

# Niemann-Pick type C (NPC): Canadian Management Guidelines

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## Disclosure

These guidelines represent a consensus opinion of a pan-Canadian, multidisciplinary panel of health care professionals that are involved in the care of patients with Niemann Pick C disease. Initial work on the guidelines was facilitated through the Canadian Chapter of the National Niemann-Pick Disease Foundation (CCNNPDF) and the working group has been lead by Dr. Serge Melançon. Financial contributions have been made by Actelion Pharmaceuticals Canada Inc. (Laval, Québec, Canada) in the form of travel grants and some of the authors have received honoraria as speakers, consultants and research grants. None of the authors has disclosed a financial interest in Actelion Pharmaceuticals. This document is not intended to be a comprehensive guide to the diagnosis and management of patients with Niemann Pick C disease but represents general guidelines, which in the opinion of the authors, can inform care providers about the needs of patients with Niemann Pick C. The authors have written the manuscript on their own without any input from either the CCNNPDF or Actelion Pharmaceuticals and the content of this document has been kept confidential prior to its disclosure to the public. Donna Coffin from Boolean Research Consulting Services (Westmount, Québec City, Québec) provided support for editing the document through an external contract funded by Actelion Pharmaceuticals but has no affiliation with Actelion Pharmaceuticals. The information contained in this document was obtained from a systematic review of the literature and experience of the authors in their care of patients with Niemann Pick C. There was no information from either the CCNNPDF or Actelion Pharmaceuticals that was used to construct this document.

## **Abstract**

Niemann-Pick disease type C (NPC) is a rare but fatal disorder with an incidence of 0.82 cases per 100, 000 live births. The disease is pan-ethnic, with 95% of all disease due to mutations in the *NPC1* gene and 5% in the *NPC2* gene. It can manifest at any age with severe neurodegenerative symptoms, visceromegaly, and cholestasis, and in adults can present with psychosis, dementia and no organomegaly. The diagnosis of NPC can be challenging due to non-specific symptoms and the limited availability of diagnostic tests. There is no cure for NPC, treatment is supportive, aimed at symptom control and comfort, as the degenerative symptoms progress. These guidelines cover the clinical features, diagnosis, treatment and the evidence for using miglustat in patients with NPC in Canada. The guidelines are compared to the United Kingdom National Commissioning Group (2009) and the European Working Group guidelines (2009) for NPC.

## **Keywords**

Niemann-Pick C, diagnosis, management, substrate reduction therapy

## Introduction

This document, entitled 'Niemann-Pick Type C: Management Guidelines' has been developed by a working group of experts in Niemann-Pick disease Type C (NPC) comprised of physicians and allied health professionals. It is the result of several meetings and discussions on the best care practices in addition to an extensive review of the literature. It outlines the current knowledge on the epidemiology of NPC patients, as well as the diagnosis, monitoring and treatment strategies for patients with NPC in Canada. This document is intended to be used as a resource for care providers (neurologists, primary care physicians, geneticists, paediatricians and other health professionals) to help recognize the signs and symptoms, methods used for diagnostic testing, genetic counselling and clinical management of patients with NPC.

## Pathology and Pathophysiology

NPC disease is a neuro-degenerative disorder that can present at any age from newborn infants to adults. The fundamental problem in NPC is an accumulation of unesterified (free) cholesterol that is not available for cellular processes.<sup>1 2</sup> The unesterified cholesterol accumulates due to impaired egress from late endosomes and lysosomes (LE/L). Trafficking of unesterified cholesterol out of LE/L is mediated first by NPC2 protein which binds the side chain of cholesterol. The cholesterol is then bound on the N-terminal region by NPC1 protein.<sup>3</sup> Approximately 95% of NPC disease is caused by mutations in the *NPC1* gene with a minority due to mutations in the *NPC2* gene which code for NPC1 and NPC2 (epididymal secretory protein E1) proteins, respectively.<sup>4</sup> All cases of NPC are inherited in an autosomal recessive manner. A previous classification of Niemann-Pick type D, which was based on a cluster of cases in Nova Scotians with a G992W mutation in NPC1 has been reclassified as NPC.<sup>5-7</sup> The

I1061T variant is found among patients of Spanish ancestry. A novel c.467T>G (p.Met156Arg) mutation in the *NPC1* gene also is found in the Stoney Nakoda Nation (originated from the Sioux nation) in Southern Alberta that causes NPC<sup>8</sup>.

The liver is the chief non-neural organ of injury. Low-density lipoprotein (LDL) mediated uptake of cholesterol through endocytosis and hydrolysis by hormone sensitive lipase is the main source of unesterified cholesterol. Murine models of NPC show that cholesterol accumulation leads to hepatocyte injury and cell death.<sup>9</sup> In the lungs, lipid-laden foamy macrophage accumulation, fibrosis and lipoid pneumonia can occur.<sup>10</sup> In the brain, intraneuronal cholesterol accumulation may lead to lower cholesterol levels in myelin, neurofibrillary generation and tau protein aggregation.<sup>11</sup> In addition, there is also accumulation of other lysosomal-derived lipids.<sup>12</sup>

## **Epidemiology, Signs and Symptoms**

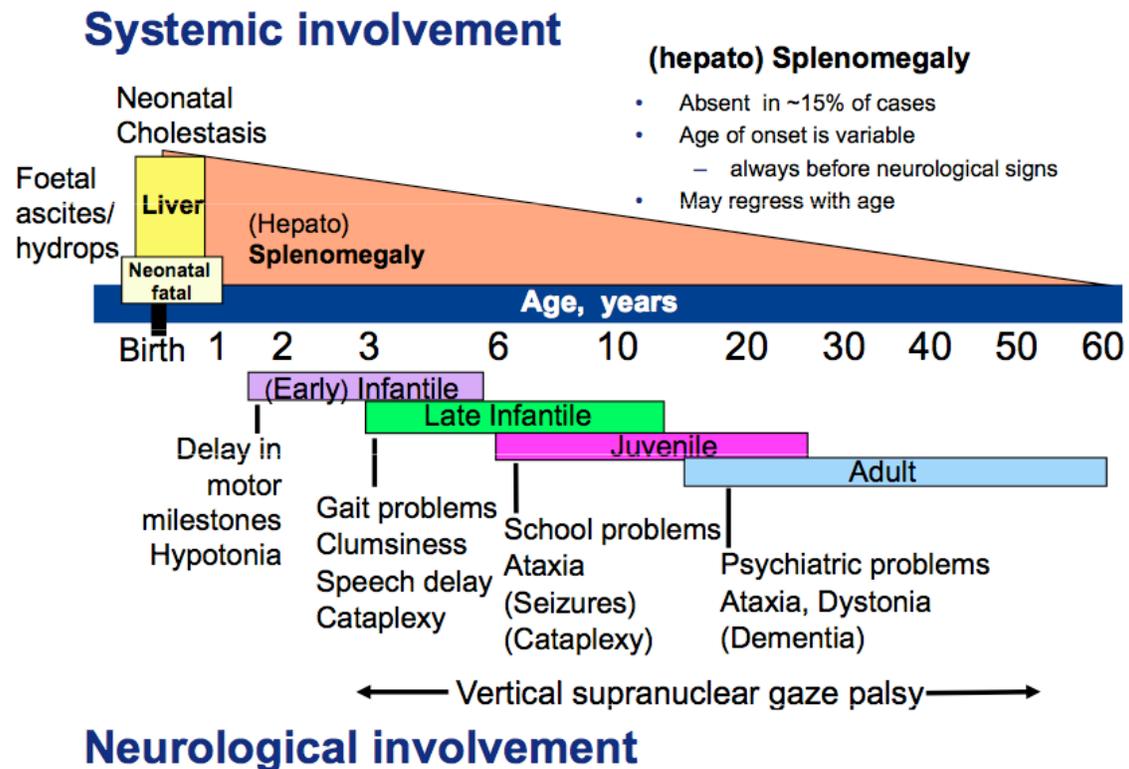
The most recent estimate of the incidence of NPC is 0.82/100 000, based on 63 cases of NPC diagnosed in French hospitals during 2000-2009 versus the number of births during the same period.<sup>13</sup> This estimate increases to 0.96 / 100,000 if prenatal cases from terminated pregnancies during the same period (n=11) are included.<sup>13</sup> Estimates of incidence of NPC are believed to be an underestimation, due to a combination of factors, including low clinical awareness, heterogeneous symptomatology, low availability of testing procedures and high fatality rates<sup>4, 13, 14</sup>. Although the disease is always fatal, life expectancy varies and is partially based on age of onset of neurological symptoms<sup>14</sup>, with most patients dying between the ages of 10 and 25.<sup>4</sup>

NPC can present anywhere between the perinatal period to adulthood (Figure 1).<sup>4, 13-20</sup>

The most common form, termed the 'classical' presentation, is also referred to as the late-infantile or juvenile form presenting in children less than 5 years of age to adolescence <sup>21</sup>. The history will typically involve a brief period of post-natal jaundice which may be followed years later with hepatosplenomegaly, ataxia, fine motor difficulties and developmental delay. Associated findings can include seizures, gelastic cataplexy and supranuclear gaze palsy. As the disease progresses, the psychomotor delay progresses, dystonia, choreoathetosis, spasticity and dysphagia also develop. Children have major motor impairment including clumsiness, cataplexy, cerebellar ataxia as well as dysarthria, dystonia and dysphagia. Abnormal velocity of horizontal saccadic eye movements (HSEM), vertical supranuclear gaze palsy (VSGP) and seizures are quite frequent.<sup>14</sup> Among juvenile patients (6-15 years of age), difficulties in school, learning disabilities and behavioral problems become evident.<sup>13, 14</sup> Perinatal and infantile presentation of NPC can be rapidly progressive. The perinatal presentation typically involves cholestatic jaundice and persistent hepatosplenomegaly, which may resolve prior to the onset of liver failure. The infantile form can present with hepatosplenomegaly. Adult-onset disease may be milder than the 'classical' form, but can present initially as psychosis, depression, dementia or a movement disorder, typically without organomegaly. Clinical distinction between disease due to either *NPC1* or *NPC2* mutations is difficult. However, some children with *NPC2* mutations can have early pulmonary involvement and a rapidly fatal course.<sup>22</sup>

**Figure 1.** Overview of Niemann Pick C. Adapted from Vanier MT. Niemann-Pick disease type C

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## Diagnosis

The diagnosis of NPC is often difficult due to the heterogeneous and non-specific nature of the symptoms. A diagnosis of NPC can be established by identification of disease-causing mutations in either the *NPC1* or *NPC2* genes as a first line test and in situations where the familial mutation is already known (such as for prenatal testing or to test family members). Not all DNA sequence variants necessarily cause the disease and in situations where a novel or unexplained variant is found, biochemical test correlation is essential for diagnosis and/or making treatment decisions.

Still widely regarded as the standard, a diagnosis of NPC can also be established in most cases using cultured skin fibroblasts. These cells show accumulation of unesterified cholesterol using filipin staining and reduced cholesterol esterification.<sup>23-25 26</sup> Most classical patients display very positive cholesterol esterification patterns while 15% of the patients show moderately positive results.<sup>25</sup> The procedure requires a small sample of skin obtained under local anesthesia as an outpatient procedure. It is a simple procedure, but nevertheless is still distressing to children. Equivocal results should be verified using gene sequencing.

Gene sequencing is available in Canada in a number of different centres. The biochemical assays in skin fibroblasts are not available in Canada and require practitioners to apply for funding for tests outside the country – this can lead to further delays in obtaining a diagnosis and raise the possibility of denial of funding. *We therefore support the option of the first test for NPC being mutation analysis of NPC1 and NPC2 genes for Canadian patients.*

## **Symptomatic Treatment**

There is no cure for NPC. Treatment is primarily supportive, aimed at symptom management, and includes control of seizures, provision of nutritional support, prevention and treatment of aspiration pneumonia, treatment of psychiatric manifestations and supportive treatment of liver disease (which may be severe).

There are no controlled trials evaluating the use of supportive therapies; however, our shared clinical experience indicates that supportive measures can improve quality of life and comfort in patients with NPC. Seizures, including myoclonic seizures, generally respond at least partially to anti-epileptic drugs until a fairly advanced stage of the disease. Cataplexy can usually be controlled by clomipramine, imipramine, protriptyline, or modafinil<sup>13, 27-29</sup> and anti-

cholinergic agents.<sup>2 30</sup> Anti-cholinergic agents have been reported to improve dystonia and tremor in some patients. Physiotherapy is useful in the management of spasticity and the prevention of contractures. Melatonin may be helpful to treat insomnia. Patients with a slow disease course may benefit from individualized education programs. Proper management of infections and of feeding difficulties (gastrostomy tubes) are essential at an advanced stage of the disease.<sup>13</sup>

## **Disease Modifying Strategies**

Therapeutic strategies based on the premise that cholesterol is the offending metabolite were first tested in the early 1990's.<sup>31, 32</sup> Cholesterol lowering therapy, using various combinations of cholestyramine, lovastatin, nicotinic acid and dimethyl sulfoxide was unsuccessful in demonstrating neurological improvements in NPC patients, despite lowering hepatic and plasma cholesterol. Liver transplantation may help manage the hepatopathy, but does not yield an improvement in neurological symptoms nor ultimately change the disease course.<sup>33, 34</sup> Bone marrow transplantation may improve the lung disease, but has only been reported in one case study; a 16 month old boy with NPC2 with follow-up to 24 months of age.<sup>35</sup>

Miglustat, also known as N-butyl-deoxynojirimycin, NB-DNJ and OGT 918, is an iminosugar inhibitor of glucosylceramide synthase. Miglustat was originally approved for the treatment of non-neuronopathic Gaucher disease in Canada on March 31, 2004 and for NPC on March 4, 2010. Miglustat has been shown in randomized controlled clinical trials and case-series to have disease-modifying effects.<sup>36-40</sup> In NPC cells, there is not only accumulation of unesterified cholesterol, but also other lipids such as sphingomyelin, glucosylceramide, GM2 / GM3 gangliosides, and lysophosphatidic acid.<sup>1, 41</sup> Although miglustat is not known to directly affect cholesterol trafficking, it is a form of substrate reduction therapy (SRT) which acts by inhibiting the first step in glycosphingolipid biosynthesis. By reducing glycosphingolipid accumulation, miglustat is thought to improve overall endosomal function including cholesterol

trafficking. Inhibition of the biosynthesis of glycosphingolipids in the brain appears to prevent the accumulation that is thought to cause the brain damage, which is a prominent feature of NPC. When administered to *npc1* mutant mice and cats, miglustat resulted in delayed onset of the neurological symptoms in both species and yielded 20% longer survival in mice.<sup>42</sup> In a recent study, miglustat treatment delayed the onset of neurological signs in cats, increased their lifespan, was associated with decreased GM2 ganglioside accumulation in the cerebellum and improved Purkinje cell survival.<sup>43</sup>

## **Studies Using Miglustat in NPC**

Published data on the efficacy and safety of miglustat in NPC is limited to one randomized controlled trial (RCT) with its 2 extension studies and a number of observational studies. The RCT assessing the efficacy of miglustat in patients with NPC was conducted between 2003-2007.<sup>36</sup> Forty-one neurologically symptomatic patients with NPC were enrolled into the 12-month study. Twenty nine patients with juvenile / adult NPC ( $\geq 12$  years of age) were randomized to receive miglustat or standard care and a second group of 12 paediatric patients (age 4-11) were enrolled in an open-label miglustat (dose adjusted for body surface area) arm of this study. Most patients were ambulatory, but at baseline, had cognitive impairment, ataxia, and gaze palsies. After 12 months, juvenile/adult and pediatric patients using miglustat showed an improvement in the primary endpoint, mean HSEM (horizontal saccadic eye movement) velocity, and either maintained or showed improved swallowing ability, auditory acuity, ambulation and cognition compared to patients on only standard of care. However, improvements were not seen for these parameters among the cohort of patients less than 12 years. The most commonly reported adverse events, occurring more often in miglustat treated juvenile/adult patients versus standard care included diarrhoea, flatulence, weight loss and abdominal pain, but growth was not affected. Peripheral neuropathy (a complication of

therapy which has been reported in Gaucher disease patients treated with miglustat) did not differ between treatment and control groups. Three patients withdrew for reasons not related to miglustat use.

An open label extension of this study has been reported for the paediatric patients<sup>44</sup> and juvenile/adult patients<sup>45</sup> separately. In this extension trial, the disease course stabilized in 68% of patients treated for at least 12 months, based on a composite assessment of HSEM velocity, ambulation, swallowing and cognition. Among the paediatric patients, disease progression was stabilized in 80% of patients up to 24 months<sup>44</sup>. Six additional patients withdrew during the 12 months open label extension of which two were due to adverse events (diarrhoea and neuropathy), two based on patient request due to worrying about side effects of miglustat and the remainder were for reasons not related to miglustat use.

Other experience with miglustat use in NPC comes from case reports or case series, which have focused on only selective responses. Observations reported in some patients have included improvements in balance, seizure frequency and cognitive function,<sup>39, 46</sup> walking and swallowing,<sup>38, 47</sup> and resolution of cataplexy.<sup>29</sup> Negative responses have been worsening of myoclonus, resolved by adjusting dosage.<sup>47</sup> A case series of 5 children examined the effects of long-term treatment for a median of 4 years (range 4.1 to 6.1 years). Improvements in swallowing function and cognitive function were reported in the first 3-6 months, but deterioration in ambulation after 2 years of treatment was also noted. However, drug treatment was interrupted for 6 months, which may have influenced these results.<sup>48</sup>

## **Timing of Initiation of Therapy**

Supportive therapy for patients and their families can be initiated immediately after the diagnosis has been made. The management of NPC is multi-disciplinary and should include the primary care provider, social services, physical, occupational and speech therapy, a physician experienced in following patients with NPC to serve as a resource (such as a medical geneticist,

metabolic physician, neurologist) and any sub-specialty services as needed.

NPC is a heterogeneous disease and there is no single age that can be specified at which to start treatment with miglustat. Most of the miglustat treatment experience with NPC patients is on cases with the classical presentation and in adults. Overall, the majority of patients with NPC treated with miglustat show stabilization of neurologic features, but only a minority of treated patients (12-15%) show an improvement in neurological findings like ambulation, manual dexterity, and swallowing. Currently, there are no biomarkers that reliably predict the severity of the disease. Clinicians typically rely on the onset of disabling symptoms, such as cognitive impairment, or difficulties with walking or swallowing, which are generally the result of irreversible brain damage, as the first neurologic findings of NPC. Optimal results would be more likely achieved if treatment were initiated before the onset of these disabling neurologic symptoms. However, it should be emphasized that there are currently no clinical trials documenting the efficacy of the drug in the primary prevention setting. Thus, no evidence-based recommendation can be made to support treatment prior to the onset of neurologic symptoms.

If a decision is made to start treatment of miglustat prior to the onset of neurologic symptoms, detailed discussion with the family is mandatory to inform them of the lack of clinical trial evidence supporting this approach. It is clear that the penetrance of neurologic symptoms is close to 100%, providing the patients do not die of visceral disease. Some generalizations can be made, although many exceptions exist. Generally, the earlier the onset of neurological symptoms, the more rapidly progressive the disease<sup>49</sup>. Within families, the onset of neurologic symptoms often occurs at a similar age in family members with NPC, although exceptions to this rule exist<sup>50</sup>. Limited data on genotype-phenotype correlation exist and is generally not helpful in predicting the prognosis in the case of individual patients. These factors should all be considered when forming a decision about when to initiate therapy.

Each individual case must be carefully considered in order to decide when to start therapy. Earlier start of therapy may be appropriate in some cases. For example, in a family where other affected members developed neurologic findings by the age of 10 years, it might be desirable to start treatment before this age. It should be noted that most patients are only diagnosed with NPC when they present with neurologic symptoms. Thus, the number of cases where pre-symptomatic therapy would be possible is expected to be very small. Patients should meet requirements for eligibility for miglustat use in their health care region (Table 1). In patients with early-infantile onset disease, it can take 6 months to 1 year to see discernable clinical benefits. In patients with later-onset disease, it can take 2–3 years to see clinical benefits.<sup>51</sup> The goals of any treatment should be discussed with the family before the initiation of therapy. Miglustat should not be expected to restore normal neurologic function but may stabilize the deterioration in certain features (discussed under “Studies Using Miglustat in NPC”) in some patients who are not at advanced stages of disease. This means that there is the likely scenario of patients who may deteriorate or develop some serious, life-threatening co-morbidity where there is no evidence for continued use of miglustat (Table 1). With or without the use of miglustat, supportive therapies for patients should always be considered.

Most patients with NPC reported world-wide have received miglustat for less than 5 years; the effects of longer term therapy in NPC are not known. As miglustat inhibits the synthesis of multiple glycosphingolipids and glycosphingolipids are needed for myelin development, theoretical concerns have been expressed about the use of miglustat in very young patients. A clinical trial in patients between the ages of 4 and 12 years did not show adverse effects on development<sup>44</sup>, however, the data are limited to patients below the age of 4 years. There are significant side effects of the drug, including diarrhea, flatulence, weight loss, tremor, and possibly peripheral neuropathy<sup>52</sup>. Although the gastrointestinal side effects are controllable by dietary manipulation, they can negatively impact the quality of life of patients, particularly those who do not yet have neurologic symptoms.<sup>52</sup>

There is currently no evidence to support the use of miglustat in patients with a perinatal or severe infantile presentation (such as hydrops fetalis) or with advanced neurological disease or visceral disease without neurological symptoms.

## **Drug Safety**

The miglustat product monograph includes data on patients treated primarily for Gaucher disease in whom the dose of miglustat is lower than the dose used in NPC. However, the side effect profile of miglustat in the Gaucher patients and in the NPC patients is similar. The main side effects are gastrointestinal including diarrhea, flatulence, weight loss, and abdominal pain. Gastro-intestinal side effects were seen in 85% of patients treated with miglustat.<sup>36</sup> Weight loss was seen in 65% of patients, but did not compromise growth. Other side effects included tremor (40% in the miglustat group and 22% in the standard care group), fatigue and paresthesia (20% in the miglustat group and 0% in the standard care group). Peripheral neuropathy was seen in one patient in the miglustat group and one patient in the standard care group. During the 12 month study, 3 of 32 patients receiving miglustat withdrew because of adverse events: one because of insomnia and confusion, one because of diarrhea (with co-existent Crohn's disease) and one because of lethargy, memory impairment, and depression. There were no deaths during the 12-month study.<sup>36</sup>

Gastrointestinal side effects of miglustat are likely related to inhibition of disaccharidases in the intestine. These side effects can often be effectively reduced with a low carbohydrate diet and, when needed, the use of anti-diarrheal agents.<sup>52</sup> In our experience, initiating dietary measures well before starting miglustat has been shown to prevent most of the gastrointestinal problems from happening, including severe weight loss in Gaucher patients treated in Toronto.

## Monitoring of Patients with NPC

The randomized trial published by Patterson et al in 2007 used the mini-mental status examination, standard ambulation index and a swallowing assessment to assess disease progression.<sup>36</sup> Change in saccadic eye movements is one of the earliest manifestations of disease in patients with NPC. Horizontal saccadic eye movements, which are controlled by the brain, are an objective and reliable surrogate marker of progressive brain disease and is often used as the primary endpoint in therapeutic trials of NPC patients. Therapeutic intervention in patients with early onset of changes in saccadic eye movement, prior to the development of advanced, irreversible brain damage, is likely to produce better clinical outcomes than in patients with significant general neurological impairment. The measurement of HSEM is not widely available in Canada, must be made by a neuro-ophthalmologist and requires specialized equipment and the mini-mental status examination may be difficult to administer in young children.

Iturriaga et al developed a disability scale for patients with NPC which assesses the categories of ambulation, manipulation (e.g. ability to use hands to perform activities of daily living), language, and swallowing, on a scale of 1 to 5.<sup>16</sup> This scale was not available for the clinical trial of Patterson (2007), however, it is potentially valuable for the assessment of the effectiveness of ongoing treatment and has been used in at least one large observational study.<sup>46</sup> It is easy to perform and can be administered at the bedside.

We recognize that the specialized methods used in research trials to monitor signs and symptoms of NPC may not be available in Canada or may require specialized equipment or personnel to perform. Our collective experience in different regions of the country suggests that there is a rational approach that can provide practitioners with a framework to monitor their patients (Table 2). The care must be tailored to each patient and available resources, but the

suggestions can serve to provide the practitioner with an overview of the areas in which major clinical changes might be expected in patients with NPC. Not all assessments will be necessary or indicated, depending on the age of the patient and the stage of the disease.

## **Anesthesia for Patients with NPC**

Patients with NPC undergo a high number of diagnostic and therapeutic procedures during the course of their disease. Due to the typical young age of patients at diagnosis and to the cognitive impairment often associated with NPC, they are more likely to require general anesthesia for these procedures, including non-invasive procedures.

Based on a prospective study of 32 NPC patients (median (range) age 3.7 years (0.25 – 33 years) undergoing diagnostic procedures requiring general anesthesia, the risk of peri-anesthetic morbidity should be considered and the risks and benefits of any procedure be considered carefully.<sup>53</sup> When possible, procedures that allow for an alternative to airway instrumentation should be considered. Depending on the clinical condition of the patient, the need for overnight monitoring after the procedure should be planned in advance. Patients with hepatosplenomegaly can have increased abdominal pressure and decreased functional residual capacity. The combination of these features and procedures requiring prolonged time spent in the prone position may lead to hypoxemia and metabolic acidosis (Dr. Aneal Khan, personal observations). Pre-operative sedation should be considered to ease inhalation induction or insertion of an intravenous catheter in patients, especially if there is neurological and/or cognitive impairment. The schedule of pre-operative medications, especially all anti-convulsants, should be maintained and the timing of the last dose relative to the need stop oral intake before a procedure should be reviewed with the anesthetist. Intravenous induction could be used if trying to avoid the use of sevoflurane and avoidance of anti-cholinergic agents especially if the patient has swallowing difficulties.

## **Dietary Adjustments during the use of Miglustat**

Miglustat, while successful in inhibiting glucosylceramide synthase enzyme, is non-specific and is also a weak inhibitor of other enzymes. These include  $\alpha$ -glucosidase, disaccharidase and potentially lactase. Therefore the digestion of starch, a polysaccharide, and the subsequent hydrolysis and absorption of oligosaccharides are affected. There may also be a degree of lactose intolerance. These may contribute to the common adverse effects, which may be dose dependent, that have been associated with this drug: diarrhea (ranging from mild to severe) in approximately 80% of patients, abdominal cramping and/or flatulence (approximately 50%) and weight loss (mean loss 6-7%). It has also been shown that there are adaptive mechanisms that occur as the symptoms were alleviated with time.

Based on the known adverse effects of miglustat, it is considered advisable to reduce complex carbohydrates in the diet for a period of 6-8 weeks. Lactose containing products should be taken conservatively. Simple sugars (mono and disaccharides) do not need to be limited. If extra energy is needed to avoid weight loss or promote growth (such as in children), this can be achieved through calories from proteins, fats, vegetables and fruits as tolerated. When patients are first considered for miglustat, they are asked to complete a 7-day food record, record their weight, daily bowel movements, other health history information and send this information to a dietitian. Patients typically start the diet 1 to 2 weeks in advance of beginning miglustat.<sup>52</sup>

## **Alternatives to Miglustat**

Other small molecule therapies that have been either proposed as a treatment for NPC or have failed to show an adequate clinical response in human cases or lack of published trials

thus far include: cholesterol-lowering agents, cyclodextrin, allopregnanolone, and antisense oligonucleotides. Interestingly, although the pathophysiology of NPC is thought to be primarily due to the accumulation of unesterified cholesterol in both neural and non-neural tissues, drugs that reduce cholesterol synthesis and accumulation have not been successful in altering the disease course.<sup>31</sup>

The genetic defect in NPC also leads to a reduction in the ability of neural stem cells to both renew themselves and differentiate into neurons, astrocytes, and oligodendrocytes in animal models<sup>54</sup>.

One mice study showed that NPC mice treated with the commonly used anticonvulsant, valproic acid, improved the ability of neuronal stem cells to renew themselves and differentiate, but the study does not document what effects the drug had on clinical manifestations of disease in these animals.<sup>55</sup> The mechanism by which the valproic acid was thought to improve neuronal differentiation is postulated to be inhibition of histone deacetylase which is an enzyme which compacts DNA so that it is more difficult to transcribe.

Thus, at the current time, there are no other disease modifying therapies available for NPC patients. In a patient's cultured skin fibroblasts, an antisense oligonucleotide was able to rescue non-sense mediated mRNA decay when the mutation was a cryptic donor splice site.<sup>56</sup> In myelinating cells, the synthesis of neurosteroids takes place using cholesterol and initially converting it to pregnanolone in the mitochondria. The finding of low levels of allopregnanolone, a product of pregnanolone, lead to an experiment in NPC1<sup>-/-</sup> mice showing a single subcutaneous injection of allopregnanolone increase life span.<sup>57</sup> However, it has been shown that cyclodextrin (a compound used to deliver the allpregnanolone) alone could ameliorate the pathophysiology in NPC mice.<sup>58-60</sup> So far, there have been no published clinical trials on results using allopregnanolone or cyclodextrin showing efficacy in humans. An observational study in 2 patients reported improvement in organomegaly but did not prevent the neurological disability<sup>61</sup>.

## Comparison with other National Guidelines

Guidelines on the diagnosis and management of NPC were developed by a European Working Group in Paris 2009<sup>51</sup>, and updated in Paris 2011.<sup>62</sup> The United Kingdom National Commissioning Group have also developed guidelines (2009), which are not yet published. The European Working Group guidelines are similar to these Canadian guidelines, however, while both the Canadian and UK guidelines recommend pre-symptomatic treatment in certain cases, the European Working Group does not recommend miglustat therapy for pre-symptomatic individuals. The UK guidelines are similar to these in that they recommend that treatment be considered for all patients with NPC, regardless of the presence of neurological symptoms, and should be stopped if patients develop life-threatening disease complications or progressive cognitive decline, however, they differ slightly in the recommended follow-up assessments (based on local availability).

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