

Niemann-Pick Disease Type C in Adulthood – A Psychiatric and Neurological Disorder

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Abstract

Niemann-Pick disease type C (NPC) is a rare neurovisceral lipid storage disorder resulting from autosomal recessively inherited loss-of-function mutations in either *Npc1* or *Npc2*. This disrupts intracellular lipid transport, leading to the accumulation of lipid products in the late endosomes and lysosomes. Affecting both children and adults, it exhibits a less rapid disease course in older patients, where it is characterised by slow cognitive decline, neuropsychiatric illness, ataxia and dystonia. As NPC is heterogeneous in presentation, it is often misdiagnosed as other movement or psychiatric disorders, highlighting the need for better awareness of this disease among clinicians. NPC is a progressive disorder and the only currently available disease-specific drug for its treatment is miglustat, which has shown positive outcomes in clinical studies. While other medications have been tested in animal models with encouraging results, they have yet to be trialled in human subjects.

Keywords

Niemann-Pick disease type C (NPC), adult-onset, lipid storage disorder, genetic mutation, neuropsychiatric disorder, miglustat, vertical gaze palsy, misdiagnosis, glycosphingolipids, progressive disorder

Disclosure: Mark Walterfang has served on local and international advisory boards for Actelion, which is the manufacturer of miglustat (Zavesca). Dennis Velakoulis has no conflicts of interest to declare.

Received: 25 May 2010 **Accepted:** 14 June 2010 **Citation:** *European Neurological Review*, 2010;5(1):83–7 DOI:10.17925/ENR.2010.05.01.83

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Support: The publication of this article was funded by Actelion. The views and opinions expressed are those of the authors and not necessarily those of Actelion.

Niemann-Pick disease type C (NPC) is a rare and fatal neurovisceral lipid storage disorder that affects both children and adults. Whereas the disease in children is characterised by mental retardation, seizures and often rapid neurodegeneration, in adults the disease is characterised by slow cognitive decline, major neuropsychiatric illness and the development of ataxia and dystonia.¹

The data are limited in terms of the epidemiology of NPC. This disease is pan-ethnic, and two genetic isolates have been described in French Arcadians in Nova Scotia and Spanish Americans in South Colorado.² The prevalence of NPC in the general population has been estimated at between one in 100,000 and one in 150,000 live births,^{3–6} although the incidence in the genetically isolated populations is higher.^{2,7} Of these cases, approximately 20% experience symptomatic onset during adolescence and adulthood,⁸ resulting in an estimated adult prevalence of one in 500,000 to one in 750,000. Although adult onset is technically defined as symptoms presenting at 18 years of age or over, it may be more relevant to separate both adolescent- and adult-onset from childhood-onset NPC. In the adolescent-onset group, the first obvious neurological or psychiatric symptoms appear at 13–14 years of age, and this group of patients is generally phenotypically different from the early-onset (infantile or juvenile) patient group.^{9–10}

While there is no exact figure for the mean age at onset of adult NPC, most patients develop initial signs during the second or third decade,¹¹

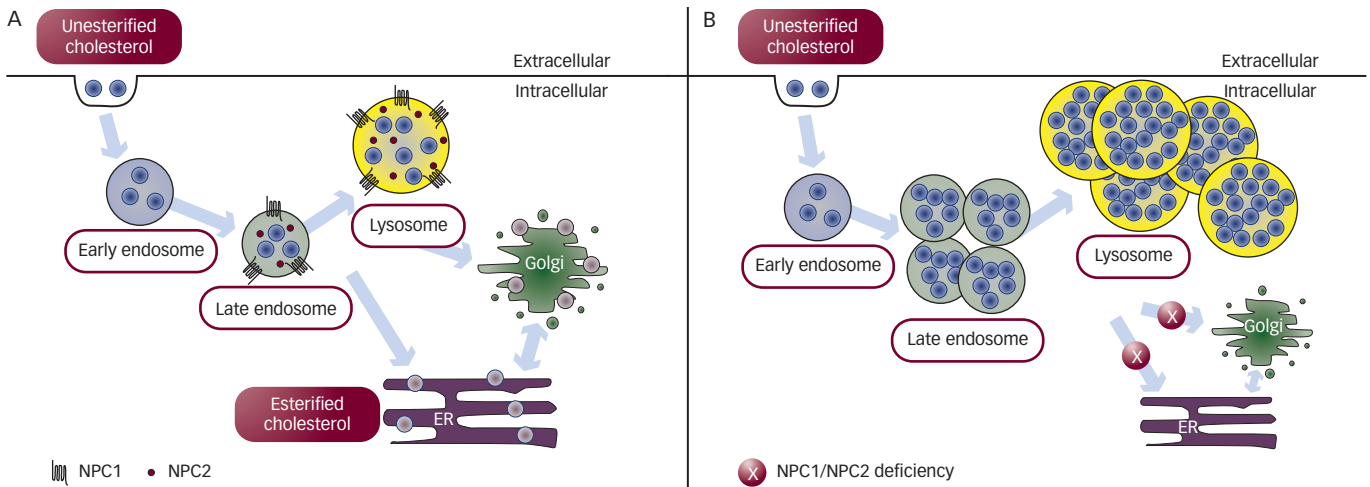
although presentation in the sixth decade has been reported.⁹ Like childhood and adolescent NPC, adult NPC is a progressive disorder and patients usually succumb to illness in their late 30s or 40s.¹¹ The atypical presentation of NPC in adults often leads to its misdiagnosis as other movement disorders or major psychiatric illness.^{9,11,12} Given the progressive nature of NPC, the high likelihood of misdiagnosis and the presence of available treatment, it is important to increase awareness of this disease among clinicians and provide better knowledge of its manifestation and management.

Pathogenesis of Niemann-Pick Disease Type C

NPC results from autosomal recessively inherited loss-of-function mutations in either *Npc1* (chromosome location 18q11)^{9,13} or *Npc2* (chromosome location 14q24.3).^{9,14} Approximately 95% of NPC patients are found to have mutations in the *Npc1* gene,¹³ which encodes a multipass transmembrane protein, NPC1, localised to the late endosome and lysosome.^{15–17} This protein contains a sterol-sensing domain,¹⁸ and the traditional view is that NPC1 co-ordinates the transport of low-density lipoprotein (LDL)-derived unesterified cholesterol from late endosomes and lysosomes to other intracellular compartments,^{19,20} although more recent evidence suggests its primary chaperone role is with sphingosine and that loss of function results in cholesterol accumulation indirectly via altered calcium homeostasis.²¹ Conversely, approximately 5% of NPC patients exhibit mutations in *Npc2*.¹⁴ The gene product of *Npc2*, NPC2, is a small,

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Figure 1: Lipid-trafficking Defects in Niemann-Pick Type C Disease¹¹



A: Normally, lipoprotein cholesterol particles enter the endosomal network, where unesterified cholesterol and companion lipids are then trafficked from late endosomes and lysosomes to the Golgi apparatus, endoplasmic reticulum and other intracellular compartments. B: Niemann-Pick (NP) C1 or NPC2 defects inhibit the transport of unesterified cholesterol and sphingolipids from late endosomes and lysosomes, leading to their accumulation at these sites. ER = endoplasmic reticulum.

Table 1: Clinical Signs of Niemann-Pick Type C Disease in Adulthood

Clinical Sign	Presentation in Patients (n=67*) (%)
Ataxia	76
Vertical supranuclear ophthalmoplegia	75
Cognitive disorder	61
Dysarthria	63
Movement disorder	58
Splenomegaly	54
Psychiatric	45
Dysphagia	37
Pyramidal	19
Hepatomegaly	19
Epilepsy	16
Deafness	4
Cataplexy	4

*n=68 for splenomegaly and hepatomegaly. Data reproduced from Sevin et al., 2007.⁹

soluble protein that is localised to lysosomes and is also secreted.²² With a putative cholesterol-binding domain,²³ NPC2 is also involved in the transport of sterols between multiple intracellular organelles, and mutations affecting the area around this domain impair binding and movement of cholesterol within the cell.²⁴

Although either of two different protein mutations may be responsible for NPC, both result in identical disease phenotypes that are biochemically and clinically almost indistinguishable.¹¹ Evidence suggests that NPC1 and NPC2 function in the same pathway to regulate intracellular lipid transport.²⁵ A reduction or loss of function in either of these proteins results in lipid-trafficking defects and an accumulation of unesterified cholesterol, glycosphingolipids and other lipid components in the late endosomes and lysosomes of most cell types (see Figure 1).^{8,19,20,26–28} These lipids are then unable to reach their intended destinations, which include the Golgi apparatus and the endoplasmic reticulum. This leads to negative cellular effects in the liver, spleen and brain.¹¹ In neurons, a number of metabolic functions are disrupted, which in turn leads to cytoskeletal dysfunction, ectopic dendritogenesis, meganeurites and altered myelination. NPC is

associated with the toxic production of GM gangliosides, particularly GM2 and GM3 gangliosides,²⁹ in neurons that appear to underpin the neurological and psychiatric consequences of the illness.⁹

Currently, over 230 disease-causing mutations of the *Npc1* gene have been identified, with a subset of mutations specifically affecting the cysteine-rich luminal loop of the protein.⁹ This not uncommonly results in the 'variant' biochemical phenotype, and is often associated with less severe defects in cellular LDL cholesterol trafficking than the 'classic' phenotype.^{8,30} Data from case studies suggest that this variant phenotype occurs more frequently in later-onset disease⁹ and may account for the slower illness course seen in many adults.

Signs and Symptoms

Clinically, NPC is an extremely heterogeneous disease and its presentation varies greatly among patients. A review of 13 adult cases from a comprehensive study and 55 other cases of NPC examined the frequency of a number of commonly occurring clinical characteristics (see Table 1).⁹ In adult patients, the first indication may be a motor sign such as tremor, ataxia, vertical gaze palsy or dystonia resulting in disturbances to speech, swallowing, vision, gait and fine motor control. As these symptoms may be rather subtle at onset, it is not uncommon for patients not to be aware of them; instead, family members and friends may notice slight alterations in the way the patient walks and/or talks.

By contrast, non-motor signs can also be the first notable sign in adult NPC. This includes major neuropsychiatric illnesses, often in the form of a schizophrenia-like psychotic disorder.¹² However, NPC can also present as a mood disorder and may occasionally follow childhood attention-deficit disorders. An initial psychotic disease can sometimes precede the onset of any motor symptoms by up to 10 years.³ While most, if not all, adult patients show difficulties in vertical gaze (vertical supranuclear ophthalmoplegia) at disease onset, NPC remains heterogeneous in its clinical manifestations and the initial presentation of adult patients may be motor or neuropsychiatric in nature.^{9,12} Because of this clinical heterogeneity, adult NPC patients may present to psychiatrists as well as neurologists. Motor symptoms that occur after the initial presentation of psychiatric illness are not uncommonly

attributed to the effects of medication, particularly dystonia in the setting of antipsychotic medication usage.

The fact that adult patients often present with neuropsychiatric illness prior to exhibiting motor and/or cognitive impairments¹² may relate to the differential effect of the underlying pathophysiology on white and grey matter structures. There is some evidence for this from a recent neuroimaging study showing widespread white matter deficits and relatively restricted grey matter deficits in adult-onset disease,³¹ and this hypothesis is also supported by a study using the NPC knockout mouse that shows significant axonal changes occurring prior to neuronal loss.³² This may provide at least a partial explanation as to why adult patients often present with neuropsychiatric illness prior to exhibiting motor and/or cognitive impairments. Early disruption to 'macroconnectivity' (due to disrupted axonal and myelin structure) and 'microconnectivity' (due to altered synaptic structure and function) leads to a functional disconnection that predisposes to major mental illness such as schizophrenia. This is then followed by more widespread neuronal dysfunction and loss that results in frank movement disorder and cognitive impairment.¹² The characteristic vertical gaze palsy is caused by a striking vulnerability of neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus to disrupted intracellular lipid storage.³³ Ataxia results from an apparent vulnerability of cerebellar Purkinje neurons to the underlying disease process.^{34,35} Cognitive impairment, which usually involves significant memory and executive dysfunction, may result from the disruption to cellular functioning, including the deposition of neurofibrillary tangles, in major structures involved in these functions, such as the hippocampus, thalamus and higher cortex.^{36–38}

Differences Between the Symptoms of Childhood and Adult Niemann-Pick Disease Type C

Childhood-onset patients often present with intellectual retardation, seizures and more obvious visceral signs, such as hepatosplenomegaly, compared with adults.^{39,40} Children experience a more rapid disease course and deteriorate more quickly.^{41–43} This is partially related to the nature of the mutation in the individual patient (with I1061T being a common cause of juvenile-onset illness),⁹ although other factors including gender may be involved.⁴⁴ Adults generally have a slower disease progression⁴⁵ and milder splenomegaly that is often clinically missed.⁴⁶

Diagnosis of Niemann-Pick Disease Type C

The most common and most reliable test for diagnosing NPC is filipin staining of fibroblast cells,⁴⁶ whereby skin fibroblasts are cultured in LDL-enriched medium, fixed and stained. Cholesterol-filled perinuclear vesicles of NPC cells are observed under fluorescence microscopy. Approximately 85% of cases possess this classic pattern of lipid storage.⁴⁶ Individuals with the variant phenotype tend to exhibit a lower, more variable level of storage that can lead to difficulties in diagnosis.^{47,48} However, incubation with LDL under specific conditions can optimise test results and facilitate NPC identification.⁴⁸

While filipin staining remains the accepted standard for the diagnosis of NPC, other options are available, including the detection of any reduction in the rate of cholesterol esterification and genotyping.⁴⁶ Mutation analysis of the gene to determine the illness associated with mutations is definitive, although clinically filipin staining is often sufficient to make a diagnosis of NPC. A more recent development that may obviate the need for skin biopsy and specialised laboratories

trained in the filipin-staining diagnostic process involves the assay of circulating oxidised forms of cholesterol, some forms of which are markedly elevated in both childhood and adult-onset NPC disease (Daniel Ory, personal communication).

Considering the heterogeneous presentation of NPC, particularly in adults, it is not surprising that individuals with this illness are often misdiagnosed. As previously discussed, NPC is characterised by a wide variety of symptoms that can appear at different points during the disease course.^{41,45} A review of adult NPC cases demonstrated a mean diagnostic delay of 6.2±6.4 years.⁹ Adult-onset patients will often present with some subtle signs and be diagnosed with schizophrenia for many years before being recognised as having NPC.¹² In the presence of major psychiatric illness, the development of any motor signs may be incorrectly attributed to psychotropic medication, further delaying proper testing and diagnosis. This often lengthy diagnostic delay highlights the need for better clinician awareness of the signs and symptoms of NPC. Recognition that isolated splenomegaly or hepatosplenomegaly could indicate NPC should allow for earlier detection of the disease prior to neurological involvement. However, as NPC can present purely as a psychiatric disorder, accurate diagnosis is often challenging.⁹ It is possible that covert signs may be present prior to more obvious symptomatic disease, which strongly indicates the need for a thorough neurological examination for ataxia and vertical gaze palsy in all patients presenting with a psychotic illness.

The Natural History of Niemann-Pick Disease Type C

A recent study by Wraith et al.⁴⁹ focused on the progression of NPC in adults and children, assessing the course of neurological deterioration in 57 patients. This retrospective observational cohort study asked physicians to complete online questionnaires for their patients at diagnosis and at up to three follow-up visits. Disease progression was measured using an NPC-specific disability scale that consisted of four parameters of neurological disease progression: ambulation, manipulation, language and swallowing. The annual rate of change in each parameter and the composite score using a linear mixed model analysis was calculated to determine disease progression. Patients were also classified based on the number of worsening parameters during the observation period.

The rate of deterioration was found to be similar across all four parameters and the mean annual disease progression was +0.12 units (95% confidence interval [CI]). Of the patients with at least one year between diagnosis and last visit (n=49), 42 (86%) had disease progression and only seven (14%) had stable disease. The authors concluded that there was progression in all four parameters of the disability scale that demonstrated a continuous progression of neurological manifestations. In keeping with previous reports, disease progression was more rapid in patients diagnosed in early childhood relative to those diagnosed later in life,⁴⁹ suggesting that early-onset disease follows a more rapid and fulminant course.

A review of 94 NPC cases in the UK⁴⁵ further confirmed the wide phenotypic variability of NPC. The recognition of late-onset disease is improving as biochemical diagnosis is increasingly being applied in adult neurology clinics. This report underscored the progressive nature of NPC and the neurological and (in some patients) neuropsychiatric decline seen in individuals with NPC. Understanding the natural history of NPC is necessary to prepare for the future

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healthcare needs of patients (and their cost implications) and to evaluate the long-term effects of therapies in development.⁴⁵

Current Therapeutic Options

Supportive Measures

Management of NPC has traditionally been with symptomatic treatments that alleviate aspects of the disease and improve quality of life.⁴⁶ For instance, physicians frequently treat dystonia and tremor with anticholinergic, beta-blocking and antispasmodic drugs, dystonia in some patients with levodopa and seizures with antiepileptic medications. Tricyclic antidepressants and central nervous system stimulants may help in controlling cataplexy.^{50,51} Similarly, antipsychotics are generally used to manage secondary psychiatric illnesses, particularly schizophrenia, with a preference for lower-potency or atypical agents that are less likely to cause or worsen dystonia. Speech therapy to minimise the risk of aspiration and physiotherapy for gait disturbances can be effective in reducing the risks associated with these clinical manifestations of NPC. These supportive measures prolong the lives of patients by preventing hospitalisations from falls or aspirations, which can often lead to pneumonia and death. While these therapeutic options can lessen the burden of NPC, they do not alter the underlying course of the disease or specifically target NPC.

Cholesterol-lowering Agents

As cholesterol has been thought to be an offending metabolite in NPC, a strategy that had been put forward for treating this disease was to use various cholesterol-lowering agents in an attempt to decrease intracellular cholesterol storage in patients.⁴⁶ Although certain combinations of cholestyramine, lovastatin, nicotinic acid or dimethyl sulphoxide did lower unesterified cholesterol levels in the liver and blood with minimal side effects, there has been no evidence showing any appreciable clinical benefit.^{52,53}

Targeted Therapy

Substrate reduction therapy with miglustat (N-butyldeoxynojirimycin) was recently approved for the treatment of the progressive neurological manifestations of NPC in adults, adolescents and children in a number of countries, including those of the EU.⁵⁴ This small iminosugar molecule is capable of crossing the blood-brain barrier⁵⁵ and acts as a reversible competitive inhibitor of glucosylceramide synthase, which normally catalyses the first committed step in glycosphingolipid synthesis.^{56,57} By reducing the activity of this enzyme, miglustat decreases the production of the toxic GM2 and GM3 gangliosides,⁴⁶ and it is the first approved disease-modifying therapy for NPC.

Encouraging data from pre-clinical studies in murine and feline NPC models⁵⁸ eventually led to a prospective randomised controlled clinical trial.⁵⁹ In this trial, NPC patients 12 years of age and older (n=29) were randomised to receive either miglustat at a dose of 200mg three times a day (n=20) or standard care (n=9) for 12 months, while another cohort of children less than 12 years of age (n=12) were given miglustat at a dose adjusted for body surface area. The primary end-point for all subjects was disease progression based on horizontal saccadic eye movement (HSEM) velocity.

After 12 months, patients treated with miglustat showed improvement in HSEM velocity compared with those receiving standard care.⁵⁹ The difference in improvement reached statistical significance when individuals using benzodiazepine medications, which are known to affect SEM, were excluded from both groups. Swallowing capacity and

stable auditory acuity improved in treated individuals over 12 years of age and a slower deterioration in ambulatory index was observed. Adverse events were largely mild to moderate in severity, with the most frequent negative effects associated with treatment being diarrhoea, flatulence, weight loss and abdominal pain. Two patients 12 years of age and older and one child receiving miglustat withdrew from the study due to an adverse event. Overall, miglustat was shown to stabilise neurological disease over 12 months with acceptable safety and tolerability.⁵⁹

A non-controlled, open-label extension⁶⁰ of the above trial allowed patients to continue using miglustat for a further 12 months for a total of up to 24 months of treatment. These long-term data further supported findings that miglustat therapy stabilises neurological disease in NPC patients and is well tolerated in both adults and children.⁶⁰ As miglustat is currently the only targeted treatment available for NPC, a strong argument exists that it should be offered as soon as symptoms are observed and a diagnosis is made in order to minimise and arrest neuronal loss, and potentially to alter the illness course. The relatively brief clinical experience with miglustat limits any conclusions in terms of how long it may delay sentinel medical events, the need for full nursing care or death. Studies are ongoing to determine its effect on these disease end-points.

Treatments in Development

Although miglustat is currently the only agent that has been tested in humans, several drugs have shown some benefit in pre-clinical studies in animal models. The histone deacetylase inhibitor valproic acid was able to enhance neuronal differentiation and restore impaired astrocytes in defective neural stem cells in NPC1^{-/-} mice; this treatment reduced cholesterol levels, thereby promoting cholesterol homeostasis in the brain.⁶¹ Imatinib therapy inhibits the proapoptotic c-Abl/p73 system and was shown to preserve Purkinje neurons and reduce cell apoptosis in the cerebellum in addition to improving neurological symptoms and increasing survival of NPC mice.⁶² Neither of these treatments has been trialled in adult NPC patients, although the use of valproic acid for mood disorders has been described in adolescent and adult patients with neuropsychiatric disease.^{3,12}

Recent data demonstrated that early treatment with sterol-binding agents such as 2-hydroxy- β -cyclodextrin in NPC mice could substantially decrease cholesterol concentrations in the liver and spleen while improving both liver dysfunction and neurodegeneration.⁶³ Derived from the common spice turmeric, curcumin is a potent antioxidant and may also have positive effects on NPC disease.²¹ Additional data from clinical studies will be required to confirm these promising outcomes and assess the long-term effects these drugs have in humans.

The Future of Niemann-Pick Disease Type C Research and Management

Much remains unclear about the neuropathology of NPC. A better understanding of the underlying pathophysiology of NPC will allow for the development of more targeted treatments to join miglustat in the armamentarium of tools available for treating NPC. There are many potential points in the pathway of glycosphingolipid synthesis that may be altered by targeted small molecules. Therapies that are able to stop the progression of the disorder or prevent its onset in persons carrying the mutation would be of great value. This would

require the introduction of more human data on illness effects and progression to merge with the existing animal models. Expansion of non-invasive neuroimaging techniques will be needed to allow for the probing of brain changes *in vivo*.^{31,64} Currently, miglustat remains the only disease-specific drug available for adults and children suffering from NPC. The high rate of schizophrenia-like psychosis in NPC also makes it an interesting disease model and illness phenocopy to study with the aim of further understanding the neuropathology of major mental disorders. ■



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