Niemann Pick Disease Type C

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Synonyms of Niemann Pick Disease Type C

- NPC
- NPD-C

Disorder Subdivisions

- Niemann Pick Disease Type 1C
- Niemann Pick Disease Type 2C

General Discussion

Summary
Niemann-Pick disease type C (NPC) is a rare progressive genetic disorder characterized by an inability of the body to transport cholesterol and other fatty substances (lipids) inside of cells. This leads to the abnormal accumulation of these substances within various tissues of the body, including brain tissue. The accumulation
of these substances damages the affected areas. NPC is highly variable and the age of onset and specific symptoms can vary from one person to another, sometimes even among members of the same family. NPC can range from a fatal disorder within the first few months after birth (neonatal period) to a late onset, chronic progressive disorder that remains undiagnosed well into adulthood. Most cases are detected during childhood and progress to cause life-threatening complications by the second or third decade of life. NPC is caused by mutations in the NPC1 gene (NPC type 1C) or the NPC2 gene (NPC type 2C) and is inherited in an autosomal recessive manner.

Introduction
NPC belongs to a larger group of more than 50 disorders known as lysosomal storage disorders. Lysosomes are membrane-bound compartments within cells. They contain enzymes that break down large molecules such as proteins, carbohydrates and fats into their building blocks. Abnormal functioning of a transport protein leads to the accumulation of cholesterol and other fatty substances in various tissues of the body, including brain tissue. NPC used to be grouped together with two other disorders, named Niemann-Pick disease type A and Niemann-Pick disease type B. However, researchers have determined that the underlying defect in types A and B involves mutations in the SMPD1 gene and deficiency of the enzyme acid sphingomyelinase, which does not occur in NPC. Niemann-Pick disease types A and B are now considered a distinct disorder called acid sphingomyelinase deficiency. NORD has a separate report in the Rare Disease Database on this disorder.

Niemann-Pick disease type D is an obsolete term for a condition in a group of individuals in Nova Scotia, Canada who have NPC due to a specific founder mutation of the NPC1 gene. This form is clinically indistinguishable from NPC. Additional terms have been used in the past to describe NPC including DAF syndrome, juvenile dystonic lipidosis, lipid histiocytosis, and sea blue histiocyte disease. These terms are now considered obsolete.

Symptoms

Many classification systems break down NPC based upon the age of onset of the disorder, often designating forms as perinatal (shortly before and after birth), early infantile (age 3 months to <2 years), late infantile (age 2 to < 6 years), juvenile (age 6 < 15 years) and adult (age 15 years and greater). NPC is described as a neurovisceral disorder, or a disorder affecting both the neurological system and various internal organs (viscera) particularly the liver and spleen. Symptoms arise at different times and follow independent progression. Systemic symptoms precede the development of neurological symptoms in most cases. Onset of neurological symptoms is often slow and may occur over time.

Because NPC is a highly variable disorder, it is important to note that affected individuals will not have all of the symptoms described below and that every individual case is unique. Some children will develop severe, life-threatening complications early in life; others have mild disease that may go undiagnosed well into adulthood. Parents should talk to their child’s physician and medical team about the specific symptoms and overall prognosis.

In perinatal NPC, the accumulation of fluid in the fetal abdomen (fetal ascites) may be present. Ascites persists after birth. These infants often have prolonged severe cholestatic liver disease, which refers to the interruption or suppression of the flow of bile from the liver (cholestasis). Features of cholestasis include yellowing of the skin, mucous membranes and whites of the eyes (jaundice), failure to thrive, and growth deficiency. Enlargement of the liver (hepatomegaly) and/or spleen (splenomegaly) may also occur. Lipid-containing cells called foam cells may accumulate in the lungs, resulting in lung disease. Liver and lung disease can progress to cause life-threatening complications during this period. Approximately half of these
children will recover only to develop neurological symptoms later in childhood, adolescence or adulthood.

When onset is in the early infantile period (2 months to 2 years), affected infants may present with abnormal enlargement of the liver and spleen as the only noticeable symptoms (isolated hepatosplenomegaly) and that may remain the only symptom for many years. In other cases, additional symptoms develop including lack of muscle tone (hypotonia) often by 1 or 2 years of age. Affected infants may also experience delays in the acquisition of skills requiring the coordination of mental and physical activities (delayed psychomotor development).

A characteristic early finding in children with NPC is impairment of the ability to look upward and downward (vertical supranuclear gaze palsy or VSGP). Specifically, affected children lose their ability to rapidly move their eyes up and down. Consequently, affected infants or children may blink their eyes, jerk their heads or make abnormal movements in order to compensate for this loss. Eventually, vertical eye movements are lost and, side to side (horizontal) eye movement is affected.

Hearing loss can occur in some individuals with NPC. Affected individuals may develop high frequency sensorineural hearing loss, in which hearing loss is caused by impairment of the auditory nerves to transmit sensory input to the brain. Up to 74% of individuals develop clinically significant hearing loss in at least one ear. Hearing loss may be the first problem seen in adults.

The so-called “classic” presentation of NPC is during middle to late childhood. Clumsiness or difficulty in drawing and writing are often noted by teachers and parents. VSGP may be first noticed during this time in the course of a careful neurological examination or if more noticeable by the parents. In some cases, other neurological abnormalities may be the first apparent symptom, specifically cerebellar ataxia, which causes a lack of muscle coordination. Children with cerebellar ataxia often have difficulties with balance and trouble walking (unsteady gait) and may be considered clumsy or fall frequently. Affected children may also experience progressive difficulty speaking (dysarthria) resulting in slurred speech and eventually speech that is unintelligible. Children may lose previously acquired speech skills. Difficulty swallowing (dysphagia) may also develop and can become progressively worse, so that modifications, such as thickening fluids or using special utensils may be recommended. Eventually a feeding tube may be required to maintain adequate nutrition. The dysphagia can lead to trouble swallowing saliva and other secretions. This may result in the breathing in of foreign material into the airways and lungs (aspiration pneumonia).

During this time, affected individuals may also develop slowly progressive impairment of intellectually ability (cognitive impairment) that can initially be mistaken for learning disabilities. Furthermore, psychiatric disturbances and the progressive loss of memory and intellectual ability (dementia) can develop.

Additional neurologic findings can include drooling, epileptic seizures, and cataplexy, a condition characterized by a sudden loss of muscle tone and strength (cataplexy) that can cause a sudden head drop or a weak, rubbery sensation in the legs, or in severe cases collapse. Cataplexy is often caused by strong emotions and in individuals with NPC that emotion is usually laughter (gelastic cataplexy). Dystonia, a large group of movement disorders, is also common. Dystonia is generally characterized by involuntary muscle contractions that force the body into abnormal, sometimes painful, movements and positions (postures). Some individuals may develop a tremor marked by rhythmic, jerking movements (myoclonic tremor). Sleep disturbances or irregularities such as narcolepsy or sleep apnea have also been reported.

Adolescent or adult onset of NPC may be associated with a similar neurological presentation as occurs in cases with childhood onset (as described above). However, the rate of progression is often much slower.
Specific manifestations may vary, but can include cerebellar ataxia, dysarthria, dysphagia, cognitive impairment, and other movement disorders such as dystonia or tremor. VSGP is invariably present, but can be difficult to appreciate early on. Although systemic symptoms are more common in infancy or childhood, they can also occur in individuals with adolescent or adult onset NPC. Isolated splenomegaly may be the presenting symptom in some adolescents or adults.

Psychiatric issues that have been described in individuals with adolescent onset of NPC include learning difficulties, behavioral problems, difficulty with expressive language, and attention deficit-hyperactivity disorder. A schizophrenic-like psychosis may occur in some affected individuals. Adults greater than 30 years of age may experience impairment of executive function (dysexecutive syndrome), which can be characterized by problems with complex thinking and reasoning tasks such as difficulty with organization and planning.

In some cases, older adults may first be misdiagnosed with dementia or psychiatric illness such as major depression or schizophrenia. Individuals have been described in the medical literature with other psychiatric manifestations such as obsessive-compulsive disorder, bipolar disorders, and hallucinations.

After a long term gradual neurological decline the cause of death is often aspiration pneumonia leading to respiratory failure or intractable epilepsy not responding to medical intervention.

**Causes**

NPC is caused by a mutation in one of two genes, either the NPC1 gene or the NPC2 gene. Approximately 95% of cases are caused by NPC1 mutations. Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a mutation of a gene occurs, the protein product may be faulty, inefficient, or absent. Depending upon the functions of the particular protein, this can affect many organ systems of the body, including the brain.

Investigators have determined that the NPC1 gene is located on the long arm (q) of chromosome 18 (18q11.2). The NPC2 gene is located on the long arm of chromosome 14 (14q24.3). Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated “p” and a long arm designated “q.”

Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. Recessive genetic disorders occur when an individual inherits the same abnormal gene for the same trait from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. The risk for two carrier parents to both pass the defective gene and, therefore, have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%. The risk is the same for males and females.

The NPC1 and NPC2 genes contain instructions for producing (encoding) proteins. The exact function of these proteins is not fully understood and, unlike other lysosomal storage diseases, they are not enzymes. Enzymes are specialized proteins that break down other chemicals in the body. Researchers do know that the protein products of these genes are involved with the movements (trafficking) of large molecules within cells.
When these genes are mutated, insufficient levels of functional versions of their protein products are made, which causes the abnormal accumulation of cholesterol in the peripheral tissues of the body as well as the accumulation of cholesterol and glycosphingolipids (complex compounds consisting of fatty material and carbohydrates) within the brain. However, the accumulation of these materials causes the various symptoms of NPC.

**Affected Populations**

NPC affects males and females in equal numbers and can affect individuals of any ethnic background (panethnic). NPC is estimated to occur in 1 in 100,000-120,000 live births. However, many cases go misdiagnosed or undiagnosed, making it difficult to determine the disorder’s true frequency in the general population.

**Related Disorders**

Symptoms of the following disorders can be similar to those of NPC. Comparisons may be useful for a differential diagnosis.

Differential diagnosis for NPC can vary based upon the age of onset. Newborn and infantile cases can resemble a variety of disorders including alpha-1-antitrypsin deficiency, tyrosinemia, other lysosomal storage diseases including Niemann-Pick disease type A or Gaucher disease, diseases that cause neonatal cholestasis such as idiopathic neonatal cholestasis, and various congenital infections. Childhood onset cases may need to be differentiated from various metabolic disorders including other lysosomal storage diseases, maple syrup urine disease, GM2 gangliosidosis, organic acidemias, attention deficit hyperactivity disorder (ADHD), learning disabilities, dopa-responsive dystonia, Wilson disease, and certain mitochondrial disorders. Adult onset cases may need to be differentiated from Alzheimer disease, frontotemporal dementia, progressive supranuclear palsy, Pick disease (an adult-onset type of frontotemporal dementia unrelated to Niemann-Pick disease), and various psychiatric disorders. (For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database.)

**Standard Therapies**

**Diagnosis**

A diagnosis of Niemann-Pick disease type C is based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation and a variety of specialized tests. Proper diagnosis of NPC requires physicians to suspect the diagnosis based upon symptoms, whereupon it is necessary to perform appropriate biochemical tests and a skin biopsy. A blood test for NPC is being developed and should soon be readily available. Additionally, many physicians have little or no knowledge of NPC. Consequently, affected individuals and families often face a frustrating delay in diagnosis.

Clinical experts on NPC have developed a Suspicion Index Tool to help physicians unfamiliar with the disorder diagnose NPC (Wraith JE, 2014). This tool creates a risk prediction score based on the specific manifestations present in an individual case, broken down into visceral, neurological, and psychiatric categories. Initially, the tool has proven more effective in diagnosing individuals over the age of 4 than under the age of 4. Further study and refinement of the Suspicion Index Tool is necessary to determine its usefulness in clinical practice.

**Clinical Testing and Workup**
In individuals suspected of NPC, physicians may take a skin biopsy, which is the surgical removal of a small sample of skin. This skin sample is sent to a laboratory capable of performing biochemical tests that are indicative of NPC. Connective tissue cells known as fibroblasts are obtained from the skin sample and grown in a laboratory (cultured fibroblasts). These cells are studied to see how they handle the chemical conversion or processing of cholesterol (esterification) and they are also stained with a chemical called filipin, which is visible under ultraviolet light. A filipin test can reveal the abnormal accumulation of fatty material in lysosomes. Other tests obtained on the fibroblasts can also rule out other conditions.

Molecular genetic testing can confirm a diagnosis of NPC. Molecular genetic testing can detect mutations in one of the two specific genes known to cause NPC, but is available only as a diagnostic service at specialized laboratories.

A blood-based test has been developed for NPC and should soon be available through specialized diagnostic laboratories.

Treatment

Treatment of NPC may require the coordinated efforts of a team of specialists. Pediatricians, neurologists, ophthalmologists, pulmonologists, gastroenterologists, and other healthcare professionals may need to systematically and comprehensively plan an affected child’s treatment. Psychosocial support for the entire family is essential as well. Genetic counseling may be of benefit for affected individuals and their families.

Current treatment is directed toward the specific symptoms that are apparent in each individual. Difficulty swallowing (dysphagia) should be monitored and evaluated regularly, to minimize the risk of aspiration. Swallowing difficulties may first be managed by softening solids and thickening liquids. A speech therapist can work with the individual to optimize swallowing function. Eventually, the implantation of a gastrostomy tube may be required. With this procedure, a thin tube is placed into the stomach via a small incision in the abdomen, allowing for the direct intake of food or medicine.

Seizures often respond, at least partially, to anti-seizure medications (antiepileptics). Eventually, in an advanced stage of the disease, seizures may no longer respond to such medications (refractory seizures). Cataplexy may be treated by specific drugs including tricyclic antidepressants and central nervous system stimulants such as clomipramine, protriptyline or modafinil. Drugs that block the neurotransmitter acetylcholine (anticholinergic agents) have been effective in treating dystonia and tremor. Botulinum toxin can be used to treat severe dystonia. Drugs have also been used to treat various psychiatric illnesses, such as antipsychotic medications to treat psychosis and antidepressants to treat mood disorders.

The sleep abnormalities observed in NPC are also diverse. Many individuals suffer from poor sleep quality due to fragmented myoclonus during slow wave sleep. In addition total sleep time, REM and slow wave sleep percentage may be decreased. Some individuals may suffer from insomnia which can be linked to underlying psychiatric diseases, such as anxiety or depression. Sometimes, when hypotonia is severe, especially in combination with enlarged adenoids and tonsils there may be disordered breathing with long respiratory pauses during sleep (obstructive sleep apnea). This diagnosis often requires an overnight sleep study. If the obstructive sleep apnea is severe, the patients may need a machine supplying a mild air pressure with a mask to keep the airways open during sleep (positive pressure ventilation). Insomnia and other sleep problems should be treated with melatonin and if needed nocturnal sedatives.

Various services that may be beneficial to affected patients include an individualized educational plan, encompassing physical therapy, speech therapy and occupational therapy.
A controlled study and several anecdotal case reports have shown that miglustat (Zavesca®) may be able to slow or stop the progression of neurological symptoms associated with NPC. Miglustat blocks the creation (biosynthesis) of glycosphingolipids, which is one of the substances that accumulate in the brain of individuals with NPC. The U.S. Food and Drug Administration (FDA) has not approved miglustat for the treatment of individuals with NPC, although the drug is approved for the treatment of another lysosomal storage disease known as Gaucher disease. Miglustat has been used off-label in the U.S. to treat individuals with NPC. In the European Union, miglustat under the brand name Zavesca® has been approved for the treatment of progressive neurological manifestations of NPC in both adult and pediatric patients. In Japan, miglustat was approved for the treatment of NPC in 2012 under the brand name, Brazaves®.

Investigational Therapies

Several therapies have been studied or are currently being studied to assess their long-term safety and effectiveness as potential treatments for individuals with NPC. In addition to miglustat, such therapies include curcumin, cyclodextrin, and vorinostat. Curcumin is a component of turmeric, an Indian spice found in some curries. Curcumin has demonstrated some anti-inflammatory effects in regard to NPC. Cyclodextrin are molecules comprising starch and sugar rings that may be able to help brain cells discharge (efflux) cholesterol. Vorinostat is a histone deacetylase inhibitor that has shown some ability to reverse the accumulation of unesterified cholesterol in cells. More research is necessary to determine the long-term safety and effectiveness of such therapies for the treatment of individuals with NPC.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, in the main, contact:
www.centerwatch.com

For more information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/

Niemann Pick Disease Type C Resources

NORD Member Organizations:

(To become a member of NORD, an organization must meet established criteria and be approved by the NORD Board of Directors. If you're interested in becoming a member, please contact Susan Olivo, Membership Manager, at solivo@rarediseases.org.)

CLIMB (Children Living with Inherited Metabolic Diseases)
Climb Building
176 Nantwich Road
Crewe, CW2 6BG United Kingdom
Phone #: 440-845-2412173
800 #: N/A
e-mail: enquiries@climb.org.uk
Home page: http://www.Climb.org.uk

GOLD, Global Organisation For Lysosomal Diseases
3 Albion Rd
Chalfont St Giles
Buckinghamshire, HP8 4EW United Kingdom
Phone #: 441-494-870708
800 #: N/A
e-mail: enquiries@goldinfo.org
Home page: http://www.goldinfo.org

National Niemann-Pick Disease Foundation, Inc.
401 Madison Avenue
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PO Box 49
Fort Atkinson, WI 53538-0049
Phone #: 920-563-0930
800 #: 877-287-3672
e-mail: mnpdf@nnpdf.com
Home page: http://www.nnpdf.org

National Tay-Sachs and Allied Diseases Association, Inc.
2001 Beacon Street
204
Brookline, MA 02146-4227 USA
Phone #: 617-277-4463
800 #: 800-906-8723
e-mail: info@ntsad.org
Home page: http://www.NTSAD.org

Other Organizations:

Ara Parseghian Medical Research Foundation
4729 E Sunrise Dr.
Suite 327
Tucson, AZ 85718-4535 USA
Phone #: 520-577-5106
800 #: --
e-mail: victory@parseghian.org
Home page: http://www.parseghian.org

Genetic and Rare Diseases (GARD) Information Center
PO Box 8126
Gaithersburg, MD 20898-8126
Phone #: 301-251-4925  
800 #: 888-205-2311  
e-mail: N/A  
Home page: http://rarediseases.info.nih.gov/GARD/

**Hide & Seek Foundation for Lysosomal Disease Research**  
6475 East Pacific Coast Highway Suite 466  
Long Beach, CA 90803  
Phone #: 877-621-1122  
800 #: N/A  
e-mail: info@hideandseek.org  
Home page: http://www.hideandseek.org

**Instituto de Errores Innatos del Metabolismo**  
Carrera 7 No 40 - 62  
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Phone #: 571-320-8320  
800 #: N/A  
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Home page: http://www.javeriana.edu.co/ieim/programas_jeim.htm

**Niemann-Pick Disease Group (UK)**  
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Tyne and Wear, NE37 2SQ United Kingdom  
Phone #: 004-401-914150693  
800 #: N/A  
e-mail: niemann-pick@zetnet.co.uk  
Home page: http://www.niemannpick.org.uk

**NIH/National Institute of Neurological Disorders and Stroke**  
P.O. Box 5801  
Bethesda, MD 20824  
Phone #: 301-496-5751  
800 #: 800-352-9424  
e-mail: N/A  
Home page: http://www.ninds.nih.gov/

**Vaincre Les Maladies Lysosomales**  
2 Ter Avenue  
Massy, 91300 France  
Phone #: 016-975-4030  
800 #: --  
e-mail: accueil@vml-asso.org  
Home page: http://www.vml-asso.org

References
TEXTBOOKS

JOURNAL ARTICLES


INTERNET


Report last updated: 2014/10/15 00:00:00 GMT+0
Miglustat: A Review of Its Use in Niemann-Pick Disease Type C

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Abstract Miglustat (Zavesca®, Brazavase®), a small iminosugar molecule that reversibly inhibits glucosylceramide synthase, is the only disease-specific drug approved for the treatment of progressive neurological manifestations of Niemann-Pick disease type C (NP-C) in adult and paediatric patients. NP-C is a rare, autosomal-recessive lipid storage disorder characterized by impaired intracellular lipid trafficking and progressive neurological symptoms leading to premature death. In a randomized clinical trial, long-term extension studies and a retrospective observational cohort study, treatment with oral miglustat stabilized key neurological manifestations of NP-C (including horizontal saccadic eye movement peak velocity, ambulation, manipulation, language and swallowing) in paediatric and adult patients with the disease. The therapeutic effects of miglustat in stabilizing or slowing disease progression have been confirmed in other reports in the clinical experience setting. The primary tolerability issues associated with miglustat are mild to moderate gastrointestinal effects (e.g. diarrhoea, flatulence and abdominal pain/discomfort) and weight loss, which usually occur during initial therapy and are generally manageable. In the absence of a cure, miglustat is a valuable agent to reduce the progression of clinically relevant neurological symptoms in paediatric and adult patients with NP-C, which is considered a significant achievement in the treatment of this disease.

1 Introduction

Niemann-Pick disease type C (NP-C) is a rare, neurodegenerative, autosomal-recessive lipid storage disorder that occurs in all ethnic groups. It is estimated to occur in ≈ 1 in every 120,000 live births, but this is likely to be an underestimation, as NP-C is often misdiagnosed or detected after considerable delay [1, 2].

NP-C is caused by mutations in the NPC1 gene in the majority (95%) of cases and in the NPC2 gene in ≈ 4 % of cases, with many novel mutations in these genes having
been, and continuing to be, identified [1, 3–8]. As a result of these mutations, patients with NP-C have impaired intracellular lipid trafficking, which leads to the accumulation of lipids in the perinuclear lysosomes [9–11]. This, in turn, causes the build-up of excess lipids in various tissues. Accumulation of unesterified cholesterol, sphingomyelin, phospholipids, and glycosphingolipids in the liver and spleen may result in visceral symptoms, such as organomegaly and liver dysfunction; and the accumulation of glucosylceramide, lactosylceramide, and GlcCer and GlcCer gangliosides in the brain may be a factor in at least some of the neurological manifestations of NP-C [9–11].

The clinical presentation of Niemann-Pick type C is extremely heterogeneous, and is characterized by a wide range of non-specific neurological, systemic and/or psychiatric symptoms that arise at different ages and progress at different rates [1, 2, 12–15]. Ocular motor abnormalities [e.g., vertical supranuclear gaze palsy (VSGBP) and impaired saccadic eye movement (SEM)] are often the first manifestations of the disease, and are present in the majority of patients [1, 2, 12, 14, 16]. Hepatosplenomegaly is present in \( \approx 85\% \) of patients with NP-C, has a variable age of onset and may regress with age [1]. Importantly, the age of onset of systemic symptoms is not related to that of neurological manifestations, which may follow years or even decades later [2].

A major influence on the progression and prognosis of NP-C is the age of onset of neurological manifestations, which may be broadly grouped as follows [1, 2]:

- **Pre/perinatal.** Neurological involvement is not shown during the neonatal period. Visceral manifestations include neonatal cholestasis. Liver failure occurs in \( \approx 10\% \) of patients, with death usually occurring before the age of 6 months. Severe respiratory insufficiency (together with hepatosplenomegaly or more severe liver disease) may present in some infants and may also be fatal.

- **Early-infantile** (onset at 2–3 months to \( <2\) years of age). Neurological involvement may initially include delays in motor milestones and hypotonia.

- **Late-infantile** (onset at 2 to \( <6\) years of age). Neurological involvement may initially include gait problems, clumsiness, speech delay, ataxia, and VSGP.

- **Juvenile** (onset at 6–15 years of age). Neurological involvement may initially include VSGP, school problems, ataxia and sometimes seizures and cataplexy. This is the most common form of the disease in many countries.

- **Adolescent/adult** (onset at \( >15\) years of age). Neurological involvement may initially include VSGP, ataxia and dystonia. Patients may also display dementia and psychiatric illnesses.

It is important to identify NP-C early in the course of the disease; however, given the nonspecific and heterogeneous nature and subtle onset of the clinical signs and symptoms of NP-C, it is challenging to diagnose [1, 2, 8, 17, 18]. There is often a delay of several years between the first appearance of symptoms and diagnosis. In order to enhance the identification of NP-C among patients suspected of having the disease, the NP-C suspicion index screening tool [18] has been developed, in which the predicted risk of NP-C is determined by assessing visceral, neurological and psychiatric signs and symptoms that are specific to NP-C, and by taking into account the family history of the patient. A key diagnostic test of NP-C is the demonstration of abnormal intracellular cholesterol trafficking using the filipin stain on a fibroblast culture from a skin biopsy. When possible, filipin staining examinations should be performed in parallel with DNA sequencing of the NPC1 and NPC2 genes [1]. Of note, plasma levels of certain cholesterol oxidation products (oxysterols) are potential new sensitive and specific biomarkers for the clinical screening of NP-C [1, 19, 20]. Correlations between certain oxysterol plasma levels and disease severity, as well as age at neurological disease onset, have been shown in patients with NP-C [20]. Limited data indicate that measurement of plasma oxysterols may provide a sensitive and reliable method of screening patients for NP-C [21, 22].

NP-C is associated with premature death, with the majority of patients dying within 5–20 years of disease onset, with death being delayed longer in patients who are older at the time of onset [1, 2, 12–15].

As there is no curative treatment for NP-C, the goals of treatment in patients with NP-C are to improve health-related quality of life (HR-QOL) and stabilize or slow disease progression through the use of appropriate symptomatic treatments (e.g., sedatives, antiepileptic drugs, antipsychotics, anti-diarrhoeal agents, drugs used to treat dystonia, tremors and drooling, and other interventions) and disease-specific therapies [1]. Miglustat [Zavesca® (EU and many other countries), Brazaves® (Japan)] is a small iminosugar molecule that reversibly inhibits glycosphingolipid synthesis. It is the only disease-specific drug approved for the treatment of progressive neurological manifestations in adult and paediatric patients with NP-C [23]. Miglustat is also approved for the treatment of adults with mild to moderate type 1 Gaucher’s disease in whom enzyme replacement therapy is unsuitable [23]; however, a discussion of its use in Gaucher’s disease is beyond the scope of this review.

2 **Pharmacodynamic Properties**

Miglustat is a small water-soluble iminosugar that is derived from the naturally occurring glucosidase inhibitor
deoxyxojirimycin [23–25]. It reversibly inhibits glucosylceramide synthase, the enzyme that catalyzes the primary step in glycosphingolipid synthesis [23–26], with a concentration of 20–37 μM producing 50% inhibition [23]. This inhibition reduces production of glycosphingolipids, thereby reducing their accumulation in the lysosomes [23–25]. The substrate reduction activity of miglustat provides the rationale for its use in NP-C, as the neurological manifestations of the disease are thought to be secondary to the abnormal accumulation of glycosphingolipids in neuronal and glial cells [23].

Miglustat reduced glycosphingolipid accumulation and the accompanying neuropathological changes, delayed the onset of neurological symptoms and increased in survival in murine and feline models of NP-C [27, 28]. Studies in patients with NP-C have shown that treatment with oral miglustat has beneficial effects on lipid-trafficking defects [29, 30]. Treatment with oral miglustat depleted glycosphingolipids, thereby reducing pathological lipid storage, improving endosomal uptake and normalizing lipid trafficking in peripheral blood B lymphocytes [29]. Reversal of membrane lipid abnormalities in fibroblasts, with substantial reductions in glycosphingolipid levels in fibroblasts, and partial restoration of lipid rafts and the enzymatic activities of mitochondrial inner membranes complexes II and IV, have also been shown in patients receiving miglustat [30].

Miglustat also provided protection against oxidative stress [31], which appears to be increased in patients with mutations in the NPC1 gene [31–33]. Moreover, beneficial effects on axonal degeneration, as measured by CSF levels of the biomarker total-tau protein, were also shown in patients receiving miglustat [34, 35].

Treatment with miglustat is frequently associated with gastrointestinal adverse effects (see Sect. 5) [23], which are similar to those seen in patients with congenital carbohydrate intolerance disorders [36]. An in vitro study indicated that the intestinal carbohydrate malabsorption induced by miglustat is due to the reversible and primarily competitive inhibition of intestinal disaccharidases that cleave α-glycosidically linked carbohydrates [36]. Inhibition of β-galactosidase by miglustat was negligible, and did not appear to diminish normal lactose digestion [36].

In mice, long-term treatment with high-dose miglustat [8 or 16 times the highest recommended human dosage for 2 years, or 33 times the highest recommended human dosage for 1 year followed by 19 times the dosage for 1 year (dosage adjusted for weight and differences in fecal excretion)] resulted in an increased incidence of inflammatory and hyperplastic lesions in the large intestine [23]. There was a statistically significant increase in the incidence of carcinomas in the large intestine in the group receiving the highest dose, but there were no drug-related increases in the incidence of tumour in other organs. It cannot be excluded that these findings may be relevant to humans [23].

In rodent studies, miglustat had reversible adverse effects on sperm parameters (motility and morphology), which led to reductions in fertility [23, 37–39]. In contrast, oral miglustat 100 mg twice daily for 6 weeks did not appear to affect human spermatogenesis in a study in five healthy male volunteers [40]. Nevertheless, until further information is available, male patients should use reliable contraceptive methods during miglustat treatment and for 3 months after discontinuation [23]. Female patients of childbearing potential should also use contraceptive methods, as reproductive toxicity, including dystocia, has been associated with the use of miglustat in animal studies [23].

3 Pharmacokinetic Properties

The limited data on the pharmacokinetic properties of clinically relevant dosages of miglustat are derived from studies in healthy volunteers and small numbers of patients with various conditions, including NP-C, Gaucher’s disease, Fabry’s disease and HIV-1 infection, and are reported in the manufacturer’s summary of prescribing information [23]. The pharmacokinetic profile of miglustat in patients with NP-C is similar to that in healthy volunteers, and does not appear to be altered by age, body mass index, gender or race [23].

Miglustat has a dose-linear and time-independent pharmacokinetic profile [23]. Following oral administration, miglustat is rapidly absorbed, with a time to maximum plasma concentration of 2 h in healthy volunteers [23]. The absolute bioavailability of miglustat has not been determined. The intake of food with miglustat decreased the rate of absorption of the drug, but did not have clinically relevant effects on the extent of exposure to the drug in a study in healthy adult volunteers [23, 41].

Miglustat crosses the blood–brain barrier, which is important with regard to its beneficial effects on the neurological manifestations of NP-C [23, 42] (Sect. 4). The steady-state concentration of miglustat in cerebrospinal fluid (CSF) was 31.4–67.2% of that in plasma in six patients with type 3 Gaucher’s disease [23]. Miglustat does not bind to plasma proteins and has an apparent volume of distribution of 83 L [23]. In tissue distribution studies in mice [42], miglustat was present in a number of organs and tissues considered to be of importance in relation to the long-term beneficial effects of the drug.

The apparent elimination half-life of miglustat is 6–7 h [23]. The apparent oral clearance of miglustat is 230 ± 39 mL/min, with a decrease in oral clearance .
associated with decreasing renal function. According to
data from a very limited number of patients with Fabry's
disease, oral clearance decreased by 40, 60 and at least
70 % in patients with mild, moderate or severe renal
impairment, respectively [23]. The initial dosage of mi-
glustat should be reduced in patients with mild or moderate
renal impairment; the use of the drug in patients with
severe renal impairment is not recommended (Sect. 6) [23].
Pharmacokinetic data in patients with hepatic impairment
are not available.

The major route of excretion is renal, with unchanged
drug accounting for 70–80 % of a dose [23]. Following
administration of a single radiolabelled dose of miglustat
100 mg, 83 and 12 % of radioactivity were recovered in
the urine and faeces, respectively. Of the several metabo-
lites of miglustat recovered in the urine and faeces, mi-
glustat glucuronide was the most abundant, accounting for
5 % of the total dose. One or more unidentified metabolites
may have a very long half-life, as the terminal half-life of
radioactivity in the plasma was 150 h. At steady state, such
metabolites may accumulate and reach concentrations that
are greater than those of the parent drug [23].

As miglustat crosses the placenta, it should not be used
during pregnancy [23]. Miglustat should not be taken
during breast-feeding, as it is not known whether it is
secreted in breast milk [23].

4 Therapeutic Efficacy

The efficacy of miglustat in the treatment of neurologi-
cal manifestations of NP-C has been evaluated in an open-
label, randomized, controlled 12-month trial in patients
aged ≥12 years, which included an additional paediatric
cohort of children aged <12 years (Sect. 4.1) [43]. The
12-month trial was followed by open-label 12-month
extension studies, which, in turn, were followed by a
continued extension phase (Sect. 4.2) [44, 45].

As clinical trials of miglustat in the treatment of NP-C
are limited due to the rare nature of the disease, there is a
need for reports of the effects of the drug in clinical
practice settings. Such reports include a pivotal, multi-
centre, observational, retrospective cohort study of patients
with NP-C who received treatment with miglustat (Sect.
4.3) [46], reports from the international NP-C registry
(Sect. 4.4) [47], as well as a number of other case reports,
case series and cohort studies (Sect. 4.5) [48–74]. Some
data are available only as abstracts [47–49, 52, 53, 56, 62,
63, 65, 66, 69, 71–73].

In all studies and reports, the usual dosage of miglustat
was 200 mg three times daily in adults and was adjusted
according to body surface area (BSA) in paediatric
patients.

4.1 Randomized, Controlled, 12-Month Trial

The 12-month trial in patients aged ≥12 years (n = 29)
and its paediatric cohort (n = 12) enrolled patients with
NP-C (confirmed by reduced cholesterol esterification
and abnormal filipin staining in cultured fibroblasts) who
were capable of cooperating with the physical examination
and other testing [43]. Patients with clinically significant diar-
rhoea without definable cause within 3 months before
enrolment, significant gastrointestinal disorders or other
intercurrent illnesses were excluded from the trial [43].

Patients aged ≥12 years were randomized to receive
miglustat 200 mg three times daily (n = 20) or no study
drug (n = 9); the cohort of 12 paediatric patients received
BSA-adjusted doses of miglustat [43]. All patients received
standard symptomatic care, such as individualized phar-
macotherapy (e.g. analgesics, antibacterials, anti-diarrhoeal
agents, sedatives, hypnotics, antiepileptic drugs, drugs used
to treat dystonia, and other agents used to treat the symp-
toms of NP-C) and physical, speech and occupational
therapy prescribed by each patient's primary paediatrician
or neurologist. Patients were assessed at baseline, 1 week
after treatment initiation and then monthly. The dosage of
miglustat could be modified when clinically indicated [43].

In the trial in patients aged ≥12 years [43], mean patient
ages were 25.4 and 22.9 years in the miglustat and control
groups. Clinical manifestations of NP-C were generally
shown in numerically greater proportions of patients in the
miglustat group than in the control group at study entry.
For example, VSGP was shown in 100 and 78 % of
patients in the miglustat and control groups, cognitive
impairment was shown in 90 and 78 %, ataxia in 100 and
56 %, speech difficulties in 90 and 44 %, and dystonia in
70 and 44 %, respectively. In the paediatric cohort, mean
patient age was 7.2 years. 100 % of patients had VSGP,
67 % had cognitive impairment, 83 % had ataxia and 42 %
had dystonia. The median duration of exposure to miglustat
was 364.5 (range 180–429) days in patients aged
≥12 years and 371 (range 71–400) days in the paediatric
cohort [43].

The change from baseline in horizontal SEM velocity
(HSEM-α; the estimated slope of the linear regression line
of peak duration vs. amplitude of HSEM in one eye) was
the primary efficacy endpoint [43]. At each timepoint, two
assessments of HSEM were performed with a break of at
least 1 h separating each assessment; assessors were blin-
ded to the treatment status of the patients. Secondary
efficacy endpoints included changes from baseline in
HSEM-β (defined as the intercept of the linear regression
line of peak duration vs. amplitude of HSEM in one eye),
swallowing ability, auditory acuity, ambulatory ability and
cognition. Analyses were conducted in the efficacy set
(defined as all randomized patients who received at least
Table 1: Effects of oral miglustat 200 mg three times daily on clinically relevant Niemann-Pick disease type C parameters in an open-label, randomized 12-month trial in evaluable patients aged ≥12 years [43]. All patients received standard symptomatic care.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Miglustat (n = 13–20)</th>
<th>Control (n = 7–9)</th>
<th>BGD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HSEM-α</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline in all pts (primary endpoint) (ms/deg)</td>
<td>-0.431</td>
<td>0.074</td>
<td>-0.518 (-1.125 to 0.089)</td>
</tr>
<tr>
<td>Mean change from baseline excluding pts receiving benzodiazepines (ms/deg)</td>
<td>-0.485</td>
<td>0.234</td>
<td>-0.718** (-1.349 to 0.088)</td>
</tr>
<tr>
<td><strong>Ambulatory index</strong></td>
<td>2.4</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Mean baseline value</td>
<td>2.6</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>0.2</td>
<td>0.7</td>
<td>-0.715 (-1.438 to 0.007)</td>
</tr>
<tr>
<td><strong>Mini-mental status examination score</strong></td>
<td>22.8</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>Mean baseline score</td>
<td>24.0</td>
<td>23.1</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>1.2</td>
<td>-0.3</td>
<td></td>
</tr>
<tr>
<td><strong>No difficulty swallowing</strong></td>
<td>At baseline (5 mL of water; 1 tsp of puree; 1 tsp of soft lumps; one-third of a cookie) [% of pts]</td>
<td>60; 85; 80; 65</td>
<td>75; 88; 75; 75</td>
</tr>
<tr>
<td>At last assessment (5 mL of water; 1 tsp of puree; 1 tsp of soft lumps; one-third of a cookie) [% of pts]</td>
<td>85; 95; 80; 85</td>
<td>75; 88; 63; 63</td>
<td></td>
</tr>
</tbody>
</table>

*BGD* between-treatment difference (ANCOVA adjusted for baseline and centre), **HSEM-α** horizontal saccadic eye movements velocity, *pts* patients

- *p* = 0.044, **p** = 0.028 vs. control
- Six pts (five in the miglustat group and one in the control group) were excluded
- On a scale of 0 (fully active) to 9 (restricted to wheelchair); lower scores indicate better ambulation
- A total score ≥24 is considered normal; higher scores indicated better mental status

One dose of study medication and had at least one post-baseline assessment. In patients aged ≥12 years, comparisons between the miglustat and control groups were performed using ANCOVA (with baseline and centre as covariates), using baseline values and either month 12 values or the last available value obtained during treatment [43].

Treatment with miglustat was associated with improvements in HSEM velocity [43]. At month 12 or the last available value in patients aged ≥12 years, mean **HSEM-α** decreased (i.e. improved) from baseline in the miglustat group and increased in the control group, but the between-group difference was not statistically significant (Table 1). However, when six patients who were taking benzodiazepines, which are known to impair saccadic eye movement, were excluded from the analysis, changes in baseline in mean **HSEM-α** significantly (*p* = 0.028) favoured miglustat over control (Table 1). In the paediatric cohort, HSEM-α improved at 12 months, with a mean change from baseline of −0.465 ms/deg [43].

Changes from baseline for the secondary endpoints of HSEM-β (between-group difference: −0.722; 95% CI −7.781 to 6.337), ambulation (assessed using the ambulatory index; Table 1), cognition (assessed using the mini-mental status examination; Table 1) slightly favoured miglustat over control; however, between-group differences were not statistically significant [43]. Auditory acuity was normal in most patients at baseline (75 and 80% for the right and left ears, respectively in the miglustat group and 100% for both ears in the control group). At the last assessment, normal auditory acuity for both ears was shown in one additional patient in the miglustat group; in contrast, two patients in the control group developed abnormal hearing acuity. Results for these endpoints were not reported for the paediatric cohort [43].

Relative to baseline in patients aged ≥12 years, there was a 10–25% increase in the proportions of miglustat recipients who reported no difficulty in swallowing water, puree or one-third of a cookie (no change with regard to swallowing soft lumps), whereas the proportions of standard therapy recipients who reported no difficulty in swallowing water or puree remained stable, and those for soft lumps or one-third of a cookie decreased by 12% (Table 1) [43]. The between-group difference in the proportion of patients with no difficulty swallowing one-third of a cookie (the most difficult substance to swallow) significantly favoured miglustat over control at 12 months (Table 1) [43].
At baseline, few (<20%) pediatric patients had difficulties in swallowing the four substances and improvement was not anticipated [43]. After treatment for 12 months, a worsening in the ability to swallow water, purée, soft lumps or one-third of a cookie was observed in 3 (27%), 2 (18%), 1 (9%) and 2 (18%) of 11 patients, respectively [43].

4.2 Extension Studies

Results from long-term, open-label extensions of the randomized trial suggest that treatment with miglustat stabilizes disease progression in patients with NP-C [44, 45].

In the extension study in patients aged ≥12 years, 15 patients completed 24 months of miglustat treatment [44]. Relative to baseline, mean HSEM-α stabilized at 24 months (3.04, 2.57 and 3.27 ms/deg at baseline, 12 and 24 months, respectively), mean HSEM-β slightly deteriorated (19.51, 22.98 and 24.85 ms/deg), and ambulation also slightly deteriorated (mean ambulation index scores 2.13, 2.20 and 2.40) in the completers. In six 24-month completers in whom MMSE scores were available, only minimal changes in cognition were reported (mean MMSE scores 19.50, 21.17 and 19.33 at baseline, 12 months and 24 months, respectively). Depending on the substance assessed, swallowing remained stable or improved relative to baseline in 79–93% of patients who received miglustat for 24 months [44]. Overall disease stability was assessed by considering individual responses to the key parameters of neurological disease in 19 patients who received at least 12 months of miglustat. After treatment, neurological disease was considered to be stable in 13 patients and deteriorated in six patients (at baseline, three, one and two of these patients had severe, moderate and mild disease, respectively) [44].

In the extension study in the paediatric cohort, ten children completed a total of 24 months of treatment [45]. Relative to baseline at 24 months, mean HSEM-α stabilized (2.18, 1.69 and 2.11 ms/deg at baseline, 12 months and 24 months, respectively), and mean HSEM-β slightly deteriorated (28.96, 33.66 and 33.47 ms/deg) in nine completers with available HSEM data. Ambulation also slightly deteriorated from baseline at 24 months, as shown by mean ambulation index scores 2.0, 2.3 and 2.6 at baseline, 12 and 24 months, respectively, in ten completers. Most patients continued to be able to swallow all four substances at 24 months. With regard to the ability to swallow one-third of a cookie, eight patients continued to be able to swallow this substance easily at 24 months (all of these patients were able to swallow it easily at baseline), one showed an improvement, and one showed a deterioration. Overall, eight patients were considered to have stable neurological disease, with the remaining two patients showing deterioration over 24 months [45].

4.3 Observational, Retrospective Cohort Study

The approval of miglustat for the treatment of NP-C in the EU was also based on the results of the observational, cohort study that assessed the effects of miglustat on neurological disease progression in 66 patients with NP-C in the clinical practice setting [46]. The cohort included patients with confirmed NP-C treated with miglustat outside the context of clinical trials at 25 expert centres in 12 EU and non-EU countries.

A previously published disability scale for NP-C [13] was modified and used to examine the effects of miglustat treatment on ambulation, manipulation, language and swallowing [46]. Each parameter was scored from 0 (best) to 1 (worst), with five severity categories for ambulation and manipulation, and four categories for manipulation and swallowing. The mean of all four parameter scores was used to calculate a composite disability score for each patient. Assessments of disability were collected from the time of diagnosis, the start of miglustat treatment and at the last clinical contact [46].

Mean patient ages were 9.7 years (range 0–32 years) at the time of diagnosis, and 12.8 years (range 0.6–43 years) at the time when miglustat was started [46]. The mean time between diagnosis and the start of miglustat was 3.1 years (range 0–15.2 years). Both the mean and median duration of miglustat treatment was 1.5 years (range 0.1–4.5 years). At the time that data were collected for the study, 54 (82%) patients were still receiving miglustat, and 12 (18%) had discontinued treatment for one or more reasons (adverse events in six patients, death in four, perceived lack of efficacy in two, other reasons in three, and lost to follow-up in one) [46].

At the time of diagnosis, the mean composite disability score was 0.20 units [46]. Between diagnosis and treatment, mean annual disease progression was 0.11 units. However, after initiation of miglustat, disease progression stabilized, as shown by a mean annual disease progression of −0.01 units between treatment start and last visit. Although disease progression decreased in each of the subgroups categorized by the age of NP-C diagnosis, the response to miglustat was less marked in 22 patients aged <6 years at diagnosis than in 15 patients aged 6–11 years at diagnosis and 20 patients aged ≥12 years at diagnosis; the mean difference in composite disability scores before and after treatment was −0.070 versus −0.157 and −0.162 units/year, respectively. The response to miglustat was more marked in a subgroup of 43 patients with progressive neurological disease between diagnosis and the start of treatment than in the all-patient group (mean change in annual composite disability scores on treatment −0.210 vs. −0.125 units/year) [46].

Improvements were shown in each of the four individual parameter scores [46]. At the time of diagnosis, mean
scores for ambulation, manipulation, language and swallowing were 0.18, 0.27, 0.16 and 0.12 units, respectively. These functions deteriorated prior to the initiation of miglustat, but stabilized during miglustat therapy. At the last clinic visit, ambulation, manipulation, language and swallowing scores stabilized or improved in 76.6, 76.2, 77.0 and 81.0 % of evaluable patients, respectively [46].

Overall, three or more parameters stabilized or improved in most patients, including 75.4 % of patients in the overall population, 65.4 % of patients aged <6 years at diagnosis, 70.6 % aged 6–11 years at diagnosis and 90.9 % aged ≥12 years at diagnosis [46]. Patients with stabilization/improvement in three or more parameters had numerically higher mean values with regard to age at diagnosis (1.3 vs. 5.6 years), interval between diagnosis and treatment start (3.4 vs. 2.5 years), mean age at treatment start (14.6 vs. 8.0 years) and composite disability score at diagnosis (0.19 vs. 0.17 units) than patients who did not have stabilization/improvement in three or more parameters [46].

4.4 International Disease Registry

In 2009, an ongoing, international disease registry for patients with NP-C was initiated to describe the natural history and clinical course of the disease and the treatment experience of patients in the clinical practice setting [14]. Participating sites are encouraged to enrol all consecutive patients with a confirmed diagnosis of NP-C, regardless of their treatment status, in this prospective, observational cohort study [14].

According to recent NP-C registry data [47], disability status stabilized in the majority of patients receiving continuous treatment with miglustat. In the 80 of 190 enrolled patients who had received continuous miglustat, the mean age of enrollment was 17.8 years, the mean observation period was 1.2 years, and 10, 24, 24 and 16 had early-infantile, late-infantile, juvenile and adolescent/adult onset of neurological manifestations, respectively (in the remaining six patients, age at neurological onset was not collected for five patients and one patient had no neurological manifestation at enrolment in the registry). Mean composite disability scores were 0.39 (n = 75) at baseline and 0.45 (n = 76) at last follow-up. In 72 evaluable patients, disability status improved or remained stable (defined as a lowering/no change of at least three domain scores) in 52 (72 %) and worsened (defined as a lowering/no change in less than three domain scores) in 20 (28 %) [47].

4.5 Other Reports in the Clinical Practice Setting

Table 2 provides a summary of other reports of clinical experience in patients with NP-C when miglustat was started after the onset of neurological symptoms [48–50, 52–72, 74]. Overall, clinical benefits were associated with the initiation of miglustat therapy after the onset of neurological symptoms of NP-C in the clinical practice setting (Table 2). These benefits were generally modest, suggesting that miglustat may slow, but not prevent, the progression of neurological abnormalities. In clinical practice studies that reported results in subgroups of patients with infantile and juvenile NP-C [54, 55, 59], a better response to miglustat was usually shown in patients with juvenile NP-C than in those with infantile NP-C (Table 2). Likewise, a better response to miglustat was generally shown in patients who started treatment at less advanced stages of NP-C (Table 2).

Although miglustat is currently indicated to treat neurological symptoms in patients with NP-C, very limited data indicate that it may be effective when used to prevent neurological symptoms before they appear [74]. In a case series, two children aged 7 and 19 months with infantile NP-C received miglustat before the onset of neurological symptoms. Both children remained free of neurological manifestations after receiving miglustat for 7 and 5 years, respectively [74]; however, as the natural evolution of the disease in these patients cannot be known, it is difficult to ascertain the extent to which the drug delayed the clinical symptoms.

Case series have indicated that miglustat has shown beneficial effects on dysphagia in patients with NP-C when assessed using instrumental methods [i.e. videofluoroscopic swallowing studies (VFSS) of liquid barium] [50, 51]. Swallowing function generally improved or stabilized in VFSS studies during up to 4 years of miglustat treatment in children (Table 2) [50, 51]. Other reports in the clinical practice setting have also shown improvements in swallowing difficulties as assessed by clinical judgment in patients with NP-C receiving miglustat [50, 55, 59–61, 63, 67, 68].

Individuals with NP-C have a number of changes in brain white matter, which may be involved in the range of impairments seen in the disease [54, 75–80]. Treatment with miglustat was associated with improvements in brain white matter dysfunction in studies in adults with NP-C (Table 2) [67, 73]; however, consistent brain responses to miglustat were not shown in studies in children [54] (Table 2). Further studies are needed to link MRS findings to markers for diagnosis, illness severity, disease progression and clinical outcomes in patients with NP-C.

5 Tolerability

In the clinical studies in patients with NP-C (Sect. 4.1 and Sect. 4.2), diarrhoea and flatulence were common...
Table 2: Effects of oral miglustat in the treatment of Niemann-Pick disease type C in case reports/series (n = 1–22) in the clinical practice setting. Miglustat was administered after the onset of neurological symptoms according to the manufacturer’s recommendations.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description of pts at initiation of miglustat (treatment duration)</th>
<th>Effect of miglustat on neurological symptoms and other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abi-Warde et al. [48]a</td>
<td>6 pts aged 2–13 years with NP-C (6–22 months)</td>
<td>Response to treatment varied, with neurological stabilization in 2 pts and deterioration in 4 pts; trend for stabilization in pts treated at an early stage of disease</td>
</tr>
<tr>
<td>Bandeira et al. [49]a</td>
<td>3-year-old pt with severe infantile NP-C (1 year)</td>
<td>Stabilization of symptoms during the first 6 months of treatment, followed by disease progression</td>
</tr>
<tr>
<td>Chien et al. [50]</td>
<td>5 pts aged 9–14 years with infantile or juvenile NP-C (4–6 years)</td>
<td>General improvement of swallowing function (assessed by VFSS) during the first 6 months, followed by stabilization; cognition remained stable; ambulatory function remained stable for at least 2 years, then tended to deteriorate</td>
</tr>
<tr>
<td>Fecarotta et al. [51]a</td>
<td>4 pts aged 0.9–12 years with severe-infantile, late-infantile or juvenile NP-C (3–4 years)</td>
<td>3 pts with dysphagia at baseline: early improvements in swallowing ability assessed by VFSS and reductions in penetration/aspiration, with benefits being sustained during up to 4 years of miglustat therapy</td>
</tr>
<tr>
<td>Halioglu et al. [52]a</td>
<td>2 pts aged 12 and 18 years with infantile or juvenile NP-C (17 and 4 months)</td>
<td>1 pt without dysphagia at baseline: swallowing function remained stable for 40 months of miglustat therapy; improvements in swallowing function were shown in parallel with improvement or stabilization of neurological condition</td>
</tr>
<tr>
<td>Hasanoglu et al. [53]a</td>
<td>4 pts aged 1–5 years with infantile NP-C (not reported)</td>
<td>Neurological status stabilized in both pts</td>
</tr>
<tr>
<td>Héron et al. [54]</td>
<td>20 pts aged 2 months to 14 years with perinatal, early-infantile, late-infantile or juvenile NP-C (2 months to 5 years)</td>
<td>Stabilization or improvement in neurological symptoms in 2 pts; treatment discontinued because of intractable diarrhea in 1 pt; results NR for 1 pt</td>
</tr>
<tr>
<td>Karimzadeh et al. [55]</td>
<td>16 pts aged 8 months to 22 years with perinatal, early-infantile, late-infantile or juvenile NP-C (6–26 months)</td>
<td>Perinatal NP-C: disease evolution not applicable (pt died at 4 months of age)</td>
</tr>
<tr>
<td>Early-infantile NP-C: neurological symptoms worsened in 6 pts, initially improved then worsened in 1 pt, and stabilized in 1 pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late-infantile NP-C: neurological symptoms worsened in 2 pts, worsened transiently then improved in 2 pts, stabilized in 2 pts and improved in 2 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile NP-C: neurological symptoms worsened in 1 pt, worsened then improved in 1 pt and improved then stabilized in 1 pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No consistent patterns of change in MRS findings or response to miglustat were shown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolnikova et al. [56]a</td>
<td>3 pts (age NR) with juvenile NP-C (NR)</td>
<td>Perinatal NP-C: neurological symptoms improved in the pt</td>
</tr>
<tr>
<td>Early-infantile NP-C: neurological symptoms improved in 1 pt and stabilized in 1 pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late-infantile NP-C: neurological symptoms improved in 2 pts and stabilized in 3 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile NP-C: neurological symptoms stabilized in 6 pts; 2 additional pts had severe neurological disease and died due to aspiration pneumonia after ~2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paciorkowski et al. [57]</td>
<td>3-year-old pt with perinatal NP-C (1 year)</td>
<td>Stabilization of neurological symptoms, with only discrete changes; treatment-emergent acute psychotic disorder led to treatment discontinuation in 1 pt</td>
</tr>
<tr>
<td>Pérez-Poyato [58]</td>
<td>3 pts aged 1–14 years with early infantile, late infantile or juvenile NP-C (2–4 years)</td>
<td>Dementia, motor function and gait deterioration progressed despite treatment</td>
</tr>
</tbody>
</table>

Δ Adis
Table 2 continued

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description of pts at initiation of miglustat (treatment duration)</th>
<th>Effect of miglustat on neurological symptoms and other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pineda et al. [59]</td>
<td>16 pts aged 1–15 years with early-infantile, late-infantile or juvenile NP-C (0.5–4 years)</td>
<td>Early- and late-infantile NP-C: neurological symptoms, disability and cognition deteriorated. Juvenile NP-C: neurological symptoms, disability and cognition remained relatively stable. Cerebral hypometabolism (evaluated by positron emission tomography) progressed in pts with early- or late-infantile NP-C, but remained relatively stable in pts with juvenile NP-C.</td>
</tr>
<tr>
<td>Santos et al. [60]</td>
<td>10-year-old pt with NP-C (1 year)</td>
<td>Improvements in neurological symptoms, disability, cognitive function and depression; attention and affective problems were sustained for 1 year.</td>
</tr>
<tr>
<td>Skorpen et al. [61]</td>
<td>4-year-old pt with late-infantile NP-C and frequent seizures (4 years)</td>
<td>Expected deterioration of neurological function was delayed; disability generally stabilized and quality of life of pt and family improved; pt died at 8 years of age (possibly because of acute cardiac arrest).</td>
</tr>
<tr>
<td>Sreekantan et al. [62]</td>
<td>5-month-old with early-infantile NP-C (4 years)</td>
<td>Early treatment stabilized the disease, with slow improvement in neurological symptoms and no signs of regression at 4 years of age.</td>
</tr>
<tr>
<td>Tekturk et al. [63]</td>
<td>10-year-old pt with NP-C and refractory epilepsy (3 months)</td>
<td>Seizures stopped and difficulty in swallowing resolved; other neurological symptoms stabilized.</td>
</tr>
<tr>
<td>Zawrowski et al. [64]</td>
<td>9-year-old pt with NP-C and catalepsy (16 months)</td>
<td>Cataleptic attacks disappeared after 6 months of treatment; other neurological signs and symptoms stabilized with improvements in some parameters.</td>
</tr>
<tr>
<td>Adults [70, 71, 72], mixed age groups [66–69] or age NR [55, 72]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cada et al. [65]</td>
<td>2 pts with NP-C [age and onset NR (NR)]</td>
<td>Disease stabilized and neurological signs improved. Most patients showed improvement or stabilization of neurological conditions.</td>
</tr>
<tr>
<td>Fuccarotta et al. [66]</td>
<td>22 pts aged 0.6–44 years with NP-C (0.3–3.5 years)</td>
<td>Mild improvement or stabilization in swallowing, dysarthria, awareness and ambulation.</td>
</tr>
<tr>
<td>Galanaud et al. [67]</td>
<td>3 pts aged 21–38 years with juvenile or adult NP-C (2 years)</td>
<td>Improvements in markers of white matter dysfunction (i.e. normalization of choline peak in cerebral white matter) were within 12–18 months, with this effect being maintained over time.</td>
</tr>
<tr>
<td>Ginocchio et al. [68]</td>
<td>10 pts aged 4–31 years with early-infantile, late-infantile or juvenile NP-C (mean 4 years)</td>
<td>Neurological status progressed slower than would be expected from the natural history of the disease; response was better in pts with juvenile disease than in those with infantile disease.</td>
</tr>
<tr>
<td>Jacklin et al. [69]</td>
<td>11 pts aged 7–29 years with NP-C (2–7 years)</td>
<td>Initial stabilization of disease progression, followed by clinical deterioration.</td>
</tr>
<tr>
<td>Jamrozik et al. [70]</td>
<td>21-year-old pt with NP-C with late-onset ataxia (NR)</td>
<td>Fluctuating improvements in co-ordination, gait, dysphagia, speech and normalization of mood; gait-palsey developed during treatment.</td>
</tr>
<tr>
<td>Jesos et al. [71]</td>
<td>33-year-old pt with adult NP-C (NR)</td>
<td>Improvement in disability; no change in saccadic eye movement.</td>
</tr>
<tr>
<td>Lorenz et al. [72]</td>
<td>12 pts with NP-C [age and onset NR (1 year)]</td>
<td>Mental deterioration improved in 1 pt, stabilized in 9 pts, and progressed in 2 pts.</td>
</tr>
<tr>
<td>Sedel et al. [73]</td>
<td>13 pts with NP-C [age and onset NR (0.5–1 year)]</td>
<td>Choline/N-acetyl aspartate ratios in brain white matter (assessed by MRS) improved (i.e. decreased) in 11 pts during the first 6–12 months of treatment with miglustat; improvements were only visible after 1 year in some pts; only one patient with improvement in MRS showed clear clinical progression. Choline/N-acetyl aspartate ratios in brain white matter worsened (i.e. increased) in 2 pts during the first 6 months of treatment; longer follow-up was not available.</td>
</tr>
</tbody>
</table>

MRS magnetic resonance spectroscopy, NP-C Niemann-Pick disease type C, NR not reported, pt(s) patient(s), VFSS videofluoroscopic swallowing studies

a Available as an abstract

b Dysphagia assessed by VFSS; part of a larger study [66]
treatment-emergent adverse events [43-45]. Such events occurred mostly during the initial weeks of therapy and were generally mild to moderate in severity; however, diarrhoea may be severe and persistent in some patients. Diarrhoea and flatulence are among the adverse events most commonly considered to be related to study medication [43-45]. Miglustat inhibits intestinal disaccharidase enzymes (Sect. 2), which leads to the suboptimal hydrolysis of carbohydrates and results in osmotic diarrhoea and altered colonic fermentation [81].

In the 12-month trial, the treatment-emergent gastrointestinal disturbances of diarrhoea, flatulence, abdominal pain, nausea, vomiting and abdominal distension were respectively reported in 85, 70, 50, 35, 30 and 20 % of 20 patients aged ≥12 years receiving miglustat [43]. In contrast, treatment-emergent diarrhoea was reported in 44 % of nine patients in the control group, with none of the patients reporting any of the other gastrointestinal disturbances. In the cohort of 12 children aged <12 years receiving miglustat, diarrhoea was reported in 67 % of patients and flatulence in 33 % [43].

During long-term treatment, the overall incidence of treatment-emergent diarrhoea, flatulence and abdominal pain was 89, 64 and 25 % during up to 66 months of treatment in patients aged ≥12 years [44], and 67, 33 and 0 % during up to 52 months of treatment in paediatric patients [45]. Over time, the proportion of patients with diarrhoea decreased and/or stabilized: diarrhoea was reported in 86 % of patients aged ≥12 years during the first 6 months of miglustat treatment, 52 % after 1 year, 47 % after 2 years and 54.5 % beyond 3 years [44], and in 60 % of paediatric patients at 1 year, 20 % at 2 years and 43 % at 3 years [45]. Anti-diarrhoeal medication (mainly loperamide) was received by 42.9 % of patients aged ≥12 years over the course of the trial and its extensions [44].

Miglustat therapy is associated with generally mild or moderate losses in weight [23, 43-45, 81], with the greatest prevalence of weight loss being observed between 6 and 12 months of treatment [23]. In the extension study in patients aged ≥12 years, a decrease in weight was reported in 75 % of patients, with a mean change from baseline of -2.81 kg at 24 months and -2.76 kg at 48 months [44]. In the extension study in the paediatric cohort, 25 % of patients overall had a weight loss that was considered related to miglustat treatment [45], with the prevalence decreasing from 30 % at 1 year to 20 and 14 % at 2 and 3 years, respectively [45]. There was no clinically relevant deterioration of growth curves over time in juvenile [44] and paediatric patients [45] in the clinical trial and its extensions. However, during the early phase of miglustat treatment, reduced growth has been reported in some paediatric patients with NP-C. During treatment with miglustat, the weight and height gain of paediatric and juvenile patients should be monitored, and the benefits and risks of continued treatment for the individual should be reassessed if necessary [23].

Tremor and other nervous system disorders represent typical manifestations of NP-C and are generally considered unrelated to treatment with miglustat [44, 45]. Overall, in the clinical trial and its extensions, tremor was reported in 16 of 28 (57.1 %) of patients aged ≥12 years receiving miglustat [44], and 7 of 12 (58 %) of paediatric patients [45]. Tremor was generally mild or moderate in intensity, but was severe and considered related to study medication in two patients aged ≥12 years [44].

No serious adverse events in the clinical trial and its extensions were considered to be related to miglustat therapy [43-45].

In the clinical trial and its extensions, treatment with miglustat was discontinued because of adverse events in four patients aged ≥12 years (one each because of insomnia and confusional state (not considered related to miglustat), diarrhoea attributable to Crohn’s disease, disease progression and axonal neuropathy and tremor) [43, 44], and two paediatric patients (one each because of lethargy memory impairment and depression and Crohn’s disease) [43, 45].

No pattern of clinically relevant abnormal laboratory findings were observed in the clinical trial and its extensions [44, 45]. Monitoring of platelet counts is advised in patients with NP-C who have platelet counts below the lower limit of normal prior to initiating miglustat therapy, as mild reductions in platelet counts below the lower limit of normal (without an association with bleeding) have been observed in some patients prior to and during miglustat therapy [23]. During the clinical trial and its extensions, mean platelet counts decreased from baseline; however, changes were not considered clinically relevant, with none of the patients aged ≥12 years having a platelet count <100 x 10^9/L [44] and none of the paediatric patients having a platelet count <120 x 10^9/L [45].

Further evidence of the safety of miglustat is available from reports of clinical experience in patients with NP-C (Sects. 4.4 and 4.5). Where reported, miglustat was generally well tolerated, with mild and transient diarrhoea, flatulence and/or weight loss being the most commonly reported adverse events [48-50, 52-60, 63, 67, 68]. Reductions in miglustat dosage and/or treatment interruption or discontinuation because of adverse events were seldom required [48, 53, 54, 56, 67, 68].

6 Dosage and Administration

In the EU, oral miglustat is approved for the treatment of progressive neurological manifestations in adult and
paediatric patients with NP-C [23]. It should be used under the
direction of physicians who are knowledgeable in the
management of NP-C.

The recommended dosage of miglustat in adults and
adolescents (age ≥12 years) is 200 mg three times daily
[23]. In children aged <12 years, the recommended dosage
of miglustat is based on the patient’s BSA as follows:
200 mg three times daily in those with a BSA > 1.25 m²;
200 mg twice daily in those with a BSA > 0.88–1.25 m²;
100 mg three times daily in those with a
BSA > 0.73–0.88 m²; 100 mg twice daily in those with a
BSA > 0.47–0.73 m²; and 100 mg once daily in those with
a BSA ≤ 0.47 m². Diarrhoea may necessitate a temporary
dose reduction in some patients. Miglustat can be admin-
istered with or without food [23].

As exposure to miglustat is increased in patients with
renal impairment (Sect. 3), miglustat should be initiated at
lower dosages in patients with renal impairment than in
those with normal renal function [23]. In adults with
adjusted creatinine clearance rates of 50–70 or 30–50 mL/
min/1.73 m², miglustat treatment should be initiated at
respective dosages of 200 and 100 mg twice daily. In
children aged <12 years with mild or moderate renal
impairment, the dosage should be adjusted for BSA. The
use of miglustat is not recommended in adults or children
with severe renal impairment (creatinine clearance rate of
<30 mL/min/1.73 m²) [23]. Miglustat should be used with
cautious in patients with hepatic impairment, as the use of
the drug has not been evaluated in this patient population.

The benefits of miglustat treatment on neurological
manifestations of NP-C should be evaluated on a regular
basis (e.g. every 6 months), with a re-appraisal of miglustat
continuation conducted after at least 1 year of treatment
[23].

Local prescribing information should be consulted for
further information relating to miglustat, including special
warnings and precautions.

7 Miglustat in Niemann-Pick Type C Disease: Current
Status

Miglustat, the only NP-C-specific therapy currently avail-
able, is approved for the treatment of progressive neuro-
logical manifestations of NP-C in EU countries, as well as
a number of other countries worldwide (e.g. Argentina,
Australia, Brazil, Canada, Chile, Colombia, Japan, Mexico,
New Zealand, Russia, South Korea, Switzerland and Tur-
key) [82].

The approval of miglustat in the treatment of progressive
neurological manifestations of NP-C was based on
data from a randomized clinical trial (Sect. 4.1), long-term
extension studies (Sect. 4.2) and a retrospective
observational cohort study (Sect. 4.3). These studies indi-
cated that miglustat stabilized key neurological manifes-
tations of NP-C (e.g. ambulation, manipulation, language
and swallowing), as well as HSEM peak velocity. As
saccadic eye movement characteristics correlate with
disease severity and duration measures and specific neuro-
logical functions, they provide an index of NP-C severity
and may be useful in evaluating disease progression and
response to treatment [83]. The therapeutic effects of mi-
glustat in stabilizing or slowing disease progression have
been confirmed in reports in the clinical experience setting
(Sects. 4.4 and 4.5). Of note, neurological manifestations
of NP-C typically include dysphagia, which may lead to food
or fluid aspiration [84]. As bronchopneumonia subsequent
to food or fluid aspiration is a major cause of mortality in
patients with NP-C [84], the improvements or stabilization
of swallowing function shown with miglustat may reduce
the risk of aspiration pneumonia and its associated mor-
tality [84].

The primary tolerability issues associated with miglustat
are mild to moderate gastrointestinal effects (e.g.
diarrhoea, flatulence and abdominal pain/discomfort) (Sect. 5).
These effects can generally be managed with anti-propuls-
ive medication (e.g. loperamide), individualized dietary
modulation (e.g. reduced consumption of dietary sucrose,
lactose and other carbohydrates) and/or a temporary
reduction in miglustat dose [23, 81]. Dietary interventions,
particularly if started at or before the initiation of miglustat
therapy, may also reduce the magnitude of changes in
weight that may occur during miglustat therapy [81].

In conclusion, in the absence of a cure, miglustat is a
valuable agent to reduce the progression of clinically rel-
ent neurological symptoms in paediatric and adult
patients with NP-C, which is considered a significant
achievement in the treatment of this disease. According to
current international guidelines for the diagnosis and
management of NP-C [1], all patients with neurological,
psychiatric or cognitive manifestations at diagnosis of NP-
C should be offered treatment with miglustat based on
potential improvements in, or maintenance of, HR-QOL. In
patients with NP-C, the clinical benefits of miglustat may
be discernible only after 6 months to 1 year of treatment,
or even longer in patients with slowly progressive disease
[1]. The response of patients with perinatal and infantile
forms of NP-C may be less appreciable than those with
juvenile or adult forms of the disease (Sect. 4), as patients
with early-onset forms of NP-C generally have greater
symptom severity and more rapid disease progression [1,
12–15]. Patients whose diagnosis of NP-C resulted from
sibling screening or systemic symptoms should be moni-
tored regularly for the appearance of neurological mani-
festations, with initiation of miglustat treatment considered
at the first signs of the onset of neurological disease [1].
The response to miglustat is generally better in patients who started treatment at less advanced stages of NP-C than in those who started at more advanced stages (Sect. 4). The effects of miglustat on neurological manifestations should be evaluated on a regular basis (Sect. 6), with treatment generally continued as long as there are discernible therapeutic benefits with an acceptable tolerability and safety profile. Decisions to alter or stop therapy should be based on individual patient characteristics and should involve consultation with patients and family members [1].

Data selection sources: Relevant medical literature (including published and unpublished data) on miglustat in patients with Niemann-Pick type C disease was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) (searches last updated 23 November 2013), bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug. Search terms: Miglustat, Niemann-Pick disease type C, Niemann-Pick disease. Study selection: Studies in patients with Niemann-Pick type C disease who received miglustat. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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The Videofluoroscopic Swallowing Study Shows a Sustained Improvement of Dysphagia in Children With Niemann–Pick Disease Type C After Therapy With Miglustat

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Niemann–Pick disease type C (NPC) is a rare autosomal recessive lysosomal storage disorder characterized by defective intracellular lipid trafficking, with secondary accumulation of free cholesterol, sphingosine, and glycosphingolipids. NPC is clinically characterized by a wide spectrum of manifestations with progressive visceral and neurological involvement, including dysphagia. Neurological manifestations represent the most debilitating findings. Swallowing impairment is a frequent cause of morbidity and disability in NPC patients and progressive dysphagia may be considered a marker of neurological progression. Recently, substrate reduction therapy with miglustat has been proposed for the treatment of neurological manifestations in NPC patients. This observational study reports on the long-term use of miglustat in four pediatric patients with NPC and shows the efficacy of the treatment to improve or prevent dysphagia, and persistence after 3 years of treatment or more. We used a videofluoroscopic analysis of liquid barium swallowing to provide additional information on patterns of impairment of the swallowing mechanism and to detect aspiration. In three patients showing dysphagia and aspiration we observed the improvement of the swallowing function and the sustained absence of barium aspiration in the airways after miglustat treatment, while the patient with normal swallowing function at baseline did not show any deterioration. We suggest that the videofluoroscopic study of swallowing should be routinely used to monitor the effects of treatment on swallowing ability in NPC patients.

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Key words: Niemann–Pick disease type C; miglustat; videofluoroscopic swallowing study; dysphagia; children

INTRODUCTION

Niemann–Pick disease type C (NPC) is a rare autosomal recessive lysosomal storage disorder characterized by defective intracellular lipid trafficking, with secondary accumulation of free cholesterol, sphingosine, and glycosphingolipids (GSLs). NPC is estimated to affect 1 in 150,000 newborns. NPC is genetically heterogeneous, as it can be caused by mutations in one of two genes, either NPC1 or HEI/NPC2 [Nauckeckiene et al., 2000; Bauer et al., 2002]. Mutations in NPC1 account for more than 95% of all NPC disease patients, whereas mutations in HEI/NPC2 account for the remaining 5%. A complex pattern of intracellular lipid storage has been observed, with the profile of abnormal lipid levels varying among tissues. Marked accumulation of sphingosine and of several GSLs, including GM2 and GM3 gangliosides, has been shown in neurons [Vanier, 1999; Zervas et al., 2001a]. Recent findings suggest that sphingosine storage is an initiating factor in NPC1-disease pathogenesis that causes altered calcium homeostasis, leading to the

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secondary storage of GSLs and cholesterol [Lloyd-Evans et al., 2008].

NPC is clinically characterized by a wide spectrum of manifestations with variable age at onset [Vanier and Millat, 2003]. Progressive visceral and neurological signs and symptoms are the main clinical features. Neurological findings in NPC include cerebral supranuclear gaze palsy, ataxia, dystonia, dysphagia, seizures, progressive dementia, psychiatric syndromes, and gelastic cataplexy. Most NPC patients with neurological impairment show difficult swallowing and progressive dysphagia may be considered a marker of disease progression. Swallowing impairment is a frequent cause of morbidity and disability in NPC patients, as the development of secondary chronic malnutrition could be as serious a concern as aspiration and hypoxemia. Oral feeding eventually becomes impossible and gastrostomy feeding might be required.

No disease-modifying treatment is available for NPC patients. Miglustat (N-butyl-deoxynojirimycin, NB-DNJ, Zavesca®—Actelion Pharmaceutical, Inc.), a small iminosugar molecule able to cross the blood–brain barrier, reversibly inhibits glucosylceramide synthase, which catalyses the first committed step in glycosphingolipid synthesis. Inhibition of GSLs synthesis by miglustat delayed symptoms onset and prolonged survival in both murine and feline models of NPC, suggesting that GSLs storage could have a central role in the pathogenesis of neuronal damage [Zervas et al., 2001b; te Vrugt et al., 2004]. Substrate reduction therapy with miglustat has been proposed for treatment of NPC—[Lachmann et al., 2004; Platt and Jayakumar, 2008] and very recently miglustat has been approved by the European Medicines Agency (EMA) for the treatment of neurological manifestations in NPC patients. Limited experiences have been reported to date, but preliminary data from 1 year treatment of juvenile and adult NPC patients enrolled in a randomized, controlled clinical trial suggest that miglustat improves or stabilizes several neurological manifestations [Patterson et al., 2007]. Data from long-term treatment of 10 affected children enrolled in a parallel, noncontrolled study [Patterson et al., 2010] and from patients participating in further observational studies confirmed the previous results [Patterson et al., 2010; Pineda et al., 2009]. Data from literature suggest that miglustat may improve dysphagia in NPC patients but present information is limited. Clinical assessment of swallowing in adult and juvenile patients enrolled in the prospective clinical trial showed better outcome of swallowing function in treated patients compared to the standard care group, despite none of them had severe swallowing difficulties at baseline [Patterson et al., 2007]. The majority of the enrolled children did not have swallowing impairment at baseline and showed a sustained normal ability to swallow after 24 months of treatment, while the only patient having mildly impaired function at baseline worsened [Patterson et al., 2010]. These results indicate that swallowing ability does not deteriorate in miglustat-treated patients who did not show severe dysphagia before treatment. Improvement of severe dysphagia has been shown by videofluoroscopic swallowing study (VFSS) in a single reported patient following 1 year-miglustat treatment [Chien et al., 2007].

Swallowing is a complex and coordinated neuromuscular process consisting of both voluntary and involuntary activities and involving three anatomically and temporally distinct but closely interrelated stages called oral, pharyngeal and esophageal phases. Clinical evaluation of swallowing is a non-invasive tool to assess swallowing impairment and changes in swallowing ability after treatment, but the available information is limited. Instrumental evaluation supplements the clinical assessment, providing additional information. The value of videofluoroscopic swallowing study (VFSS) is the most commonly used tool for determining the nature and the extent of swallowing disorders, although it is actually performed by relatively few radiologists. Its use in children is becoming increasingly widespread, and it is considered by many specialists to be the gold standard test. Its advantages in the assessment of swallowing include the ability to provide a dynamic view of all the stages of swallowing (oral preparatory, oral, pharyngeal, and upper esophageal phases) and an accurate detection of aspiration [Horns and Ryan, 2006].

In this study we monitored the long-term effects of treatment with miglustat on swallowing ability and dysphagia in four pediatric patients with NPC disease, by radiological videofluoroscopic analysis of liquid barium swallowing.

PATIENTS AND METHODS

Four pediatric patients with NPC were recruited in an observational study at the Department of Pediatrics, Federico II University of Naples, Italy. The research was conducted in compliance with the Ethic principles of the Declaration of Helsinki. Written informed consent was obtained from patients' parents, and the procedures were approved by the local Ethics Committee. These patients are included in an investigator-initiated multi-center national trial on miglustat treatment in NPC, supported by the Italian Drug Agency (Agenzia Italiana del Farmaco—AIFA, Rome, Italy, trial identification number: FARM59T23W).

Table I summarizes the baseline clinical features of patients, their age at diagnosis and at start of treatment, the results of biochemical and molecular analysis.

The diagnosis of NPC was performed by cytochemical demonstration of cholesterol accumulation and block in LDL-induced cholesterol ester formation by filipin staining in skin fibroblasts [Penchev et al., 1985; Blanchette-Mackie et al., 1988; Vanier et al., 1991] and/or by molecular analysis. Three patients were classified into a classic biochemical phenotype as their fibroblasts showed a striking cholesterol accumulation and a severe block in LDL-induced cholesterol ester formation [Vanier et al., 1991]. Molecular analysis of NPC1 gene showed mutations in these patients, as previously reported [Fancello et al., 2009]. The biochemical assay was not performed in the fourth patient who showed a homozygous mutation of the HEH/NPC2 gene [Fancello et al., 2009]; however he had an older brother affected by NPC, died at 10 months of age, who showed a variant biochemical phenotype at filipin staining.

According to the classification proposed by Millat et al. [2005] on the basis of the age at onset of the first neurological symptoms patients were categorized as having either a severe infantile form (onset before 2 years of age), a late infantile form (onset at age >2–5 years), a juvenile form (onset between 5 and 16 years) or an adult form (onset at age >16 years).
All patients received misgustat orally with dosage ranging between 250 and 300 mg/m²/day divided in three doses for 3 years or longer (range: 36–48 months).

Swallowing impairment was assessed by videofluoroscopic swallowing study at baseline and during follow-up visits. The last available videofluoroscopic evaluation was after 48 months (Patient 1), 40 months (Patient 2) and 36 months (Patients 3 and 4) of treatment, respectively.

VFSS was performed administering 5 ml of liquid barium with progressive increases in bolus volume as tolerated. Patients able to sit unsupported seated as upright as possible and they were imaged in lateral and anteroposterior projections. Patient 4 was imaged in a semisupine position in his mother’s lap in four of five evaluations.

Assessment was performed periodically by the same radiologist. Images were observed on a monitor and recorded on videotape for further analysis.

All phases of the swallowing motion were analyzed and patients were classified as having oral and/or pharyngeal phase dysfunction, according to Gates et al. [2006]. Oral-phase dysfunction was suggested by the observation of anterior positioning of bolus, weakness of labial or buccal muscles, tongue hypomobility, incoordination of tongue motion. Pharyngeal phase dysfunction was identified by palatal hypomobility, decreased bolus propulsion, decreased pharyngeal and laryngeal sensation, decreased hyo-laryngeal elevation, reduced epiglottis deflection, abnormal laryngeal valve closure, upper oesophageal sphincter dysfunction, delay in onset of pharyngeal phase.

The severity of dysphagia was categorized by a 6-point severity rating score (Dysphagia Severity Score, DSS), ranging from normal swallowing to severe dysphagia, based on the deviation from normal swallowing and the potential for aspiration. The Dysphagia Severity Rating Scale was adapted from Gates et al. [2006] as described in Table II A. A 7-point score was attributed to