Niemann-Pick Type C Disease – Report on Results from the Niemann-Pick Type C Patient and Healthcare Professional Survey

Hans H Klünemann,[1] J Edmond Wraith[2] and Frits A Wijburg[3]

1. Director, Memory Disorders Clinic, and Vice-director, Geriatric Psychiatry, Department of Psychiatry, University of Regensburg School of Medicine;
2. Professor of Paediatric Inherited Metabolic Medicine, Genetic Medicine, Central Manchester University Hospitals NHS Foundation Trust;
3. Professor of Clinical Metabolic Diseases and Paediatrician, Department of Paediatrics, Academic Medical Centre, University of Amsterdam

Abstract

Niemann-Pick type C disease (NPC) is a rare and progressive genetic condition that is associated with an abnormal accumulation of lysosomal lipids in the body, which manifests as a variety of neurological symptoms that range greatly in severity. Management focuses largely on treating symptoms, but recent developments have led to disease-specific therapy that can slow or stabilise the progression of neurological symptoms in some patients. The Niemann-Pick type C Patient and Healthcare Professional Survey conducted interviews with parents and carers of patients with NPC and with healthcare professionals to identify areas of NPC diagnosis, management and support that need improvement. Specifically, an emphasis was placed on increased awareness of the disease and disease symptoms with enhanced communication between doctors, their colleagues and parents of patients in order to facilitate the diagnostic process and the hope for earlier diagnoses, thereby enabling access to disease-specific treatment. The survey identified a need among families of patients with NPC for more support from doctors in the provision of information about the disease and about locally based social and psychological support, and for support from healthcare organisations that should coordinate all the available services. Such co-ordination could ensure that consistent support is provided for all aspects of patient care and for patients' families and carers.

Keywords

Niemann-Pick type C, diagnosis, management, support, outlook

Disclosure: Hans H Klünemann has received speakers fees from Actelion. J Edmond Wraith has received honoraria and travel grants from Actelion, has been principle investigator in Actelion-sponsored clinical trials and is a member of the NPC Registry Board. Frits A Wijburg has received grant support, honoraria for speaking engagements and consulting fees from Shire HGT and Genzyme Corporation.
Acknowledgement: Editorial assistance was provided by Touch Briefings.
Received: 22 October 2010 **Accepted:** 10 January 2011 **Citation:** *European Neurological Review*, 2011;6(1):12–5 *DOI:10.17925/ENR.2011.06.01.12*
Correspondence: Hans H Klünemann, Department of Psychiatry, University of Regensburg School of Medicine, Universitätsstr 84, 93053 Regensburg, Germany.
E: Hans.Kluenemann@medbo.de

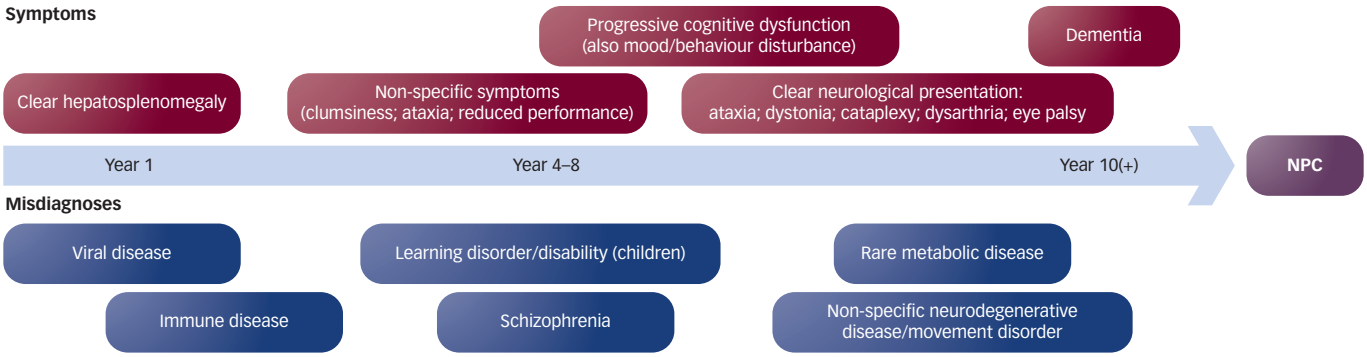
Support: The publication of this article was funded by Actelion. The views and opinions expressed are those of the authors and not necessarily those of Actelion.

Niemann-Pick type C disease (NPC) is a pan ethnic, progressive neurological condition that is estimated to affect an estimated minimum of one in 120,000 Western Europeans.[1] The neurological symptoms stem from a characteristic autosomal recessive storage of various lysosomal lipids, including unesterified cholesterol, glycosphingolipids and sphingosine. These lipids accumulate in a number of organs in tissues, most noticeably in the liver, spleen and brain.[2] This excess storage of lipids, possibly by a number of mechanisms, causes progressive and disabling neurological symptoms such as clumsiness, ataxia, cognitive dysfunction and dysphagia, with increasing severity and decreasing quality of life in the later stages of disease.[1,3,4] However, the diagnosis of NPC is complicated by the clinical spectrum of the disease itself: the wide range of symptoms are not disease-specific, nor are they limited to specific stages of disease development. NPC has four subtypes arising from different mutations in the *NPC1* gene, which codes for a membrane glycoprotein with multiple membrane-spanning domains that facilitates intracellular cholesterol trafficking and esterification. In addition, the *NPC2* gene, which encodes the HE1 cholesterol binding protein has been identified. Rare cases of NPC have been reported to have this mutation that have a pattern of lysosomal storage that is virtually restricted to neurons rather than in bone marrow and viscera as well.[5] NPC and its genetic origins are therefore varied; it can be difficult to identify and its reported incidence may be an underestimate.[6,7] Confirmation of NPC requires biochemical and genetic testing, histological analyses and imaging techniques. This often requires consultation with specialist centres, but the early symptoms must first be recognised by the initial physician for a referral to be made. Both the difficulties in diagnosis and the clinical symptoms can therefore impose a great emotional and economic burden on patients, their families and on society in general.

Management of Niemann-Pick Type C Disease

There is no cure for NPC, and treatment has historically focussed on the alleviation of clinical symptoms to improve quality of life among patients. Management of neurological manifestations has been achieved using tricyclic antidepressants, central nervous system

Figure 1: Symptom Progression from Onset of Disease and Common Misdiagnoses of Niemann-Pick Type C Disease



NPC = Niemann-Pick type C disease.

(CNS) stimulants, antiepileptic drugs and anticholinergics.[2] Supportive care in the form of physical, speech or occupational therapy are also available for the prevention or management of clinical manifestations of NPC and any associated secondary complications.[8] Disease-specific treatments were not available until the approval of miglustat (Zavesca®) in some countries in 2009 for the treatment of progressive neurological manifestations of adult patients and paediatric patients with NPC.

Current Outlook

Prognosis is poor for patients with NPC, but the rate of disease progression is highly variable between patients. This underscores the need for accurate and earlier diagnosis coupled with therapies that stabilise symptoms of NPC and improve quality of life. To address this clinical need, research is ongoing at many expert centres to provide a greater understanding of the epidemiology, pathophysiology, diagnosis and treatment of NPC.[9–12] An example of these research initiatives is the NPC and Healthcare Professional Survey.

The Niemann-Pick Type C Patient and Healthcare Professional Survey

Purpose of the Study

The NPC Patient and Healthcare Professional Survey was conducted in six countries (the UK, France, Germany, Italy, Spain and The Netherlands) with the intent of providing insight concerning the complexities of NPC diagnosis and first-hand experiences in diagnoses of NPC. In-depth qualitative interviews were performed with the parents or carers of 26 families in which one or more family members was diagnosed with NPC; 28 patients (11 males, 17 females) between the ages of three and 36 years were involved. Interviews involving families with more than one family member who had been diagnosed with NPC focused on the first member to be diagnosed. Interviews were concurrently held with four healthcare professionals who are experts in the field of diagnosis and management of NPC. These were: an NPC specialist nurse, a neurological psychiatrist, a paediatric geneticist and a paediatrician specialising in hereditary metabolic disease. The goals of this survey were threefold:

- to determine whether parent or carer experiences in the diagnosis of NPC could be used to raise awareness of NPC, thereby improving time to diagnosis and initiating effective therapy and management of the condition;
- to assess the emotional impact of the disease from the perspective of a patient or carer, the benefits of receiving a definite diagnosis, and accessibility to forms of support; and
- to determine whether differences exist between countries in terms of the diagnostic process for NPC, its emotional impact and benefits.

Table 1: Time to Diagnosis by Types of Symptoms Exhibited by Patients with Niemann-Pick Type C Disease

Major Symptoms/ Disease Stage	Key Symptoms Displayed	Time to Diagnosis
Visceral symptoms	Hepatomegaly Splenomegaly Jaundice	9 months (average)
Developmental delay	Clumsiness Ataxia Declining academic performance	6 years (average)
Psychiatric symptoms	Hallucinations Aggressive behaviour Paranoia (often in teens)	Up to 19 years

Identifying Challenges in Diagnosis

The time to diagnosis of NPC is limited by the symptomology exhibited or experienced by patients and how quickly they are recognised.[4,10,13] This emphasises the idea that greater awareness and knowledge of the disease and its manifestations among healthcare professionals could expedite referral to specialist centres. Moreover, the non-specific symptoms of NPC are such that patients may commonly be misdiagnosed, thereby unnecessarily delaying treatment. It is therefore necessary to encourage healthcare professionals to consider underlying conditions of non-specific symptoms by providing increased awareness of the disease.[13] A scheme representing the symptoms occurring over time in NPC and corresponding misdiagnoses at each stage is given in *Figure 1*.

These issues were highlighted in the interviews with parents and carers. Among the families interviewed, the average time from the onset of noticeable symptoms to diagnosis of NPC was just over five years, although the range spanned from a few months up to 19 years. It appears that the average time to diagnosis varies depending on the type of symptoms presented (see *Table 1*). Patients that exhibit severe visceral symptoms (e.g. hepatomegaly, splenomegaly or jaundice) are often immediately referred to specialist paediatricians, which results in a relatively quick diagnosis.[10] However, these symptoms are not always recognised in infancy, may subside over time by themselves and may even be attributed to viral or immune disease. NPC is more difficult to pinpoint using symptoms of developmental delay because symptoms emerge over a longer period of time and may resemble those of more common disorders (e.g. dyslexia) and general learning difficulties.

Table 2: Emotions Reported by Parents and Carers when Receiving a Diagnosis of Niemann-Pick Type C Disease

Emotion	Details
Shock	Symptoms exhibited before diagnosis may have been mild Other proposed diagnoses were less severe
Frustration	Illness was missed by experts Too much information to process Lack of support No sources to turn to for further information or help
Guilt	Regret at time lost prior to diagnosis Child may have struggled unnecessarily (e.g. in mainstream education) Feelings of responsibility over the genetically inheritable disease
Despair	Huge emotional impact of being given a diagnosis
Relief	Mystery concerning illness has been resolved No more stigma of child's behaviour or parental anxiety Can access support Can initiate treatment
Determination	Want the best quality of life for the affected family member Want to gather as much information and access support where possible Determination led to diagnosis; must continue on

Although behavioural problems and learning difficulties may lead to psychiatric referrals, it is often the case that patients are not referred to a neurologist until severe changes in behaviour, such as loss of acquired skills, or the onset of severe physical symptoms, such as seizures or cataplexy, are observed.[13] Psychiatric symptoms may take the longest to diagnose because they can easily be misdiagnosed as common conditions such as schizophrenia and bipolar disorder or non-specific neurodegenerative diseases. It is often not until a patient has shown progressive decline in cognitive function and exhibits dementia and other obvious neurological disabilities that a neurologist or metabolic disease specialist can make a diagnosis of NPC.[14]

The interviews with all participants revealed a general desire for increased communication between parents, carers and healthcare professionals, with the goal of drawing associations between symptomology and diagnosis of NPC. Greater communication between healthcare professionals in different areas of specialisation is encouraged to allow for discussion and co-operative analysis of the symptoms, potentially facilitating earlier diagnosis of NPC. Diagnosis is further complicated by the fact that a patient may be treated by several specialists in different departments for individual symptoms, which compartmentalises the disease symptoms and hinders the ability to take a holistic view of the patient's condition. More information from parents at the bequest of a healthcare professional could provide background details that, although potentially unrelated, may provide more clues about symptoms and the overall situation.

Awareness of NPC needs to be increased for facilitated diagnosis. At present, progressive neurological and cognitive decline has to be substantial in the presenting patient to warrant a referral to a neurologist or metabolic disease specialist, at which point biochemical testing or histological analyses can confirm the diagnosis of the disease.[1,13,14] The interviewed healthcare professionals have therefore proposed the implementation of a checklist of metabolic disease symptoms to speed up the diagnostic process. Moreover, increased awareness of the disease symptomology among healthcare providers, particularly specialists who may see and treat individual symptoms, could provide an even greater opportunity for earlier diagnosis and, thus, earlier treatment and stabilisation of disease progression. To better diagnose NPC and monitor its progression, test batteries have been proposed to establish neuropsychological profiles of patients. In pilot studies, these tests have shown that visuospatial working memory is less affected by the neurodegenerative process in NPC than verbal working memory.[15] Such testing is mainly carried out at neurological treatment and research centres; however, awareness of NPC should not be limited to the specialist setting. Interview responses in this survey also indicated that awareness of disease symptoms could also be increased among the community and educational setting, such as among general physicians and school doctors; this could potentially identify children with symptoms for whom further investigation is warranted.

A Confirmed Diagnosis of Niemann-Pick Type C Disease

Patients currently have an unmet need for early diagnosis.[16] Regardless of the timeframe in which their family member was diagnosed with NPC, all families interviewed agreed that early diagnosis would be helpful for several reasons: accessing support; having appropriate treatment earlier; preparing for the patient's future both emotionally and physically; and spending more quality time together before further disease progression. An early diagnosis could also help reduce the potential of feelings of guilt in parents who have passed an inheritable disease to their children and would inform them of the risk of NPC being passed to future children born. From a clinical perspective, the interviewed healthcare professionals reported that the availability of disease-specific treatment in some countries for slowing the progression of or stabilisation of neurological disease progression in NPC has considerably increased the value of early diagnosis. Parents and carers reported a wide range of emotions upon receiving a confirmed diagnosis of NPC (see *Table 2*). Notably, parents and carers had an obvious need for support systems and further information immediately following the diagnosis. Healthcare professionals therefore play an important role beyond diagnosis in managing the various challenges of an NPC diagnosis. They have the opportunity to advise and educate the family about the disease and its management and treatment, while also providing access to local patient organisations and social and psychological support. Indeed, the interviewed healthcare professionals reported that families of newly diagnosed patients are often overwhelmed with little understanding as to the weight of the diagnosis and having little or no information about the disease. The healthcare providers also noted that these families were not provided with the option or with the knowledge of how to access much needed education, social and psychological support.

The Value of Support

Caring for a seriously ill child can impose significant strains on a family. Physical strains may consist of struggles to identify available services, organising efforts across a number of medical departments and allocating increasing amounts of time towards care as the disease progresses. Emotional strains may negatively affect relationships within the entire family. According to the parents and carers interviewed, the optimal support structure is such that the parents should be at the centre of the model, surrounded by layers of support consisting of social workers, healthcare providers, local government and charities (see *Figure 2*). However, this is rarely a reality. Rather, accessible daily support is highly variable depending on where the patient lives. The child's age and local policies are the largest

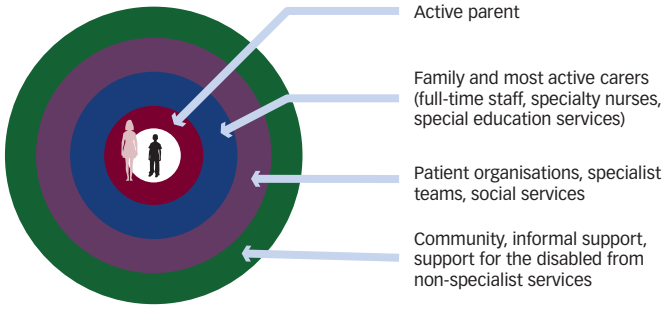
determinants of whether a family has access to financial support for alterations to the home, respite care or counselling services. Despite these limitations and the varying degree of support received by different families, the survey found that the families unanimously viewed the following as the most valuable support factors:

- A voice on the telephone – having somebody to talk to about the child's day-to-day symptoms.
- A central point of for advocacy – having somebody who is aware of all available services and treatments who can also help in preparing all necessary documentation.
- Co-ordination of services – a team that can provide consistent in-home services and support the family in patient care.

Summary and Conclusions

Insufficient knowledge and awareness of metabolic storage diseases such as NPC among general practitioners and paediatricians is a great hindrance in the diagnostic process, and can be a significant source of stress for patients and their families.[1,13,14] The results from the NPC Patient and Healthcare Professional Survey stress a need for change in this regard, advocating greater opportunities for diagnosis through increased communication, symptom recognition and better co-ordinated healthcare. A centralised team approach that allows for three-way communication between the carer/patient, healthcare providers and patient advocacy/support groups may create opportunities for earlier access to treatment and the necessary means of social support that can improve quality of life for the patient. The insight from interviews conducted with parents and carers of patients with NPC and healthcare professionals specialising in NPC identifies healthcare providers as having a crucial role to play (see *Table 3*). Raised awareness of visceral symptoms in infants may allow paediatricians to identify these early, if not first, signs of NPC, where proactive testing of neonatal splenomegaly or jaundice could yield an earlier diagnosis. Recognition of other specific symptoms that may present simultaneously could point towards a diagnosis of NPC, and in some cases it may be helpful to look beyond one area of symptomology (e.g. psychiatric symptoms) for others that do not correspond with the current diagnosis (e.g. somatic symptoms). Increased communication between specialists may create a better holistic view of the patient's condition as well. Indeed, the important step of achieving a diagnosis can then make way for the benefits of early treatment, particularly in countries where disease-specific treatment is available for slowing the progression of or stabilisation of neurological symptoms. Healthcare providers are also essential following the diagnosis because the results of this survey have shown that above all the families need support and assistance in caring for a child with NPC. In this regard, healthcare providers should direct parents and carers towards information sources and patient associations that can provide them with greater background information concerning NPC, social networks with other NPC families, and social and psychological support that allows them to be more proactive in caring for the patient (see *Table 3*). A mediating point of contact between healthcare providers and parents and carers, such as a specialist nurse, would also be able to provide healthcare advice and act as a means of support for services and day-to-day needs. ■

Figure 2: Optimal Model of Different Support Systems for Patients with Niemann-Pick Type C Disease as Suggested by Parents and Carers



Parents and carers suggested this model of different support systems extending in concentric circles from the active parent, naming varying sources of support where available.

Table 3: Proposed Routes of Action for Families, Carers and Healthcare Providers Affected by Niemann-Pick Type C Disease

Who?	What?	How?
Healthcare professionals	Increase awareness of NPC symptoms	• Increase professional knowledge of visceral NPC symptoms. This can facilitate earlier referral of infants and young children to specialists
	Consider alternative diagnoses beyond the obvious	• Look at all the symptoms being presented • Be informed about signs and symptoms of NPC • Be able to link symptoms together
	Share information	• Share disease history of a patient when referred to another specialist to provide a wider picture
Parents and carers	Share information	• Share background information and history about symptoms with the doctors • Speak to teachers to see if there are other observed symptoms and evidence of illness
	Seek support	• Be proactive in seeking support from patient organisations, social services and family networks

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1. Vanier MT, Niemann-Pick disease type C, *Orphanet J Rare Dis,* 2010;5:16.
2. Wraith JE, Baumgartner MR, Bembi B, et al., Recommendations on the diagnosis and management of Niemann-Pick disease type C, *Mol Genet Metab,* 2009;98:152–65.
3. Garver WS, Francis GA, Jelinek D, The National Niemann-Pick C1 disease database: report of clinical features and health problems, *Am J Med Genet A,* 2007;142:1203–11.
4. Imrie J, Dasgupta S, Besley GT, et al., The natural history of Niemann-Pick disease type C in the UK, *J Inherit Metab Dis*, 2007;30:51–9.
5. Klunemann HH, Elleder M, Kaminski WE, et al., Frontal lobe atrophy due to a mutation in the cholesterol binding protein HE1/*NPC2*, *Ann Neurol,* 2002;52:743–9.
6. Patterson MC, Vecchio D, Prady H, et al., Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study, *Lancet Neurol,* 2007;6:765–72.
7. Wraith JE, Imrie J, *Understanding Niemann-Pick Disease Type C and its Potential Treatment,* UK: Blackwell Publishing, 2007.
8. Patterson M, Niemann-Pick Disease Type C. Available at: www.ncbi.nlm.nih.gov/books/NBK1296/ (accessed 28 January 2011).
9. Garver WS, The National Niemann-Pick C1 database: report of clinical features and health problems, *Am J Med Genet Part A,* 2007;143:1204–11.
10. McGovern MM, Aron A, Brodie SE, et al., Natural history of Type A Niemann-Pick disease: possible end-points for therapeutic trials, *Neurology,* 2006;66:228–32.
11. Sturley SL, Patterson MC, Balch W, et al. The pathophysiology and mechanisms of NPC disease, *Biochim Biophys Acta,* 2004;1685:83–7.
12. Wasserstein MP, Desnick RJ, Schuchman EH, et al., The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study, *Pediatrics,* 2004;114:e672–7.
13. Sevin M, Lesca G, Baumann N, et al., The adult form of Niemann-Pick disease type C, *Brain,* 2007;130:120–33.
14. Walterfang M, Fietz M, Fahey M, et al., The neuropsychiatry of Niemann-Pick type C disease in adulthood, *J Neuropsychiatry Clin Neurosci,* 2006;18:158–70.
15. Klarner B, Klunemann HH, Lurding R, et al., Neuropsychological profile of adult patients with Niemann-Pick C1 (*NPC1*) mutations, *J Inherit Metab Dis,* 2007;30:60–7.
16. Sedel F, Clinical diagnosis of the adult form of Niemann-Pick type C disease, *Arch Pediatr,* 2010;17(Suppl. 2):S50–3.