease in both children and adults treated with miglustat [6–8].
Miglustat was approved in Europe for the treatment of progressive neurologic manifestations in children and adults with Niemann-Pick disease type C in early 2009 [9]. We report on early treatment with miglustat in two pediatric patients manifesting Niemann-Pick disease type C, i.e., a 7.5-year-old girl with early-infantile onset disease who began receiving miglustat at age 7 months, and a boy, the brother of a girl diagnosed with the late-infantile onset form of the disease, who began receiving miglustat at age 19 months when he was asymptomatic for neurologic signs. After 7 and 5 years of miglustat therapy, respectively, both patients remain free of the characteristic neurologic manifestations of Niemann-Pick disease type C.

Case Reports

Patient 1

This young female patient, the second child of healthy, unrelated parents, was born in late November 2004, and exhibited cholestatic jaundice, hepatosplenomegaly, and pathologically documented liver fibrosis since her first months of age. During her initial admission to the Unit of Rare Diseases at the Gaslini Institute (Genoa, Italy) at age 6 months, a neurologic examination revealed only mild axial hypotonia. An evaluation of her psychomotor development on the Griffiths scale indicated mild delayed development (performance equivalent to age 5 months). Electroencephalography, nerve conduction velocity, brainstem auditory evoked potentials, cranial magnetic resonance imaging, and magnetic resonance spectroscopy findings were all normal, but her plasma chitotriosidase activity was substantially elevated (2480 nmol/ml/hour; normal range, 2-35 nmol/ml/hour).

A diagnosis of Niemann-Pick disease type C was ascertained through filipin staining of the patient’s skin fibroblasts and by NPC1 gene mutation analysis. She was revealed to be homozygous for the mutant p.Y1019C allele. She subsequently began receiving miglustat 250 mg/m²/day three times daily at age 7 months in 2005.

At the time of this writing, this patient has been treated for a total of 6 years without interruption, with the dose of miglustat adjusted to body surface area. The miglustat has been well tolerated. She has not experienced gastrointestinal disturbances, and has demonstrated no need for dietary modifications. She currently exhibits normal psychomotor development, with no signs of neurologic impairment. Findings of neurophysiologic and neuropsychological tests remain normal. Studies performed once a year include assessments of brainstem auditory evoked potentials, magnetic resonance imaging, and Griffith mental development scale evaluations.

The patient has manifested hepatosplenomegaly since birth up to her current age (7 years). Annual ultrasound evaluation indicated that the major diameter of her spleen was 8 cm at the initiation of miglustat therapy in 2005, and 18 cm at follow-up in 2011, indicating continued splenomegaly. The patient’s plasma chitotriosidase activity also remained high, despite miglustat therapy. It was most recently measured at 4280 nmol/ml/hour in 2011 (normal range, 2-35 nmol/ml/hour).

Patient 2

This early-infantile boy with Niemann-Pick disease type C was first evaluated at age 16 months because of prolonged, isolated splenomegaly. His 8-year-old sister, who had previously presented at age 4 years with noteworthy progressive neurologic manifestations, had just been diagnosed with Niemann-Pick disease type C.

A genetic mutation analysis demonstrated that both the boy and his sister were double heterozygous for two NPC1 gene mutations (P1000R and T1203K). The boy began treatment with miglustat at age 19 months, at which point his spleen length, according to ultrasound assessment, was 10.4 cm, and his plasma chitotriosidase activity was measured at 760 nmol/ml/hour. His psychomotor development was appropriate for his chronological age, and a neurologic examination produced negative findings.

Miglustat was administered at a dose of 250 mg/m²/day for 4 years without any complaints. At age 6 years, his chitotriosidase activity remained high, at 1920 nmol/ml/hour, and the major diameter of his spleen was 13 cm (as evaluated by echography). Findings from repeated neurologic examinations were normal, and he has exhibited normal Griffith scale scores. Brainstem auditory evoked potential testing also demonstrated normal findings throughout his treatment.

The sister had begun receiving 250 mg/m²/day miglustat at age 8 years, at which point she exhibited dysmetria, assisted gait, supranuclear ocular palsy, slurred speech, and epileptic seizures (controlled by valproate). After 5 years of treatment, she is wheelchair-dependent and requires assistance with all activities. She exhibits minimal nonverbal communication, intermittent dysphagia, and seizures that are difficult to control with antiepileptic polytherapy.

Discussion

The published data are limited in regard to the clinical experience with miglustat in Niemann-Pick disease type C, and the data from clinical trials are available only in regard to patients aged 4 years or more. To our knowledge, our two patients comprise the first reported cases of Niemann-Pick disease type C in whom miglustat therapy was initiated very early in life (at less than 2 years of age) and before the onset of neurologic manifestations. Both patients have been followed during prolonged periods of miglustat therapy (for up to 7 years).

Both preclinical and clinical studies provide evidence to support the use of miglustat in Niemann-Pick disease type C. In 2001, Zervas et al. observed a delayed onset of neurologic dysfunction, increased average lifespan, reduced accumulation of brain ganglioside, and accompanying changes in neuropathology after miglustat treatment in animal models of Niemann-Pick disease type C [5]. Lachmann et al. later observed clinical stabilization and the normalization of lipid trafficking in peripheral lymphocytes in an adult patient with Niemann-Pick disease type C treated with miglustat [10]. Patterson et al. reported on data from a randomized, controlled trial with miglustat (vs standard care) in Niemann-Pick disease type C, based on 29 patients aged >12 years and 12 patients aged <12 years; all patients exhibited neurologic improvement at baseline [6]. After 1 year, the patients treated with miglustat demonstrated a stabilization of ambulatory function and improvements in swallowing and horizontal saccadic eye movements [6]. The continued follow-up of pediatric, juvenile, and adolescent/adult patients in the same cohort indicated the sustained stabilization of key neurologic disease parameters during the subsequent 12-24 months [7,8]. Safety monitoring in that extension study indicated that miglustat was generally well tolerated, with no new safety issues. Pineda et al. reported on their clinical experience with miglustat in a case series including 16 pediatric patients (aged 1-15 years) with symptomatic Niemann-Pick disease type C [11]. Although miglustat appeared to stabilize the neurologic status of juvenile-onset patients, relatively small benefits occurred in early-onset patients who were at a more advanced stage of disease at the initiation of treatment [11].

When we initiated miglustat therapy in patient 1, no disease-specific therapy for Niemann-Pick disease type C had been approved, nor had any recommendations for the
clinical management of the disease has been published. Based on early data indicating the potential for successful treatment with miglustat [10], we decided to initiate its use before the onset of characteristic neurologic manifestations, after the approval of an application to the local health authority (the Ethics Committee of Gaslini Institute). Early-onset liver disease (evident at birth), visceromegaly, and persistently high chitotriosidase levels indicate that this patient manifests the early-infantile onset form of the disease [1]. Based on published data [1,11,12], we considered it unlikely that she would have remained neurologically stable up to age 7 years without treatment. The lack of key neurologic signs of Niemann-Pick disease type C to date suggests that miglustat prevented or at least delayed the onset or progression of neurologic manifestations. However, we cannot exclude the possibility that she will develop neurologic manifestations. In addition, she is homozygous for a newly described Niemann-Pick disease type C gene mutation, and no information, to the best of our knowledge, has been published on the clinical disease phenotype of similarly affected patients. This conclusion precludes a comparison of her clinical disease course with that of a previous, untreated case.

The clinical course of Niemann-Pick type C in patient 2 was clearly different from that of his sister, who manifested a classic late-infantile Niemann-Pick disease type C phenotype with an onset of neurologic manifestations at age 4 years, but with no response to miglustat therapy initiated 4 years later. This boy has passed that age without any appearance of neurologic signs, which is encouraging. Although the apparent differences in disease course between these two siblings may be attributable in part to familial phenotypic heterogeneity, we consider it likely that miglustat has affected the disease course of patient 2.

The persistent visceral involvement and persistent increased plasma chitotriosidase observed in both cases indicate that miglustat did not affect the excess lipid storage in macrophages. Similar findings were reported by Chien et al. in two male Taiwanese patients aged 9 and 14 years, in whom both spleen size and plasma chitotriosidase activities demonstrated no notable change during 1 year of miglustat therapy [13].

The apparent stabilizing effects of miglustat on neurologic parameters, concurrent with a relative lack of effect on visceral involvement, may be attributable, at least in part, to differences in the pattern of lipid accumulation in different tissues in Niemann-Pick disease type C. The visceral accumulation of unesterified cholesterol, sphingomyelin, glycoginosphinoglycopolipids, and sphingosine leads to hepatosplenomegaly and increased chitotriosidase [14], whereas the brain's accumulation of glucosylceramide, lactosylceramide, and, in particular, GM2 and GM1 gangliosides contributes to neuronal dysfunction [1]. Based on the observed clinical changes, a miglustat-induced reduction in brain storage seems a likely mechanism through which neuronal damage can be delayed or possibly prevented. Whether miglustat exerts neuroprotective effects remains unknown.

Consensus guidelines for the clinical management of Niemann-Pick disease type C recommend the close monitoring of patients after the initiation of miglustat therapy, at the onset of neurologic signs (or at or before the anticipated time of neurologic symptom onset) in patients with a known family history and disease course [2]. Although widely accepted, this statement in our opinion is influenced by the awareness that therapies for rare diseases are often expensive, and by the fact that long-term prospective data on the effects of miglustat in Niemann-Pick disease type C are relatively sparse because of low patient numbers. However, longitudinal modeling studies based on patient cohorts with Niemann-Pick disease type C suggest that the onset of neurologic signs reflects a certain threshold level of irreversible neuronal loss or dysfunction in the central nervous system [15]. Furthermore, after neurologic signs do appear, they progress in an unbroken fashion among untreated patients [12,15]. With this information in mind, and based on our own observations, we propose that patients might derive important therapeutic gains from the initiation of miglustat therapy before the onset of irreversible damage to the central nervous system.

Although definitive conclusions cannot be drawn from the experience of a few patients, further years of follow-up should allow for a better evaluation of the long-term therapeutic effects of early intervention with miglustat in Niemann-Pick disease type C. Our findings suggest that miglustat could be more effective if it is used to prevent, rather than treat, neurologic manifestations in infantile-onset Niemann-Pick disease type C. It should be borne in mind that only a small window of opportunity may allow for effective interventions before irreversible neurologic damage occurs.

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References


Treatment with miglustat reverses the lipid-trafficking defect in Niemann-Pick disease type C

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Niemann—Pick disease type C (NP-C) is a hereditary neurovisceral lipid storage disorder. Although traditionally considered a primary cholesterol storage disorder, a variety of glycolipids accumulate in NP-C cells, which resemble those from glycosphingolipidosis patients. Substrate reduction therapy (SRT) with miglustat, an inhibitor of glycosphingolipid biosynthesis, is a novel therapy for the glycosphingolipidoses. We report the use of SRT in a patient with NP-C. We show that depletion of glycosphingolipids by miglustat treatment redness pathological lipid storage, improves endosomal uptake and normalises lipid trafficking in peripheral blood B lymphocytes. The demonstration that treatment with miglustat, which has no direct effect on cholesterol metabolism, corrects the abnormal lipid trafficking seen in B lymphocytes in NP-C indicates that glycosphingolipid accumulation is the primary pathogenetic event in NP-C. These observations support the use of SRT in patients with this devastating neurodegenerative disease. 

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Introduction

Niemann—Pick disease type C (NP-C) is a hereditary neurovisceral lipid storage disorder (Vanier and Millat, 2003). Most cases are due to mutations in NPC1, a membrane protein involved in endosomal—lysosomal transport of lipids (Liscum, 2000). Clinical manifestations are diverse (Patterson et al., 2001): neonatal hepatitis can lead to fatal cholestasis jaundice, but in older children and adults neurological disease predominates, usually accompanied by asymptomatic hepatosplenomegaly. In childhood, cerebellar ataxia and cognitive impairment progresses relentlessly with supranuclear gaze palsy, epilepsy and extrapyramidal features. The adult form of the disease is insidious but progressive dementia and psychiatric manifestations commonly supervene. Hitherto, no specific treatment has been available for NP-C.

In cultured NP-C fibroblasts, the main storage material is unesterified cholesterol and NP-C was originally considered to be a cholesterol storage disorder. More recently, it has become clear that a variety of lipids accumulate in NP-C cells (Vanier and Millat, 2003); in this respect, they resemble those from patients with glycosphingolipidoses (e.g., Gaucher disease, Fabry disease, GM1 and GM2 gangliosidoses) and share a generalised defect in lipid trafficking within the endosomal—lysosomal system (Chen et al., 1999; Silence et al., 2002). This trafficking defect is secondary to the accumulation of cholesterol (Puri et al., 1999) and glycosphingolipids (te Vruchte et al., 2004).

NP-C also shares neuropathological features with the glycosphingolipidoses. Ectopic dendritogenesis and meganeurite formation, which are characteristic of these conditions, are postulated to result from defects in the trafficking of GM2 ganglioside (Walkley, 2004). Ganglioside storage is prominent in the brains of NP-C patients (Zervas et al., 2001a), and there is evidence from murine NP-C that, in neurons, accumulation of gangliosides rather than cholesterol is the initiating event (Gandre-Lewis et al., 2003).

To investigate the contribution of glycosphingolipid storage to the pathogenesis of NP-C, NP-C mice were treated with the iminosugar miglustat (N-butyldesoxyxojirimycin), an inhibitor of glycosphingolipid biosynthesis (Zervas et al., 2001b). In these animals, reduced glycosphingolipid accumulation was accompanied by delayed onset of symptoms and increased lifespan. This novel therapeutic approach, termed substrate reduction therapy (SRT) (Lachmann and Platt, 2001), has been used successfully in mouse models of other glycosphingolipid storage disorders (Jeyakumar et al., 1999; Platt et al., 1997) and in patients with type 1 Gaucher disease (Cox et al., 2000), for which miglustat has recently been licensed (Lachmann, 2003). Clinical trials in patients with NP-C, type 3 Gaucher disease and late-onset Tay—Sachs disease are underway.
Here we report the correction of the intracellular lipid-trafficking defect by the use of miglustat in an adult patient with NP-C.

Materials and methods

Determination of miglustat concentration in plasma and cerebrospinal fluid

Samples of plasma and CSF (200 µl) were centrifuged to remove particulate material, spin filtered using a 10,000 MW cut-off filter and miglustat extracted using a combination of SCX and C18 solid phase cartridges as previously described (Mellor et al., 2000). High performance cation-exchange chromatography (Dionex, UK) was used to separate aliquots containing miglustat and an internal standard (2-methylbutyl-DNPy), and, following pulsed-amperometric electrochemical detection, compound concentration was determined by measuring relative peak areas (Mellor et al., 2000).

Cholera toxin binding assay on myeloid cells

Cell surface GM1 expression was measured on defined populations of leukaocytes by the flow cytometric quantification of cholera toxin binding (Platt et al., 1994).

Isolation of human peripheral blood B lymphocytes

B lymphocytes were separated from mononuclear cells prepared from peripheral venous blood using MACS CD19 MicroBeads (Miltenyi Biotec Ltd.) according to the manufacturer’s instructions. B lymphocytes were isolated from the patient at various time points and also from five normal control subjects (two females and three males, age range 23–46, taking no prescribed medication).

Lysotracker® staining and quantification

Isolated B lymphocytes were incubated with 200 nM Lysotracker® green (Molecular Probes) for 15 min in the dark, centrifuged at 2000 × g for 1 min in a Heraeus Biofuge A desktop centrifuge and then resuspended in 0.5 ml of FACS buffer. After running on a Beckton Dickinson FACScal flow cytometer, analyses were performed using Cellquest software.

Assessment of fluid phase endocytosis by uptake of horseradish peroxidase

Horseradish peroxidase (HRP) assays were carried out on isolated B lymphocytes as previously reported (Gu et al., 1997). B lymphocytes (approximately 5 µg total protein) were incubated with 100 µl of prewarmed 3 mg/ml HRP type VI (Sigma) in Hepes-buffered DMEM and 2 mg/ml BSA for 2 h at 37°C. Cells were spun down and the pellet washed six times with 1 ml of ice-cold PBS containing 5 mg/ml BSA. Cells were frozen until day of assay. Cells were resuspended in 100 µl of Sigma cell dissociation solution containing 0.1% Triton X-100; 5, 10 and 15 µl of this solution was added to a microtitre plate and made up to a volume of 100 µl with cell dissociation solution (no TX-100). One hundred microliters of Pierce immunopure TMB substrate reagent peroxidase assay mixture was added to each well and left until blue colour developed when 100 µl of 1 M sulphuric acid was added and the absorbance read at 450 nm.

Assessment of BODIPY-LacCer trafficking

Isolated B lymphocytes were pulse-labelled with 13 µM BODIPY-LacCer for 1 h followed by a 90-min chase in medium containing 10% FCS and observed using a Zeiss Axioplan 2 fluorescence microscope as described previously (Chen et al., 1999; Silence et al., 2002).

Results

Case history

The patient had initially presented in 1998, at the age of 31, after a fall. There was a history of clumsiness and poor coordination since childhood. Over the preceding few years, she had developed poor balance, slurred speech and memory impairment. There were dystonic movements of the upper limbs, marked cerebellar dysarthria and ataxia, a selective supranuclear palsy of downgaze and a moderate degree of cognitive impairment. The diagnosis of NP-C was made by fibulin staining of cultured skin fibroblasts to detect cholesterol storage (Vanier and Millat, 2003).

In July 2003, funding to treat the patient off-license with miglustat was obtained from her local Primary Care Trust. Miglustat 100 mg once daily was started. On this dose, plasma miglustat levels have averaged 0.44 ± 0.18 µg ml⁻¹. The only significant unwanted effect has been the loss of 5.5 kg in weight in the first 6 months of treatment (a recognised effect of miglustat; Lachmann, 2003).

Her clinical condition has remained stable over this period. Clinical monitoring of response in a slowly progressive neurodegenerative condition like NP-C is not straightforward. Although some deficits may relate to impaired neuronal function due to abnormal lipid storage, and might be improved by treatment, others are likely due to irreversible loss of neurons. If substrate reduction therapy can slow or prevent further neuronal death, then it should delay or arrest disease progression—as in the NP-C mouse (Zervas et al., 2001b). Neurological improvement might also occur as a result of the plasticity of the brain. We have not observed any progression of disease over this period of treatment. Although this could represent a beneficial effect of therapy, periods where clinical progression plateaus are observed in NP-C and related conditions. At this time we remain cautiously optimistic about her long-term clinical responses.

In other glycosphingolipidoses, it is possible to monitor response to treatment using surrogate markers of disease activity as well as clinical signs but no biomarkers of NP-C activity have been reported. In Gaucher disease, serial assay of plasma chitotriosidase gives a sensitive measure of response to enzyme replacement therapy (Hollak et al., 1994). In Fabry disease, monitoring of Gb3 concentrations in urinary sediment and tissue biopsy specimens has been used (Desnick et al., 2003). Here we show that the biochemical response of NP-C to substrate reduction therapy can be evaluated by monitoring the function of the endosomal–lysosomal system in peripheral blood cells.

To accomplish this, it was necessary to define a homogeneous population of cells that can readily be isolated and assayed immediately without the need for in vitro culture. Peripheral resting
B lymphocytes are one such population and we have developed methods to monitor lysosomal storage, fluid phase endocytosis and lipid trafficking in these readily obtained peripheral blood cells.

Inhibition of glycolipid synthesis

We have confirmed that treatment with miglustat has resulted in glycolipid depletion in our patient by serial measurement of surface GM1 expression on a subset of CD13-positive peripheral blood myeloid cells. Measurements after 2, 3, 4 and 6 months showed an average reduction in GM1 levels of 56% ± 15.2%.

Endosomal–lysosomal storage

To determine whether substrate reduction therapy affects storage in the endosomal–lysosomal system, we have monitored the volume of the late endosomal and lysosomal compartments in peripheral B lymphocytes isolated from the patient at baseline and serially after treatment with miglustat was started. LysoTracker® (Molecular Probes) is a fluorescent, cell-permeable probe that selectively accumulates in acidic organelles. After staining with LysoTracker®, B lymphocytes prepared from the peripheral blood of our patient before miglustat showed sixfold higher mean fluorescence than control B lymphocytes (Fig. 1), indicating marked expansion of the late endosomal and lysosomal compartments consequent upon pathological lipid storage. After treatment with miglustat, LysoTracker® staining of these cells has decreased towards normal, indicating a reduction in lipid storage.

![Graph showing reduction in lysosomal storage](image1)

**Fig. 1.** Reduction in lysosomal storage with substrate reduction therapy as assessed by FACS analysis of LysoTracker®-stained peripheral blood B lymphocytes. Results are plotted as a percentage of the mean fluorescence value of LysoTracker®-stained control B lymphocytes (14097 ± 1617, n = 4).

![Graph showing increase in endosomal uptake](image2)

**Fig. 2.** Increase in endosomal uptake of the fluid-phase marker horseradish peroxidase by peripheral blood B lymphocytes with substrate reduction therapy.

![Images showing inhibition of glycolipid synthesis](image3)

**Fig. 3.** Correction of abnormal trafficking of BODIPY-LacCer in peripheral blood B lymphocytes with substrate reduction therapy. Sets of fluorescence images of BODIPY-LacCer-labelled B lymphocytes are shown in a to d. For each set, image i is a composite showing representative cells from the time point and image ii is a high resolution view of a typical single cell. (a) In peripheral blood B lymphocytes from a normal volunteer, BODIPY-LacCer is trafficked primarily to the Golgi. (b) In peripheral blood B lymphocytes from the patient with NP-C before commencement of substrate reduction therapy, BODIPY-LacCer is trafficked primarily to vesicular structures resembling late endosomes and lysosomes. (c) In peripheral blood B lymphocytes from the patient with NP-C after 3 months of substrate reduction therapy, there is increased trafficking of BODIPY-LacCer to the Golgi. (d) In peripheral blood B lymphocytes from the patient with NP-C after 6 months of substrate reduction therapy, there is further normalisation of the trafficking of BODIPY-LacCer.
Fluid-phase endocytosis

One way of measuring the function of the endocytic pathway is to determine the uptake of a fluid-phase marker such as horseradish peroxidase into cells. In an in vitro model of NP-C, this assay reveals arrested transport of fluid-phase cargo to late endosomes and lysosomes (Mayran, 2003). B lymphocytes taken from our patient at baseline showed reduced fluid-phase uptake compared with control cells (Fig. 2). With the introduction of SRT, there has been progressive improvement in uptake to levels that are above the normal range. This overshoot may relate to the observation that substrate-reduction therapy with miglustat can, in vitro, lead to a slight stimulation of endosomal uptake (Silence, 2002; te Vrugte, 2004).

Trafficking of fluorescently labelled lipid

As discussed above, cultured fibroblasts from patients with NP-C and other glycosphingolipidoses show abnormalities in the intracellular trafficking of lipids (Chen, 1999). In pulse-chase experiments, fluorescently labelled lactosylceramide (BODIPY-LacCer) accumulates in endosomes and lysosomes rather than being targeted to the Golgi as it is in normal cells. We have adapted this trafficking assay for use with peripheral blood B lymphocytes.

Fig. 3a shows BODIPY-LacCer trafficking to the Golgi in peripheral blood B lymphocytes purified from a normal volunteer. When the same assay was performed on the patient before SRT was started (Fig. 3b), the fluorescent lipid was misdirected to endosomes and lysosomes. After 3 months (Fig. 3c) and 6 months (Fig. 3d) of miglustat therapy, there has been progressive normalisation of the lipid-trafficking abnormality.

Discussion

The concept of substrate reduction therapy in the glycosphingolipid storage diseases has been validated by clinical trials in Gaucher disease (Cox, 2000). Here we show for the first time that depletion of glycosphingolipids by miglustat treatment can reduce pathological lipid storage, improve endosomal uptake and normalise lipid trafficking in cells of a patient with the neurodegenerative disease, NP-C.

Historically, NP-C has been considered to be a cholesterol storage disorder. Although cholesterol-lowering therapy can reduce storage of unesterified cholesterol, it has not produced clinical benefits in NP-C patients (Patterson, 1993, 2001) or in animal models of NP-C (Erickson, 2000). Cholesterol storage contributes to the abnormal lipid trafficking, which is seen in the glycosphingolipidoses and in NP-C (Puri, 1999), but in primary glycosphingolipid storage disorders, the accumulation of cholesterol is secondary to that of glycosphingolipids (Puri, 2003). The demonstration that treatment with miglustat, which has no direct effect on cholesterol metabolism, corrects the abnormal lipid trafficking seen in B lymphocytes in NP-C indicates that glycosphingolipid accumulation, rather than cholesterol storage, is also the primary pathogenetic event in NP-C.

To have clinically significant effects, it will be necessary to inhibit glycosphingolipid synthesis in the brain. Miglustat is a small, nontoxic molecule that is able to cross the blood-brain barrier; it has therapeutic efficacy in mouse models of NP-C and other glycosphingolipidoses (Jeyakumar et al., 1999; Platt et al., 1997; Zervas et al., 2001). The concentration of miglustat in the CSF of our patient after 7 months of treatment was 0.122 ± 0.012 µg mL⁻¹, 20% of that measured in a paired plasma sample (0.603 ± 0.024 µg mL⁻¹). This bioavailability of miglustat in the human brain compares favourably with that in mice (unpublished data).

Miglustat has been shown to delay symptom onset and prolong life in a murine model of NP-C (Zervas et al., 2001). The npc1 mutation in these mice results in production of a severely truncated protein, which lacks the sterol-sensing domain (Lofthus, 1997). In human NP-C, homozygosity for mutations affecting this domain is universally associated with the most severe, infantile-onset form of disease (Vanier and Millat, 2003). Therefore, in these mice, which are effectively null mutants, the best possible result of substrate reduction therapy would be a reduction in the rate of accumulation of glycolipid and a slowing of the inevitable clinical decline. In juvenile and adult-onset human disease, it is predicted that there will be some residual NPC1 activity and in this situation treatment with miglustat may be able to reduce the glycolipid burden on the endosomal–lysosomal system to a point where cellular homeostasis can be restored. In these patients, we would expect substrate reduction therapy to be more effective with the potential to reverse glycolipid storage and arrest the disease process. The ongoing clinical trial of miglustat in NP-C will attempt to demonstrate directly an effect on clinical phenotype by using horizontal saccadic velocity as a marker of disease progression.

Although it is only licensed for use as a second line agent in type 1 Gaucher disease, in which enzyme replacement therapy is the preferred treatment, miglustat also has potential in the management of other glycosphingolipidoses that affect the brain and for which no effective treatments are currently available (e.g., type 3 Gaucher disease, Tay–Sachs disease, Sandhoff disease and GM1 gangliosidosis) (Lachmann, 2003). In their late-onset adult forms, these diseases, like NP-C, are slowly progressive and it is likely that long-term administration of substrate reduction therapy will be required before a measurable clinical response is seen. Methods that allow monitoring of functional defects at the level of the individual cell, such as those described here, will be valuable for therapeutic monitoring in these patients.

Correction of functional endosomal defects due to glycosphingolipid storage in cells from an NP-C patient by miglustat justifies the further investigation of substrate reduction therapy in patients with this devastating and, at present, untreatable neurodegenerative disease.

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Case study

Treatment of cataplexy in Niemann–Pick disease type C with the use of miglustat

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\textbf{Abstract}

Cataplexy is the sudden muscle weakness brought on by strong emotions, particularly joking, laughter, or anger. Cataplexy may involve only certain group of muscles or the entire voluntary musculature. In rare cases, symptoms of cataplexy can be seen during the course of some inherited diseases (Niemann–Pick type C (NPC), Prader–Willi syndrome, myotonic dystrophy, Norrie disease). We report the successful use of miglustat, a reversible inhibitor of the enzyme glucosylceramide synthase, approved for use in Gaucher’s disease, and which catalyses the first step in the biosynthesis of most glycosphingolipid, in a boy with NPC with cataplexy. A 9-year-old boy was admitted for assessments of frequent “drop attacks” while laughing. The filipin fluorescence tests of cultured skin fibroblasts revealed massive accumulation of unesterified cholesterol, confirming the diagnosis of NPC disease. Molecular studies confirmed the diagnosis of NPC too. After approval from the bioethics committee, miglustat was initiated on the child at 100 mg three times a day. Cataplectic attacks disappeared completely after 6 months on treatment, and patient continues to be in remission from the cataplectic attacks at 16 months follow-up. There was no further progression of neurological signs or symptoms or splenomegaly, with some improvement in cognitive function as well as social, affective and attention problems, up-gaze, and gait. Miglustat was well tolerated with no side effects observed. In summary, this is the first report of miglustat treatment of cataplexy in NPC. Long-term follow-up for continuing efficacy and tolerability in a larger cohort with NPC is needed to substantiate our observation.

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1. Introduction

Niemann–Pick type C (NPC) disease is an autosomal recessive disorder characterized clinically by neonatal jaundice, ataxia, vertical gaze palsy, dystonia, hepatosplenomegaly and progressive neuro-cognitive decline.1,2

NPC has an extremely heterogeneous clinical presentation.1,2,3 The most common (50–70%) are the late-infantile and the juvenile neurologic onset forms.3,4

Poor school performance and/or behavioral problems due to intellectual impairment and impaired fine motor movements of extremities is often the first symptom in patients with juvenile onset.5 Organomegaly may be present.6,7 Accompanying or later symptoms include ataxia and dysarthria. Cataplexy with or without narcolepsy is observed in about 20% of the cases. Supranuclear vertical gaze palsy8-10 is almost invariably present and often obvious.

The age at onset of neurological symptoms has a major influence on disease progression; if neurological symptoms arise early in life, the rate of deterioration is generally faster and premature death occurs sooner.1,2,5,7

The prevalence in Western Europe has been estimated to be approximately 0.0008-0.0007% of live births.1,2

The disease is caused by the autosomal recessive inheritance of mutations in either of two genes, NPC1 (18q11-q12) (95% of patients) or NPC2 (14q24-3),1,2 which encode proteins involved in the regulation of normal intracellular lipid trafficking through sequential activities within a common pathway.1,2,3,9

Cataplexy is the sudden muscle weakness brought on by strong emotions, particularly laughing, or anger.12-14 Cataplexy may involve only certain groups of muscles or the entire voluntary musculature.15 Preservation of consciousness and intact memory are distinctive features.15 The duration of each cataplectic attack usually ranges from a few seconds to 3 min.12 In early childhood, attacks of cataplexy may be confused with atonic seizures (drop attacks).12,15

Cataplexy represents appearance of REM sleep atonia during wakefulness.16 Many of the same cell populations in the pons and medulla that are tonically active only during REM sleep in normal individuals become active during cataplexy.17,18 Cataplexy is associated with an inhibition of monoaminergic H-reflexes and of the multisynaptic tendon reflexes.19 Muscle atonia in cataplexy is produced by direct stimulation of pontomedullary reticular formation neurons that produce inhibitory postsynaptic potentials at the level of the anterior horn cell.19

Cataplexy is a unique feature of narcolepsy.15,20,21 In rare cases, symptoms of cataplexy can be seen during the course of some inherited diseases (NPC, Prader–Willi syndrome, myotonic dystrophy, Norrie disease). There are also known as examples of symptomatic cataplexy.22-24

The treatment of cataplexy in NPC has been disappointing with variable results to use of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), or sodium oxybate.15

We report the successful use of miglustat, a reversible inhibitor of the enzyme glucosylceramide synthase which catalyses the first step in the biosynthesis of most glycosphingolipid in cataplexy with NPC.

2. Case report

A 9-year-old boy was admitted for assessments of frequent “drop attacks” while laughing, previously misdiagnosed and treated as seizures. The boy was born an uncomplicated delivery to non-consanguineous married parents with no significant family history. Developmental evaluation was significant for mild cognitive and motor delay, with unsteady and “clumsy” gait.

The child was admitted at age 7 years with worsening muscle weakness and poor motor coordination, along with new onset of frequently dropping to the floor while laughing at jokes. Consciousness remained preserved during these episodes. No history of hypersonnia, hypnagogic hallucinations, sleep paralysis, or any nocturnal automatic behavior was noted. Neurological examination was significant for mild cognitive delay, truncal ataxia, broad-based gait, disquiet intention tremor of hands, poor motor coordination, hypotonia, and wasting of muscles of arms and legs. No visceromegaly was evident during this admission. EEGs during these drop attacks failed to show any epileptiform activity. EMG showed a myopathic pattern of abnormality. MRI brain and spine and muscle enzymes were normal. Polysomnography showed fragmented sleep patterns; multiple sleep latency testing was normal, without showing any sleep onset REM, and with normal mean sleep latency. HLA testing and CSF orexin levels were not available for testing, and hence were not performed. A diagnosis of symptomatic cataplexy was made and clomipramine in doses of 10 mg in two doses was started. There was significant improvement in the drop attacks with recurrence in their frequency 5 months later.

The child was admitted a second time after one year at 8 years of age with increased number of cataplectic attacks, progressive motor dysfunction and cognitive decline. Neurological examination was significant for new onset of vertical gaze palsy, but otherwise unchanged from the previous exam. Abdominal examination showed mild splenomegaly. MRI brain and MRI spectroscopy were normal. Activity of lysosomal enzymes in white blood cells was normal. The filipin fluorescence tests of cultured skin fibroblasts revealed massive accumulation of unesterified cholesterol, confirming the diagnosis of NPC disease.

Molecular studies confirmed the diagnosis of NPC. Two NPC1 gene mutations: a previously described missense mutation (c.3433T>C p.W1145R) located on exon 22 and a novel deletion of one nucleotide c.2913delG, located on exon 20, were identified. The nature of c.2913delG (i.e., a frameshift and a premature stop codon or nonsense-mediated mRNA decay) suggested that this mutation was probably contributory. In an attempt to prove compound heterozygosity for the mutations, analysis of parents showed an NPC1 gene mutation c.3433T>C in mother, and NPC1 gene mutations c.2913delG in father. The younger sister of proband had no mutations detected.

In July 2008, treatment with miglustat was initiated. In Poland miglustat was approved for use in Gaucher’s disease
type 1 (GD1). After approval from the bioethics committee, miglustat was initiated on the child at 100 mg tid.

On follow-up at 3 months on miglustat, there was significant reduction in frequency of cataplectic attacks, which disappeared completely after 6 months on treatment, and patient continues to be in remission from the cataplectic attacks at 16 months follow-up. There was no further progression of neurological signs or symptoms or splenomegaly, with some improvement in cognitive function as well as social, affective and attention problems, up-gaze, and gait.

3. Discussion

This is the first report of successful treatment cataplexy in NPC with the use of miglustat.

TCAs form the first line of medication available for the treatment of cataplexy.\textsuperscript{25} The anti-cataplectic effect is rapid; however, rebound cataplexy typically occurs if intake is abruptly interrupted.\textsuperscript{26} SSRIs are effective, but higher doses than those used for TCAs are often needed.\textsuperscript{27,28} Sodium oxybate may be the drug of choice because of the opportunity to treat both symptoms of narcolepsy (EDS and cataplexy) at the same time.\textsuperscript{29}

There are few reports on successful treatment of symptomatic cataplexy. Smit and colleagues were the first to report successful treatment of cataplexy in NPC.\textsuperscript{31} Hawari et al. reported complete resolution of the drop attacks in patient with Coffin-Lowry syndrome with use of sodium oxybate.\textsuperscript{32}

Venkova et al. suggested that lysosomal storage products in NPC in the hypocretin-containing cells impair their function and are responsible for cataplexy.\textsuperscript{33} The concept of substrate reduction therapy in the glycosphingolipid storage diseases has been validated by clinical trials in GD.\textsuperscript{34} Miglustat treatment delayed onset of symptoms and increased lifespan in animal model of NPC.\textsuperscript{35,36} Lachmann et al.\textsuperscript{37} reported positive results with miglustat use in an adult with NPC. Chen et al. reported effective treatment in two children with NPC.\textsuperscript{38}

The most recent studies were presented by Patterson et al.\textsuperscript{49,50} In juvenile and adult-onset human disease, it is predicted that there will be some residual NPC1 activity and in this situation treatment with miglustat may be able to reduce the glycolipid burden on the endosomal-lysosomal system to a point where cellular homeostasis can be restored.\textsuperscript{39}

Miglustat is approved in the US and EU for the treatment of adult patients with mild-to-moderate GD1 disease. It is also approved in the EU for the treatment of progressive neurological manifestations in adult and pediatric patients with NPC.\textsuperscript{49}

The recommended dose for the treatment of adult with GD1 is 100 mg tid. The usual dose in adult NPC patients was 200 mg tid.\textsuperscript{40} The dose in pediatric NPC patients was adjusted according to body surface area in pediatric NPC patients.\textsuperscript{40} In our patient 100 mg tid was used.

Gastrointestinal events, mainly intermittent diarrhea have been observed in more than 80% of patients treated with miglustat.\textsuperscript{30,34} Weight loss was mild; most prevalent in the first year of treatment.\textsuperscript{34} Mild-to-moderate tremor was reported in approximately 30% of patients in all miglustat trials combined.\textsuperscript{34} Peripheral neuropathy has been reported in GD1 patients.\textsuperscript{35} The most frequently reported in NPC children were diarrhea in 67%, flatulence in 33% and weight loss in 25%.\textsuperscript{10} There were no significant side effects observed in our patient during 16 month of therapy.

In summary, this is the first report of miglustat treatment of cataplexy in NPC. Long-term follow-up for continuing efficacy and tolerability in a larger cohort with NPC is needed to substantiate our observation. In addition, early initiation with miglustat therapy should be considered in an attempt to reduce accumulation of lysosomal products in the brain associated with NPC with cataplexy.\textsuperscript{39}

References

Diagnostic and treatment implications of psychosis secondary to treatable metabolic disorders in adults: a systematic review

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Abstract

Objective: It is important for psychiatrists to be aware of certain inborn errors of metabolism (IEMs) as these rare disorders can present as psychosis, and because definitive treatments may be available for treating the underlying metabolic cause. A systematic review was conducted to examine IEMs that often present with schizophrenia-like symptoms.

Data sources: Published literature on MEDLINE was assessed regarding diseases of homocysteine metabolism (DHS; cystathionine beta-synthase deficiency [CBS-D] and homocystinemia due to methyltetrahydrofolate reductase deficiency [MTHFR-D]), urea cycle disorders (UCD; acute porphyria [POR], Wilson disease [WD], cerebrohepato-xanthomatosis [CTX] and Niemann-Pick disease type C [NPC-C]).

Study selection: Case reports, case series or reviews with original data regarding psychiatric manifestations and cognitive impairment published between January 1967 and June 2012 were included based on a standardized four-step selection process.

Data extraction: All selected articles were evaluated for descriptions of psychiatric signs (type, severity, natural history and treatment) in addition to key disease features.

Results: A total of 611 records were identified. Information from CBS-D (n = 2), MTHFR-D (n = 3), UCD (n = 8), POR (n = 12), WD (n = 11), CTX (n = 14) and NPC-C publications (n = 9) were evaluated. Six non-systematic literature review publications were also included. In general, published reports did not provide explicit descriptions of psychiatric symptoms. The literature search findings are presented with a didactic perspective, showing key features for each disease and psychiatric signs that should trigger psychiatrists to suspect that psychotic symptoms may be secondary to an IEM.

Conclusion: IEMs with a psychiatric presentation and a lack of, or sub-clinical, neurological signs are rare, but should be considered in patients with atypical psychiatric symptoms.

Keywords: Inborn errors of metabolism, Organic psychosis, Schizophrenia-like symptoms, Atypical psychosis

Introduction

A range of medical conditions may be associated with schizophrenia-like psychosis [1]. The landmark review of psychosis associated with organic disorders by Davison and Bagley, which utilized the 1957 WHO operational criteria for schizophrenia, highlighted a number of disorders where the association with psychosis significantly exceeded chance [2]. Many of the disorders identified showed pathology in the temporal lobe and diencephalon.

A large study of 268 consecutive patients with first-episode psychosis found that 6% had organic cerebral disease that was potentially causally linked with psychiatric symptoms [3], which emphasizes the importance of a thorough diagnostic evaluation to exclude underlying medical illness at first presentation. Recently, more than 60 different congenital conditions associated with psychosis were reviewed. Interestingly, some of them are not
associated with dysmorphia, mental retardation or prominent neurological features that may otherwise trigger a search for an organic cause of illness [4].

The diagnosis of medical or neurological illnesses underlying psychosis is of great importance as many of these conditions are progressive or fatal, associated with significant additional medical morbidity, and may be partially or entirely reversible with definitive treatment. Inborn errors of metabolism (IEMs) represent a particular focus for research as they are frequently under-detected or misdiagnosed, a number are treatable, and new diagnostic methods and therapies have become available.

IEMs are a group of diseases that generally result from the absence or deficiency of an intracellular component of a metabolic pathway (usually, but not exclusively, an enzyme), which may lead to altered intracellular synthesis and catabolism [5]. There are hundreds of IEMs, and many remain poorly characterized. Most result in clinical disease due to the accumulation of substances that are toxic, or interfere with, normal cellular function, or which may be due to the effects of a reduced ability to synthesize essential compounds.

The overall incidence of IEMs has been estimated to be approximately 40 cases per 100,000 live births [6]. However, this rate may be an underestimation, as new disorders continue to be discovered and characterized and because diagnostic techniques continue to improve in sensitivity and accuracy.

Up to 80% of IEMs are diagnosed during childhood, but an increasing recognition of late-onset presentations has recently raised awareness and diagnoses of adult-onset forms [7]. A number of adult-onset IEMs are associated with schizophrenia-like symptoms, including diseases of homocysteine metabolism (DHM), urea cycle disorders (UCD), porphyria (POR), Wilson disease (WD), cerebrotendinous xanthomatosis (CTX) and Niemann-Pick disease type C (NP-C) [7].

This article reports findings from a systematic literature review and provides a guide for the diagnosis of treatable IEMs associated with schizophrenia-like symptoms based on the review findings. The major features of IEMs that can be associated with psychosis are summarized, and a diagnostic algorithm to assist psychiatrists in the detection of atypical symptoms is proposed that may be related to underlying IEMs.

Methods
Review scope
A meeting was held in mid-2012 to decide which IEMs associated with psychosis are currently treatable, with the aim of conducting a systematic bibliographic search to address the clinical challenges associated with these conditions. Based on a consensus reached during that meeting, the following seven IEMs were chosen as a focus for this review: homocysteinemia due to methylenetetrahydrofolate reductase deficiency (MTHFR-D), cystathionine beta-synthase deficiency (CBS-D), UCD, POR, WD, CTX and NP-C.

Literature search methodology and data sources
The public MEDLINE database was searched according to a standard four-step protocol, as described in the following sections and summarized in Figure 1.

Identification
All terms, including complete names and abbreviations for MTHFR-D, CBS-D, UCD, POR, WD, CTX and NP-C were searched alongside the generic tag ‘psy’ using EndNote X5 software (Thomson Reuters), which enabled the identification and deletion of any duplicates. In total, 708 potentially relevant records published between January 1967 and June 2012 were identified, from which 97 duplicate records were removed. Seven separate EndNote databases were created – one for each IEM. The numbers of records for each IEM database were: MTHFR-D (n = 12); CBS-D (n = 6); UCD (n = 15); POR (n = 75); WD (n = 451); CTX (n = 15); and NP-C (n = 31). Six non-systematic literature reviews were also identified and included [7-12]. A total of 611 records were collated for screening.

Screening
Two groups worked separately in screening abstracts from relevant articles from the literature review (Group 1: M. Walterfang and H.H. Kluenemann. Group 2: O. Bonnot, D. Cohen, Sylvie Tordjman and F. Sedel). Case reports, case series with original data regarding psychiatric manifestations and cognitive impairments, and previous reviews containing relevant data were selected. Articles were excluded from full text analysis (see ‘Eligibility’ stage) according to the following exclusion criteria: 1) the article mentioned psychiatric manifestations without data pertaining to any of the seven chosen treatable diseases; 2) an unrelated article, mentioning an IEM without describing psychiatric presentations; 3) literature reviews not containing any new data and; 4) data already reported elsewhere. Screening excluded 26 of the initial records from the POR database and 400 records from the WD database. In cases where the two analysis groups did not agree, records were kept and included in the next step.

Eligibility
The same two analysis groups accessed the full texts of all remaining articles (n = 185) and checked them further for eligibility according to the same exclusion criteria used in the abstract screening stage. The numbers of
articles considered eligible after this process were: MTHFR-D (n = 12), CB5-D (n = 6), UCD (n = 15), POR (n = 49), WD (n = 51), CTX (n = 15) and NP-C (n = 31). The six previous reviews were also kept.

Inclusion
Among the eligible records, information on key IEM disease features as well as psychiatric manifestations was included from the following numbers of publications, per database: MTHFR-D (n = 3); CB5-D (n = 2); UCD (n = 8); POR (n = 12); WD (n = 11); CTX (n = 14) and; NP-C (n = 9). Including the six previous reviews, this brought the final total of source articles to 59.

Results
To understand the metabolic pathways implicated in these disorders, we will provide an explanation in the text referring directly to the cited diseases. For figures and complete presentation, we refer the reader to the KFGG website which illustrates these pathways in detail [13].

Disorders of homocysteine metabolism (DHMs)
CB5-D and MTHFR-D are two key DHMs that commonly feature psychiatric signs.

Key features of CB5-D
Homocysteinuria due to CB5-D is characterized by the involvement of the ocular, skeletal, central nervous and vascular systems. Prevalence is estimated around 1/3,440,000 birth in countries were systematic search of CB5 deficiency is provided for every newborn, however recent data from systematic search for CB5 mutation show important prevalence up to 1/20,000 [14]. Two articles that addressed psychiatric symptoms and psychosis were identified [15,16]. The disease is an autosomal recessive disorder of methionine metabolism, caused by mutations in the CB5 gene (21q22.3). CB5 normally converts homocysteine to cystathionine in the trans-sulfuration pathway of the methionine cycle, and requires pyridoxal 5-phosphate as a cofactor. The other two cofactors involved in methionine remethylation include vitamin B12 and folic acid. Clinical diagnosis of CB5-D is confirmed by blood amino acid analysis (including total homocysteine measurement), assays of CB5 enzyme activity, or screening for CB5 mutations.

Patients appear normal at birth but display a progressive disease course if left untreated. Eye anomalies include ectopia lentis (in 85% of cases) and high myopia. Skeletal changes include genu valgum and pes cavus, followed by dolichostenomelia, pectus excavatum or carinatum, kyphoscoliosis and osteoporosis. A Marfan-like body habitus may occur, with tall stature and arachnodactyly. Thromboembolism affecting both large and small arteries and veins is the most striking cause of morbidity and mortality, and affects 25% of individuals by the age of 15 years. While some individuals have a normal IQ, mental retardation is common and, when present, may progress if the disorder is left untreated. Brittle hair and livedo reticularis have also been reported.

Psychiatric signs associated with CB5-D
In one of the few studies in this field, psychiatric illness was found in 51% of cases overall, with symptoms falling into four diagnostic categories: episodic depression (10%),
chronic disorders of behavior (17%), obsessive-compulsive disorder (5%), and personality disorder (19%) [15]. In the same study, aggressive behavior and other conduct disorders were particularly common among patients with mental retardation and those who were nonresponsive to vitamin B6. In some cases, psychiatric symptoms may be the initial presenting symptom with no neurological signs [16].

Key features of MTHFR-D

MTHFR-D is another autonomic recessive trait, and is caused by mutations in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene (1p36.3). MTHFR deficiency results in abnormal intracellular folic acid metabolism, and prevents reduction of 5–10 methylenetetrahydrofolate to 5-methyltetrahydrofolate – the methyl donor for the remethylation of homocysteine into methionine. As a result, the disorder leads to MTHFR-D and consequently to homocysteinuria and homocystinuria. To our knowledge, prevalence is unknown.

The onset of MTHFR-D usually occurs during the first year of life, characterized by severe neurological signs, recurrent apnea, microcephaly and convulsions without megaloblastic anemia. However, there are some forms with onset during childhood, adolescence or adulthood that present with mental regression, ataxia and schizophrenia-like psychosis. Other symptoms such as subacute degeneration of the spinal cord have been reported.

Diagnoses of DHM are made through analysis of amino acids by chromatography and total plasma homocysteine measurement; an elevated level is defined at >100 micromol/L [17]. Methionine levels may be useful, as they are decreased in MTHFR-D and increased in Cbl-D.

There are Currently three recognized treatment modalities for DHM. For pyridoxine-responsive patients, treatment with pharmacological doses of pyridoxine combined with folic acid and vitamin B12 supplements is recommended. In pyridoxine non-responsive patients, the treatment should comprise a methionine-restricted, cysteine-supplemented diet in combination with the pyridoxine, folic acid and vitamin B12 supplementation. Betaine anhydrous is a methyl donor that may lead to lowering of homocysteine levels in MTHFR-D patients, and can be used as an adjunct to such a diet.

Homocysteine is cleared by transulfuration to cysteine and glutathione, an important antioxidant. Transulfuration requires vitamins B6 and B12. Treatment with vitamin B6, a precursor of homocysteine, can be effective in treating psychiatric symptoms if instituted early [7].

Psychiatric signs associated with MTHFR-D

Three articles were identified from the systematic literature review [18-20]. Psychiatric symptoms are not uncommon in MTHFR-D, and may be the presenting symptom [18]. Their onset may be acute or may follow a more insidious course. Acute manifestations occur mainly after surgery, and present with visual and/or auditory hallucinations, thought disorder and delusions [18]. Roze and colleagues describe two siblings (16- and 24-year-old women) with presumed late-onset MTHFR-D. Three years after the diagnosis of her older sister, the 16-year-old sister was initially seen with a 3-month history of dissociative symptoms and delusions of persecution with visual and auditory hallucinations. One month prior to hospital admission, she had also developed an unsteady gait and urinary incontinence. She was previously healthy and had been an average student. Physical examination on admission showed only an arreflexia paraparesis with an extensor plantar response on the right side and impaired vibration and position sense in the lower limbs. Diagnosis was made because her sister was known to have the disease. Combined daily treatment with intravenous hydroxocobalamin (2 mg), oral betaine (9 g), L-carnitine (3 g), and folic acid (10 mg) was started, and a dramatic clinical improvement, with the recovery of arm function and the disappearance of psychotic features and lethargy, was observed after 6 weeks.

In a different approach, a recent meta-analysis examining the association between MTHFR gene polymorphisms and psychiatric disorders demonstrated a strong association between the MTHFR C677T gene variant and unipolar depression, schizophrenia and bipolar disorder, with odds ratios of 1.36, 1.44 and 1.82, respectively [20]. Notably, the metabolic syndrome secondary to antipsychotic medication may be more frequent in patients with reduced MTHFR activity associated with schizophrenia-like psychosis [21].

It is well documented that aberrant methylated compounds are linked to mental state and behavior. A recent review of the ‘one-carbon metabolism hypothesis’ described a range of factors that can contribute to folate and/or vitamin B12 deficiency [22]. Moreover, folate is a water-soluble B vitamin involved in the synthesis, repair and methylation of DNA, leading to epigenetic regulation of crucial developmental genes implicated in the pathogenesis of schizophrenia [23,24]. Deficiency of B vitamins leads to an increased level of homocysteine, which is a highly toxic metabolite to neural and vascular development [25]. Elevated serum levels of homocysteine have also been shown to be associated with schizophrenia, although the evidence is far from conclusive [26,27].

Urea cycle disorders (UCDs)

Key features

The urea cycle is the metabolic process by which the body eliminates nitrogen. Six enzymes take part in this process; a deficiency of any one of them disrupts this
pathway and results in excess nitrogen accumulating in the body in the form of ammonia. The six UCDs include deficiency of: 1) carbamyl phosphate synthetase; 2) n-acetylglutamate synthetase; 3) ornithine transcarbamylase; 4) argininosuccinic acid synthetase (also called citrullinemia); 5) argininosuccinase acid lyase and; 6) arginase. UCD has an estimated incidence of 1.80000 [28].

If the enzyme deficiency is severe, symptoms will be present at birth and can present as irritability, nausea and vomiting followed by lethargy, seizures and poor muscle tone. If left untreated, patients can develop respiratory distress or fall victim to coma or premature death due to pathological levels of ammonia in the blood.

If the enzyme deficiency is partial, symptom onset may not occur until childhood or adulthood. In such cases, symptoms may include nausea and vomiting associated with headache and a clouded sensorium in the context of infection or a high-protein diet. Medications may worsen or trigger the disease, particularly corticosteroids and sodium valproate.

There is no cure for UCDs, although prompt diagnosis allows measures to be taken that can reduce the consequences of hyperammonemia. Measurement of plasma ammonia is key to the diagnosis of UCDs, and a treatment consisting of a protein-restricted diet and special supplements is essential [29]. In addition, several medications including sodium benzoate, sodium phenylacetate and sodium phenylbutyrate can bind with ammonia and remove it from the circulation. Hemodialysis may represent an alternative treatment, especially in emergency situations [30].

Psychiatric signs

Eight relevant articles were identified in the literature review [31-38]. Arn and colleagues [31] reported a 21-year-old white woman who presented 8 days postpartum with headache and confusion, and became uncommunicative. She was admitted to a psychiatric hospital and diagnosed with postpartum depression. Within 24 hours of admission (11 days postpartum) she became comatose and had generalized tonic-clonic seizures, decorticate posturing, and papilledema. She was treated successfully with hemodialysis and received intravenous sodium benzoate and arginine hydrochloride. Enns and colleagues reported a similar case, suggesting that UCD may present initially with postpartum psychiatric symptoms and may represent an under-recognized cause of 'postpartum psychosis.' [32]

Interestingly, late-onset (between 13 and 48 years of age in our review) UCD may present with behavioral and hallucinatory psychiatric and organic signs, often featuring vomiting, which is clearly a key trigger sign for the consideration of UCD in psychiatric situations [35-37]. Patients may have a history of anorexia and atypical depression [35] or psychosis [36], often with associated confusion [37].

Acute porphyria (POR)

Key features

The PORs comprise a group of eight hereditary metabolic diseases characterized by intermittent neurovisceral manifestations, cutaneous lesions, or the combination of both. All porphyrias are caused by a deficiency in one of the enzymes of the heme biosynthesis pathway. These deficiencies result in an accumulation of porphyrins and/or their precursors – delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) – in the liver or bone marrow. Neurological manifestations are caused by the neurotoxic effects of these precursors, particularly ALA. Prevalence is estimated around 0.54:100 000 [39].

Enzyme deficiencies in the porphyrias result from mutations of the correspondingly coded genes, and transmission of hereditary porphyrias occurs in either an autosomal dominant fashion with weak penetrance, or in a recessive manner with complete penetrance.

Clinical signs of disease usually appear in adulthood, although some porphyrias affect children. Porphyrias are classified into two groups – hepatic and erythropoietic – according to the main location of the metabolic anomaly. Chronic hepatic porphyrias and erythropoietic porphyrias manifest with bulbar cutaneous lesions or acute pain in areas exposed to the sun, without neurological symptoms. However, neuro-visceral attacks occur in patients with acute hepatic porphyrias, manifesting as intense abdominal pain (often associated with nausea, vomiting and constipation), and neurological and psychological symptoms. Two acute hepatic porphyrias (variegated porphyria and hereditary coproporphyria) may also present with cutaneous photosensitivity.

Diagnosis is mainly based on the measurement of porphyrins and their precursors in biological samples such as urine, stools and blood. The key diagnostic procedure is the measurement of ALA and PBG in urine. Genetic counseling should be offered to affected families to identify individuals susceptible to developing and transmitting the disease. Acute attacks should be treated urgently with an injection of human hemin and/or perfusion of carbohydrates.

Psychiatric signs

Twelve relevant articles were included from the systematic literature review. Psychiatric manifestations are widely known and well documented [40-43], occurring in 24–70% of patients in acute porphyria series [44,45]. The most common manifestations reported are delirium, psychosis and depression, with some authors suggesting that 40% of acute porphyrias present with delirium and hallucinations [46].
Some cases are spectacular. For example, Santosh and Mulhotta reported the case of a 13-year-old boy with six episodes of psychosis with various presentations, including delusions, hallucinations, hypomania and catatonia, but with no obvious organic signs [43]. Crimlisk described three noteworthy cases. The first was that of a 53-year-old woman with a history of cognitive decline since the age of 20, and episodes of visual hallucinations, ataxia, abdominal pain and weight loss; diagnosis was achieved after an acute vomiting episode at 53 years of age. A 52-year-old woman with a history of episodic psychiatric disturbance with associated ideas of reference, auditory hallucinations, emotional lability and abdominal pain was also described, with episodes tending to occur pre-menstrually. The third case was a young boy with a history of generalized pain, vesicular rash, fever and nausea, in whom a diagnosis was made when psychiatric symptoms (paranoid schizophrenia) appeared.

Finally, Mandoki and Summer reported a sub-acute psychiatric dysphoric presentation with emotional lability and aggression, as well as headaches and abdominal pain, in a 9-year-old girl who had a history of aggressive behavior and early anorexia [47]. The patient was diagnosed with coproporphyria – a subtype of porphyria in which psychiatric signs (labile mood and psychosis) have occasionally been described among affected children and young adults [47-51].

**Wilson disease (WD)**

**Key features**

WD is an autosomal recessive disorder with a prevalence of 6 per 100,000 of the general population [39]. A mutation in the ATP7B gene coding for a key copper transport protein leads to copper accumulation in the liver, brain, kidney and skeletal system, caused by reduced excretion in the bile [52].

In approximately half of patients, computerized tomography reveals characteristic hypodensities in the basal ganglia [53]. Virtually all patients show magnetic resonance imaging (MRI) abnormalities, including T2-weighted hyperintensities in the thalamus, brainstem and lenticular nuclei [54]. Functional imaging generally shows significant hypometabolism in the lenticular nuclei [55].

Classically, symptoms of WD appear between the ages of 6 and 20 years. Approximately one-third of patients initially present with hepatic disease, one-third with neurological symptoms, and one-third with psychiatric symptomatology. Kayser-Fleischer ring is seen in some patients during ophthalmological examinations. Between one- and two-thirds of patients report psychiatric symptoms at initial presentation [56-58]. Psychiatric signs are present in almost 50% of patients at any one time [59], and present before motor signs in 20% of cases; up to half of patients may be seen initially by a psychiatrist [60].

**Psychiatric signs**

Eleven relevant case reports or case series (psychiatric or general including psychiatric patients) were identified, and data from most of these were included in a large review [57]. Four main psychiatric symptom clusters have been identified: mood and affective change; behavior and personality change; psychosis and; cognitive impairment [61]. Personality changes are very common, particularly irritability and aggression [56,62]. Mood disturbance, including both depression and mania, is the most common formal neuropsychiatric illness [63-67]. Psychosis, delusional states and catatonia, while less frequent in WD, can be extremely disabling [56,57,60,61,68]. Schizophrenia-like symptoms were reported to be present in up to 10% of patients [63], but were less prevalent in one case series (2.4%) [69]. Whilst delusions in WD have been reported to be uncommon [60], a number of psychotic presentations meeting criteria for delusional disorder have recently been described [70-73].

Deteriorating academic performance or work function is another key neurological feature of WD. Neurologically symptomatic patients display a range of cognitive difficulties including impairments of executive function, aspects of memory and visuospatial processing [59,74,75]. In contrast, no such deficits are found in neurologically asymptomatic patients [76]. Lesions within the basal ganglia seem to be of central importance in cognitive change due to their interruption of frontal-subcortical circuits [76,77].

After initiating treatment with chelation therapy, the disease often stabilizes or improves, but disease progression during treatment is more likely for neuropsychiatric symptoms than for hepatic symptoms [78]. Resolution of neuropsychiatric illness following chelation has been reported [67,73,79,80].

The use of neuroleptic medication may be problematic due to the increased risk of movement disorder side effects in the setting of degenerative basal ganglia disease [81-84]. However, some reports suggest the relatively safe use of typical medications such as olanzapine, risperidone, quetiapine and clozapine, which each have a lower propensity to cause movement disorders [72,83,85,86]. Nevertheless, these agents should be used with caution because of the increased risk of agranulocytosis in the presence of hypersplenism or penicillamine treatment.

Treatment of mania with mood stabilizers can be difficult because valproate or carbamazepine may be contraindicated in the presence of significant hepatic impairment [84]. Lithium may also be contraindicated in the presence of renal tubular acidosis [84], although
successful lithium treatment without metabolic compromise has been reported [86,87].

Electroconvulsive therapy (ECT) has been successfully used in cases of catatonia [88], psychosis [89] and depression [90-92].

Depression has been reported as responding to both tricyclic antidepressants and selective serotonin reuptake inhibitors [91-93], although treatment-resistance to traditional antidepressants has also been described [91]. A manic switch in response to antidepressant therapy has also been described in one patient [93].

Cerebrotendinous xanthomatosis (CTX)

Key features

CTX is an autosomal recessive disease of bile acid synthesis. It is caused by mutations in the CYP27A1 gene, which is localized on the long arm of chromosome 2 and codes for the mitochondrial enzyme, sterol-27-hydroxylase. This enzyme is involved in the synthesis of chenodeoxycholic and cholic acids from cholesterol. The metabolic block resulting from the mutant gene causes a progressive storage of cholesterol and its poorly soluble by-product, cholestanol, which is deposited in many tissues including the brain and tendons [94]. A recent review found more than 500 patients with CTX reported worldwide, and identified 50 different mutations in the CYP27A1 gene associated with this disease [95]. Prevalence is estimated around 2:100 000 [96].

Clinical presentations of CTX are quite variable. The initial symptoms typically begin in childhood with nonspecific mild mental retardation, juvenile cataract, chronic diarrhea or epilepsy. Progressive neurological deterioration follows in adolescence or adulthood with acute psychiatric signs [10,97], progressive spastic paraparesis, cerebellar ataxia, polyneuropathy, epilepsy and cognitive deficits leading to severe handicap or death. These neurological signs can be accompanied by the appearance of tendon xanthomata, which are usually visible at the level of the Achilles’ tendons. An MRI of the brain typically shows a specific pattern with high signals in the dentate nuclei of the cerebellum on T2-weighted sequences [98].

Chenodeoxycholic acid is the primary treatment for CTX. This agent blocks the accumulation of cholestanol by replenishing the pool of bile acid in the liver and hepatic circulation, and shuts down the abnormal hepatic bile acid synthesis pathway. Although it is efficient at normalizing circulating levels of cholestanol, and clearly stabilizes disease progression, it does not improve already existing neurological signs. In addition, xanthomata do not decrease in size.

Psychiatric signs

Fourteen articles were identified in the systematic literature review [10,97]. Psychiatric manifestations in CTX have only been described in sporadic reports and two patient series [97,99-111]. Unfortunately, many of these cases are poorly documented and do not contain a systematic psychiatric evaluation.

Acute psychotic episodes have been described, but most psychiatric symptoms are n-specific and occur during childhood and/or adolescence [10,97]. Hyperactivity is the most common syndrome seen during youth, and is associated with cognitive impairments in speech and comprehension [112].

The Dotti et al. series described 11/13 patients (85%) with psychiatric symptoms [Note: please confirm that 11 patients out of the 13 studied had psychiatric symptoms, as queried]: five with behavioural changes, four with psychosis and two with depression [107], suggesting an over-representation of psychiatric disorders in this population. This contrasts with the documented rarity of psychiatric signs in CTX (around 10%). In the only small series specifically focusing on the psychiatric spectrum of CTX, Bergin et al. reported four patients with disparate psychiatric syndromes, including irritability and personality changes with hypersexuality, atypical psychosis and paranoid delusions, and severe catatonia [97]. Diagnoses of CTX were made on the basis of pes cavus and Achilles xanthomata in all patients, and caractacts and cognitive impairment in two cases.

Two siblings were recently described with an early psychiatric presentation comprising attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) associated with mild intellectual disability [112]. In both patients, treatment with chenodeoxycholic acid improved externalizing symptoms, and a partial recovery of cognitive impairment was observed.

Niemann Pick disease type C (NP-C)

Key features

NP-C is a pan-ethnic, autosomal recessive neurodegenerative disease with an incidence estimated between 1 case per 150 000 and 1 case per 120 000 live births [113,114]. The disease is characterized by a variety of progressive, disabling neurological symptoms including clumsiness, limb and gait ataxia, dysarthria, dysphagia and cognitive deterioration [113,115].

NP-C is associated with mutations of the NPC1 and NPC2 genes, with no primary defect in catabolic enzymes. NPC1 gene mutations are present in 95% of cases and NPC2 mutations are present in approximately 4%. At the cellular level, these mutations give rise to characteristic abnormalities in the intracellular transport of cholesterol, glycosphingolipids and sphingosine. Impaired function of the NPC1 and NPC2 gene products, which normally function cooperatively in intracellular lipid transport, leads to the accumulation of these lipids in the late-endosomal/lysosomal intracellular compartment, and excess build up