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SHORT REPORT

# Treatment of a child diagnosed with Niemann–Pick disease type C with miglustat: A case report in Brazil

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**Summary** Niemann–Pick disease type C (NPC) is an autosomal recessive neurovisceral lysosomal lipid storage disorder that leads to variable symptoms that include cognitive decline, ataxia, dystonia, cataplexy, vertical supranuclear gaze palsy, and seizures. Currently, there is no specific treatment for NPC other than palliative care. Substrate reduction therapy represents a potential strategy for treating this debilitating neurodegenerative disorder. Miglustat (Zavesca) is a reversible inhibitor of the enzyme glucosylceramide synthase, which catalyses the first step in the biosynthesis of most glycosphingolipids. Miglustat has pharmacokinetic properties that allow it to cross the blood–brain barrier, thus making it a potential therapeutic agent for treating neurological symptoms in NPC patients. We present here a case report of a Brazilian child treated with miglustat. Before treatment, the patient presented with difficulties walking and swallowing, slurred speech, moderate cognitive impairments, ataxia, ptosis, and vertical supranuclear ophthalmoplegia. On a disability scale, the patient obtained a score of 15 before treatment and 8 after treatment. Following 12 months of treatment, the patient remained stable with improvements in speech, ptosis, ophthalmoplegia, ataxia, hypotonia and seizures. The Child Behavior Checklist (CBCL) was used to assess psychopathological, behavioural and social problems before and after treatment. The CBCL showed that indices for depression, affective and attention problems were all in the normal range following treatment. Thus, for this individual miglustat was an effective, well-tolerated and efficacious medication for treatment of NPC symptoms. Follow-up maintenance studies are vital to establish whether both the efficacy and safety of miglustat persist with time.

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**Abbreviations**

| | |
|---|---|
| CBCL | Child behavior checklist |
| MRI | Magnetic resonance imaging |
| NPC | Niemann–Pick disease type C |
| q.d. | every day |
| t.i.d | three times a day |

## Introduction

Niemann–Pick disease type C (NPC) (OMIM catalogue number 257220 Type C1, and 607625 Type C2) is a rare,

autosomal, recessive, neurovisceral disorder caused by mutations in the *NPC1* (95%) or *NPC2* (5%) genes (Vanier and Millat 2003). NPC disease has a variable phenotype, whereby an alteration in cholesterol and glycolipid homeostasis leads to a broad spectrum of symptoms that include hepatosplenomegaly, liver dysfunction, and neurological abnormalities such as progressive ataxia, cataplexy, vertical supranuclear gaze palsy, seizures, and impairment of swallowing reflexes (Patterson et al 2001). As may be expected for a complex disease like NPC, development of an effective therapeutic strategy has been challenging. Medications that lower somatic serum cholesterol have failed to produce a significant impact on neurological abnormalities in NPC patients (Patterson et al 1993). Other cholesterol-lowering drugs, such as nifedipene and probucol, have not ameliorated neurological deterioration or disease progression in mice with NPC disease (Erickson et al 2000). The lack of efficacy of these cholesterol-lowering agents in eliciting a neurological therapeutic effects indicates that intracellular accumulation of glycosphingolipid may be the primary pathogenic consequence in neurons (Walkley and Suzuki 2004).

Miglustat (*N*-butyldeoxynojirimycin, Zavesca, Actelion Pharmaceuticals, Northern Ireland) is a reversible inhibitor of glucosylceramide synthase that catalyses the first step in a series of reactions in the biosynthesis of most glycosphingolipids (Saunier et al 1982). Partial inhibition allows the biosynthetic pathway to operate within a normal range for growth and development. Experiments with radiolabelled miglustat indicated that it is well absorbed and crosses the blood–brain barrier (Treiber et al 2007). Miglustat treatment delayed onset of symptoms and increased lifespan in NPC mice (Zervas et al 2001). Recent clinical trials showed significant improvements of several clinically relevant symptoms in juvenile/adult and paediatric patients with NPC. Specifically, after 12 months of treatment, patients showed improved horizontal saccadic eye movement velocity and swallowing capacity, stable auditory acuity, and slowed deterioration in an ambulatory index (Patterson et al 2007). In this report, we describe the outcome of the case of a Brazilian paediatric NPC patient treated with miglustat for 12 months.

## Methods

The research protocol was approved by our Institutional Review Board. Written, informed parental consent was obtained.

### Patient characteristics and biological diagnosis

The patient's baseline and demographic characteristics are summarized in Table 1. She was born by caesarean delivery at full term with no neonatal problems. Family history was positive for epilepsy. She presented with normal development until the age of 4 years. However, at 2 years of age, she had a history of splenomegaly for which no conclusive diagnosis was made. At 5 years of age, the patient started to exhibit learning disabilities. Examinations revealed marked cerebellar dysarthria, ataxia, intention tremor and mild cognitive impairment. At the age of 8 years, she began to develop seizures and learning difficulties.

At the age of 9 years, the patient came to our institution with psychomotor regression, slurred speech, moderate cognitive impairments, ataxia, ptosis, swallowing difficulties, and vertical supranuclear ophthalmoplegia. To control the seizures, the patient was initially prescribed valproic acid (750 mg/day). Screening for metabolic diseases and other tests, including haematological and biochemical tests, were all negative except for elevated ammonia, cholesterol and plasma chitotriosidase activities. The hyperammonaemia could have been associated with the use of valproate (Wadzinski et al 2007). Abdominal ultrasound scans showed splenomegaly despite the fact that there was no visceromegaly in the clinical examination. Bone marrow aspiration revealed the presence of foam cells. The diagnosis of NPC was confirmed by filipin staining in cultured fibroblasts, demonstrating

**Table 1** Patient's demographic and baseline characteristics

| Sex | Female |
|---|---|
| Height (cm) | 137 |
| Body weight (kg) | 28 |
| Body mass index (BMI) | 14.9 |
| Age at onset (years) | 2 |
| Age at diagnosis (years) | 9 |
| Disability scale score | 15[a] |
| Age at start of miglustat (years) | 10 |
| Chitotriosidase activity (nmol/h per ml) | 309[b] |
| Filipin staining | Positive |
| Genetic testing | ND[c] |
| Antiepileptic medications | Oxcarbazepine (420 mg t.i.d.)<br>Phenytoin (100 mg q.d.)<br>Clobazam (10 mg q.d.) |
| Other medications | Multivitamins |

[a] Disability Scale described by Iturriaga et al. (2006).
[b] Normal range: 8.8–132 nmol/h per ml.
[c] ND, not determined.

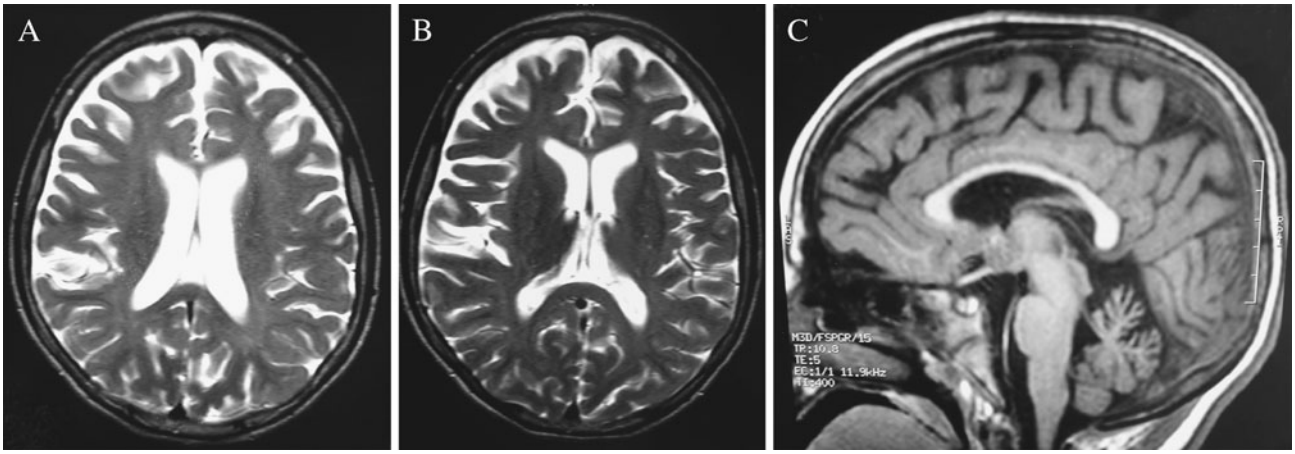


**Fig. 1** Brain MRI of our patient with NPC disease. (**A**) and (**B**) show prominent and diffuse ventricles; (**C**) shows cerebellar atrophy

massive accumulation of unesterified cholesterol in perinuclear vesicles (test performed by the Serviço de Genética Médica at the Hospital de Clinicas of the Federal University of Rio Grande do Sul). At the age of 10 years, the patient presented more evident psychomotor regression with cerebellar signs associated with pyramidal features (bilateral Babinski reflex). She also had cataplexy and frequent (≥1 per month) generalized seizures. Brain magnetic resonance imaging (MRI) revealed prominent ventricles (Fig. 1A), signal modification in the central and periventricular white matter in fronto-parietal regions with nonspecific features (Fig. 1B), and atrophy of the cerebellum (Fig. 1C).

## Treatment and assessments

Funding to treat the patient was supplied by the Brazilian State of Paraná Health Department. Miglustat treatment was initially prescribed at 100 mg t.i.d. After 10 days, the dosage was increased to 200 mg t.i.d. This dosage has been maintained for the last 12 months, with no severe adverse effects apparent at monthly physical and neurological examinations, or tracked in a side-effect log. In addition, the patient continued taking antiepileptic medications (Table 1), but with lower doses of phenytoin (50 mg q.d.).

The Child Behavior Checklist (CBCL) (Achenbach 1991) was used to assess psychopathological, behavioural and social problems before and 10 months after treatment. This checklist detects clinically significant internalizing and externalizing child behaviours and identifies risk for psychopathology (Achenbach and Ruffle 2000). The CBCL provides a total problem score and two broad-band scales (Internalizing and Externalizing) that quantify the following behavioural dimensions: depression, withdrawal, rule-breaking, aggressive behaviours, social, thought, attention problems, and somatic complaints. A computer based CBCL was used to convert raw scores to age and sex-standardized *T*-scores. A *T*-score ≥70 represents the 98th centile of the normative sample (Achenbach 1991).

## Results and discussion

In this report, we present the positive therapeutic effects of miglustat in the treatment of NPC. The results are comparable to those of other recent reports (Chien et al 2007; Lachmann et al 2004; Patterson et al 2007). Rapid symptomatic improvements were observed just 40 days after initiating treatment. Significant improvements in ataxia and dysarthria, better balance and good seizure control were observed within 40 days of commencing the drug treatment and were sustained at 12 months. The patient was wheelchair-bound before treatment, but was able to stand and walk after being on the treatment for 12 months (Fig. 2). The patient's disability score (Iturriaga et al 2006) was reduced from a pre-treatment score of 15 down to a score of 8 after treatment. The patient's seizure frequency was reduced from about three episodes per month before treatment to less than one episode per three months after 12 months of miglustat treatment. Furthermore, the patient remained stable and exhibited improvements in speech, swallowing, ptosis, ophthalmoplegia, ataxia, hypotonia and seizures.

Miglustat had a positive impact on cognitive function as well as on psychopathological symptoms of depression and of affective and thought problems as assessed by the CBCL (Table 2). Before treatment, the


**Fig. 2** Photographs of the patient before treatment (**A**) and 10 months after treatment (**B**)

patient's Total Problems and Internalizing scores were both in the clinical range, while the Externalizing score was in the normal range. The patient had presented with symptoms of depression, as well as with social, affective and attention problems. After 10 months of treatment, her Internalizing scores were in the normal range for her age and the assessment results for symptoms of depression, affective and attention problems were also all in the normal range (Table 2).

**Table 2** Parent-reported Child Behavior Checklist (CBCL) *T*-scores before and 10 months after treatment

| | Before treatment | After treatment |
|---|---|---|
| Total problems | 70[a] | 60 |
| Internalizing problems | 74[a] | 56 |
| Withdrawal | 80[a] | 64 |
| Somatic complains | 66 | 53 |
| Anxiety/depression | 68 | 52 |
| Social problems | 72[a] | 67 |
| Thought problems | 54 | 51 |
| Attention problems | 70[a] | 69 |
| Externalizing problems | | |
| Rule-breaking behaviour | 50 | 52 |
| Aggressive behaviour | 59 | 54 |
| DSM-oriented scales | | |
| Affective problems | 83[a] | 60 |
| Anxiety problems | 63 | 59 |
| Somatic problems | 61 | 50 |
| ADHD | 55 | 63 |
| Oppositional defiant problems | 52 | 52 |
| Conduct problems | 52 | 52 |

[a] The patient's Total, Internalizing, Social, Attention, and Affective problems scores were all in the clinical range before and in the normal range 10 months after commencing treatment.

In terms of side-effects, the patient initially experienced insomnia, fine tremors, and weight loss in the absence of gastrointestinal disturbances. The patient lost about 7% of her body weight during the first month of treatment. However, within four months her weight had returned to normal (BMI 15.8), the fine tremors had disappeared, and the insomnia had diminished.

The present observations in an NPC patient being treated with miglustat 10–12 months after commencing treatment reinforce other findings suggesting that miglustat is both effective and well tolerated in patients with NPC. Lachmann and colleagues (Lachmann et al 2004) were the first to report a clinical case study showing positive results of miglustat treatment in an adult patient with NPC. The report of Chien and colleagues that miglustat was an effective treatment in two children, one with infancy-onset NPC and the other with childhood-onset NPC, is also encouraging (Chien et al 2007). Moreover, a recent randomized controlled study showed miglustat to be safe and effective in juveniles/adults and children for a 12-month period (Patterson et al 2007). However, Paciorkowski and colleagues recently reported the case of a 3-year-old child who did not benefit from 12 months of miglustat treatment (Paciorkowski et al 2008). The non-responsiveness to the treatment in Paciorkowski's patient could be due to the fact that patients with neonatal-onset NPC have a more severe clinical course than patients with later-onset forms (Imrie et al 2007).

Since the initial manifestations of NPC disease vary, with systemic (hepatic, splenic and pulmonary) and neurological symptoms taking independent courses (Sevin et al 2007), it may be reasonable in the neonatal-onset severe type to start treatment with medications that lower somatic cholesterol, add to miglustat subsequently or concomitantly. Clearly, further investigations are needed, in particular trials examining patients with neonatal-onset NPC.

In summary, this is the first report of miglustat treatment of an NPC patient in Brazil, and we are continuing to monitor the patient's outcome closely. Our experience thus far suggests that miglustat, a relatively simple oral therapy, may be an effective treatment for NPC, which is an otherwise untreatable disorder.

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