Niemann-Pick type C disease: Journey to Diagnosis

A Report for Paediatricians

Introduction

Niemann-Pick type C disease (NP-C) is a rare, autosomal recessive, neurological disease affecting about one in 120,000 people. It is characterised by toxic accumulation of lysosomal lipids, such as unesterified cholesterol and glycosphingolipids, which damage cells and tissues. Although early symptoms generally affect the liver and spleen, a number of highly variable, progressive, neurological symptoms increase in both severity and effect on quality of life in the late stages of the disease.

This report draws together the results of a much-needed piece of research among NP-C patients and their families. Interviews were conducted with parents and carers of patients with NP-C to provide an insight into their experience of the journey to diagnosis, the physical and emotional impact that this can have on families and the importance of support before, during and after receiving a diagnosis of NP-C. The research was carried out alongside in-depth qualitative interviews with four healthcare professionals (HCP) who are experts in the field of NP-C diagnosis and management.

Professor Frits Wijburg addresses why the NP-C patient survey results are relevant and important to paediatricians and how learning can be taken from these findings and implemented in practice to help speed up this journey to diagnosis:

“The NP-C patient survey took a novel approach for a rare disease by asking both patients and HCPs about the different issues they were faced with when waiting for a diagnosis eventually confirmed to be NP-C. As it is a rare condition many paediatricians will not be aware of NP-C and so being able to share patient experiences from families around Europe is invaluable.

The long road to a diagnosis of NP-C is a tremendous burden for many families. Watching their loved one deteriorating and displaying increasingly debilitating symptoms that are not being recognised as caused by one disorder by their HCP can be extremely frustrating. Paediatricians need to be aware of the impact this journey to diagnosis can have on the patient and their family and to try and relieve some of this burden by making a fast and accurate diagnosis so relevant information and support can be provided. Most paediatricians know that the road to a diagnosis of NP-C can cause suffering for families and this report compiles all the data into one, comprehensive communication that reveals the full impact of the situation.

If a paediatrician does not know about the differential presentation of non-specific signs and symptoms that constitute NP-C, it will be highly unlikely that they will be able to diagnose a patient with NP-C. Although healthcare systems differ in each country, most patients will see a paediatrician when they present with neonatal liver disease, splenomegaly or hepatomegaly. Other symptoms such as clumsiness and ataxia will also be seen by paediatricians or paediatric neurologists so paediatricians play a fundamental role in making links between symptoms, which might present at different times in the child’s life and where some symptoms may appear to have been resolved, in order to make a diagnosis of NP-C.

NP-C does exist and so should be recognised by the relevant HCP. This report shows how important a diagnosis is to the patient and their family; not only is there treatment available but even without a therapy once a diagnosis is made many opportunities open up, such as access to patient support groups, family networks and access to relevant information about the disease. An early diagnosis means that treatment can be started early and the burden of unrecognised symptoms and undiagnosed disease is lifted.

The real call to action for paediatricians is to link symptoms together; if they see a patient with isolated splenomegaly or learning disabilities in combination with clumsiness or frequent falls then they should start to think NP-C. This is how a fast, differential diagnosis of NP-C will be made. Diagnostic tests should be done when there is a combination of symptoms for which there is no other explanation and especially when there is some sign of progression. Therefore education is vital, as most paediatricians will never have seen a patient with NP-C, but they need to know about this disorder and to link the symptoms in order to be able to make a fast and accurate diagnosis which will improve quality of life for the patient and family.”

Professor Frits Wijburg
Metabolic Paediatrician and Professor at the Academic Medical Centre in Amsterdam, The Netherlands

Forewords

Hans Klünemann, MD PhD

Professor of Psychiatry, University of Regensburg School of Medicine, Germany

I saw my first patient with NP-C in a memory disorders clinic in 1996. She was in her mid-forties and was referred with a diagnosis of possible Alzheimer's disease. I am certain that NP-C is often undiagnosed in adult psychiatric patients. Educating physicians about NP-C will be extremely beneficial in terms of accessing treatments for these patients.

Frits Wijburg

Metabolic Paediatrician and Professor at the Academic Medical Centre in Amsterdam, The Netherlands

During my career in metabolic diseases I have seen many patients with different metabolic disorders and I have learnt that NP-C is not only one of the more severe disorders but unfortunately also one of the most difficult to diagnose. Improving early clinical recognition is key and will decrease the often lengthy diagnostic odyssey by allowing for timely diagnosis. This report clearly shows the importance of this.

Jackie Imrie

Clinical Nurse Specialist, Niemann-Pick diseases (UK)

Having been actively involved with families with Niemann-Pick disease for over a decade I felt I had a lot of insight that I could offer the steering group. The survey results document what myself, other professionals and families have been saying for many years and hopefully we can act on these concrete findings. Not all families want contact with support groups but we need to be able to offer something to support them to suit their needs. We need to have professionals and families working together to raise awareness of Niemann-Pick disease and hopefully decrease the time to diagnosis for most families.

Bruno Bembi

Paediatrician and Geneticist, Director of Regional Coordinator Centre for Rare Diseases, University Hospital 'Santa Maria della Misericordia', Italy

Rare diseases are often under diagnosed and under managed. This is particularly the case in NP-C, where patient presentations are not homogenous. That is why it is so important to educate healthcare professionals and parents about the course of this disease and the impact on patients and families of a long journey to diagnosis. Hopefully this report will play an important role in educating and increasing understanding of NP-C.

Jim Green

Co-ordinator, International Niemann-Pick Disease Alliance (INPDA)

The collation and distribution of a patient survey for Niemann-Pick type C disease is something that has been needed for a long time. As someone who has been involved with this disease for 20 years I believe this report will help patients and their families feel less isolated by recognising the issues they face. I believe too that it clearly outlines the reasons why professionals and support networks should explore all possible ways of working together in order to provide improved diagnosis, treatment and support. I am particularly pleased that the report recognises that the issues raised are universal and unaffected by national boundaries. I hope that wherever the survey is read it will improve understanding and in so doing help those living with and managing this disease.

Sergio Vidal

Patron and member of the medical committee of the Spanish Niemann-Pick Foundation (Fundación Niemann Pick de España)

I wished to have the opportunity of sharing my personal experience as an active member of the support organisation and primarily, as a father of a child with NP-C. NP-C affects patients worldwide with the same emotional and physical impact, as highlighted in the report. This survey is very important as it is the first time that the reality of the disease known by patient organisations, NP-C patients and relatives will be collated and presented as a report. Healthcare professionals need to use this knowledge to educate themselves and others about the disease, the symptoms of the disease, how we can achieve an early diagnosis and the benefit of an early diagnosis. For patient and carers this report highlights the importance of receiving a diagnosis and the role that the patient organisation can play in supporting the patient and their family.

What is Niemann-Pick type C disease?

Niemann-Pick type C disease (NP-C) is an autosomal recessive, neurological condition characterised by toxic accumulation of lysosomal lipids, such as unesterified cholesterol and glycosphingolipids, which damage cells and tissues.[1] Although early symptoms generally affect the liver and spleen, a number of highly variable, progressive, neurological symptoms increase in both severity and effect on quality of life in the late stages of the disease (see Table 1). It is an inherited disease that may appear in young infants or not until late adulthood. Typically, it presents in mid-to-late childhood, with a child appearing clumsy and experiencing frequent falls.[1,2] However, more adults have been diagnosed with NP-C in recent years.[3]

Systemic symptoms	Neurological symptoms
Hepatomegaly (enlarged liver)	**Vertical supranuclear gaze palsy** (eye movement problems)
Splenomegaly (enlarged spleen)	**Ataxia** (balance disorder)
Neonatal jaundice	**Cognitive dysfunction** (problem with information processing or memory)
Pulmonary infiltrates	**Dysphagia** (difficulty swallowing)
	Dysarthria (slurred and irregular speech)
	Dystonia (sustained muscle contraction)
	Gelastic cataplexy (episodes of sudden muscular weakness)

Table 1. Symptoms of NP-C[1,2]

Who is affected by NP-C?

It is estimated that NP-C affects approximately 1 in 120,000 people;[3] however, the wide range of symptoms which often go undetected means that this is likely to be an underestimate.[1]

How is NP-C diagnosed?

Diagnosis of NP-C is not straightforward. The low prevalence of the disease, wide range of non-specific symptoms and oligosymptomatology (symptoms can be few and mild) mean that it can often be either misdiagnosed or may go unnoticed for many years.[1] Confirmation of NP-C involves biochemical testing (limited to a number of specialist centres), histological analyses, genetic testing and imaging techniques.[1]

How is NP-C managed?

Unfortunately there is no cure for NP-C. Current pharmacological management options include:

- Anti-cholinergics[1]
- Tricyclic anti-depressants[1]
- CNS stimulants[1]
- Anti-epileptics[1]
- Melatonin or nocturnal sedatives[1]
- Iminosugar[3]

NP-C Research

Recent progress in understanding NP-C has identified many potential targets for specific therapies that may affect disease progression or long-term outcomes. Research has focused on replacement or repair of the NP-C gene, use of cholesterol-lowering agents, neurosteroid replacement and restoration of lipid trafficking with the GTPase enzyme.[1]

References

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Overview of the NP-C Patient and Healthcare Professional Survey

The NP-C Patient and Healthcare Professional Survey provides new insight into the complexities of NP-C diagnosis. Parents, carers and healthcare professionals in six countries (UK, France, Germany, Italy, Spain and The Netherlands) shared their experiences of the journey to a diagnosis, its emotional impact on the family and the importance of a good support network when caring for a family member with NP-C.

Methodology

In-depth qualitative interviews were carried out with representatives, either parents or carers, of 26 families with one or more family members diagnosed with NP-C. A total of 28 NP-C patients aged between 3 and 36 years were involved; 11 males and 17 females. Two families had more than one family member with NP-C and their interviews focused on the first member diagnosed as, in the majority of cases, family history and previous experience usually expedited diagnosis of the second family member.

This research was carried out alongside in-depth qualitative interviews with four healthcare professionals who are experts in the field of NP-C diagnosis and management – an NP-C specialist nurse, a neurological psychiatrist, a paediatric geneticist and a paediatrician who specialises in hereditary metabolic disease.

The research was conducted by Insight Research Group in January and February 2010. The aim of conducting the research was to understand the following aspects of diagnosis:

- Whether parent or carer experiences of the journey to diagnosis could help raise awareness of NP-C and so reduce the time it takes to reach a diagnosis and start effective management of the condition
- The emotional impact of NP-C from a patient or carer perspective and the benefits of finally achieving a diagnosis of the condition and access to support
- Whether any differences exist in different countries with regard to diagnosis, emotional impact and support and to determine if it is beneficial to share practices

Results: The journey to diagnosis

Interviews with parents and carers highlighted the lengthy and challenging nature of the journey to diagnosis of NP-C. Time to diagnosis is very much influenced by the type of symptoms patients experience and how quickly they are recognised, suggesting that increased awareness and greater knowledge of NP-C symptoms amongst healthcare professionals would facilitate earlier referral for specialist care. The average time from onset of noticeable symptoms to diagnosis for the families interviewed was slightly over five years, however timescales varied from a few months to 19 years. The survey identified three specific patient types and classified them according to type of symptom presentation and time taken to diagnosis (see Table 2).

	Key symptoms	Time to diagnosis
Visceral symptoms	Hepatomegaly or splenomegaly and/or suffering from jaundice	Average 9 months
Developmental delay	Clumsiness, ataxia or declining academic performance	Average 6 years
Psychiatric symptoms	Hallucinations, aggressive behaviour or paranoia (often in their teens)	Up to 19 years

Table 2: The three types of prevalent symptoms displayed by NP-C patients

The symptoms will have been there for years, just that they become more severe. They will be severe enough to not just be noted by the patient and close family, but the doctor will also have to admit that this is not just a bad day.

Healthcare professional

In patients exhibiting severe **visceral symptoms**, such as hepatomegaly, splenomegaly or persistent jaundice, the family is usually immediately referred to a paediatrician such as an infectious disease specialist, a metabolic disease specialist or a liver specialist and reasonably prompt diagnosis follows. However, these symptoms are not always recognised in infancy and can be attributed to viral or immune disease (see Figure 1) or subside by themselves over time.

For those patients exhibiting symptoms of **developmental delay**, such as clumsiness, ataxia or reduced academic performance, diagnosis may not be confirmed until they are between four and eight years old, sometimes even later. These symptoms initially resemble more common disorders such as dyslexia, dyspraxia or general learning difficulties and the gradual decline can often be difficult to see, especially in a family environment (see Figure 1).

Whilst some parents worry that they may be over-reacting, especially if it is a first child, others instinctively know there is a problem but they may be dismissed as over-anxious or neurotic when regular medical investigation fails to identify a physical illness to explain the symptoms.

A general practitioner (GP) or community paediatrician may refer them to a psychiatrist for behavioural problems or learning difficulties but it isn't until acquired skills are lost or severe physical symptoms, such as seizures or cataplexy appear, that a patient is referred to a neurologist.

Patients presenting with **psychiatric symptoms** experience the longest journey to diagnosis – sometimes up to 19 years. Symptoms, such as mood or behaviour disturbances often emerge in the teenage years before other, physical symptoms are noticed and are commonly misdiagnosed as schizophrenia, autism with psychotic features or bipolar disorder (see Figure 1). Sometimes, their symptoms may be attributed to a rare metabolic disorder, multiple sclerosis or non-specific neuro-degenerative disease. Eventually, they develop progressive cognitive dysfunction leading to dementia as well as clear neurological symptoms such as ataxia, dystonia, cataplexy, dysarthria and eye palsy and are diagnosed with NP-C by a neurologist or a metabolic disease specialist.

There were things that we didn't even notice as parents; for example, he could no longer hold the fork properly or hold his own cup, and whilst others would take note of that, we thought that perhaps he was simply mimicking his baby brother in order to attract attention.

Parent, Germany

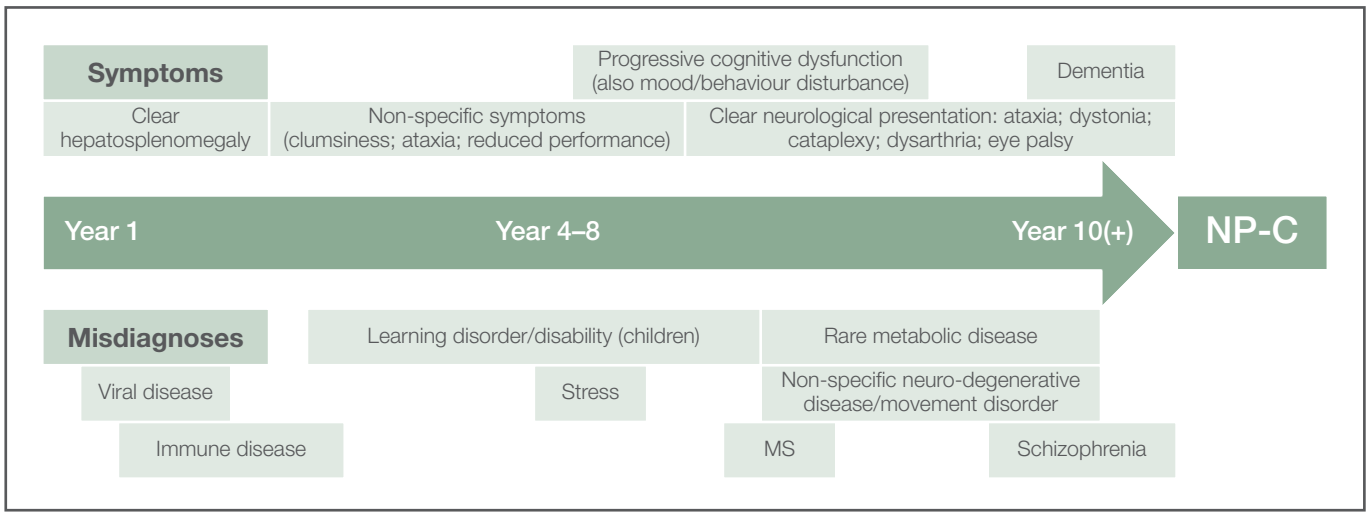

Figure 1: Common misdiagnoses of NP-C

Linking the symptoms

Interviews with parents and carers as well as healthcare professionals suggests that encouraging healthcare professionals to discuss symptoms with colleagues in other disciplines could facilitate early diagnosis by allowing symptoms to be linked together and then linked to the possibility of NP-C. Healthcare professionals could help parents by prompting them to share more background information about seemingly unrelated symptoms to ensure that healthcare professionals receive the wider picture.

Information is not always shared between departments and patients may see several different specialists for treatment of individual symptoms or be in the care of several specialists simultaneously. This may obstruct a physician from taking a holistic view of the patient's clinical signs and symptoms.

The healthcare professionals interviewed suggested that a symptom checklist for identifying metabolic disease may help reduce the time taken to confirm a diagnosis. Currently, it is only when progressive neurological and cognitive decline finally leads to referral to a neurologist or a metabolic disease specialist that NP-C is confirmed through biochemical testing or histological analyses.

Similarly, heightened awareness amongst the various specialists who may see and treat individual symptoms will also achieve greater opportunity for earlier diagnosis and initiation of early treatment to stabilise disease progression in those patients with neurological symptoms (see Table 3).

Additionally, it was felt that greater symptom awareness in the community or educational setting, for example amongst GPs and school doctors, could potentially help identify children appropriate for further investigation. The symptoms that GPs and school doctors might see include excessive clumsiness, deterioration in ability, irregular eye movements and memory difficulties.

Specialists	Typical symptoms they might see
Hepatology/liver specialists	Prolonged neonatal jaundice/hepatomegaly or splenomegaly
(Neuro-) psychiatrists	Ataxia
Paediatricians (if also see teenagers)	Dystonia
(General) neurologists	Dysarthria
Ophthalmologists	Dysphagia
	Cognitive dysfunction (may include behavioural disturbance; paranoia; hallucinations)
	Vertical supranuclear gaze palsy

Table 3: Targets and symptoms for earlier diagnosis of NP-C aimed at professionals seeing individual symptoms

Results: The emotional impact of receiving a diagnosis of NP-C

According to parents and carers interviewed, receiving a confirmed diagnosis of NP-C has a huge emotional impact on the patient's family, showing that as well as facilitating diagnosis, healthcare professionals have an important role in helping families access the information and support they need. Families may need to find local patient organisations, social services and family networks to help them to manage the challenges of coping with NP-C.

The views outlined in figure 2 were echoed by the healthcare professionals interviewed, who often encountered families of newly-diagnosed patients who do not really understand what diagnosis means, have little or no information about the disease and have no idea how to access the educational, social and psychological support they desperately need.

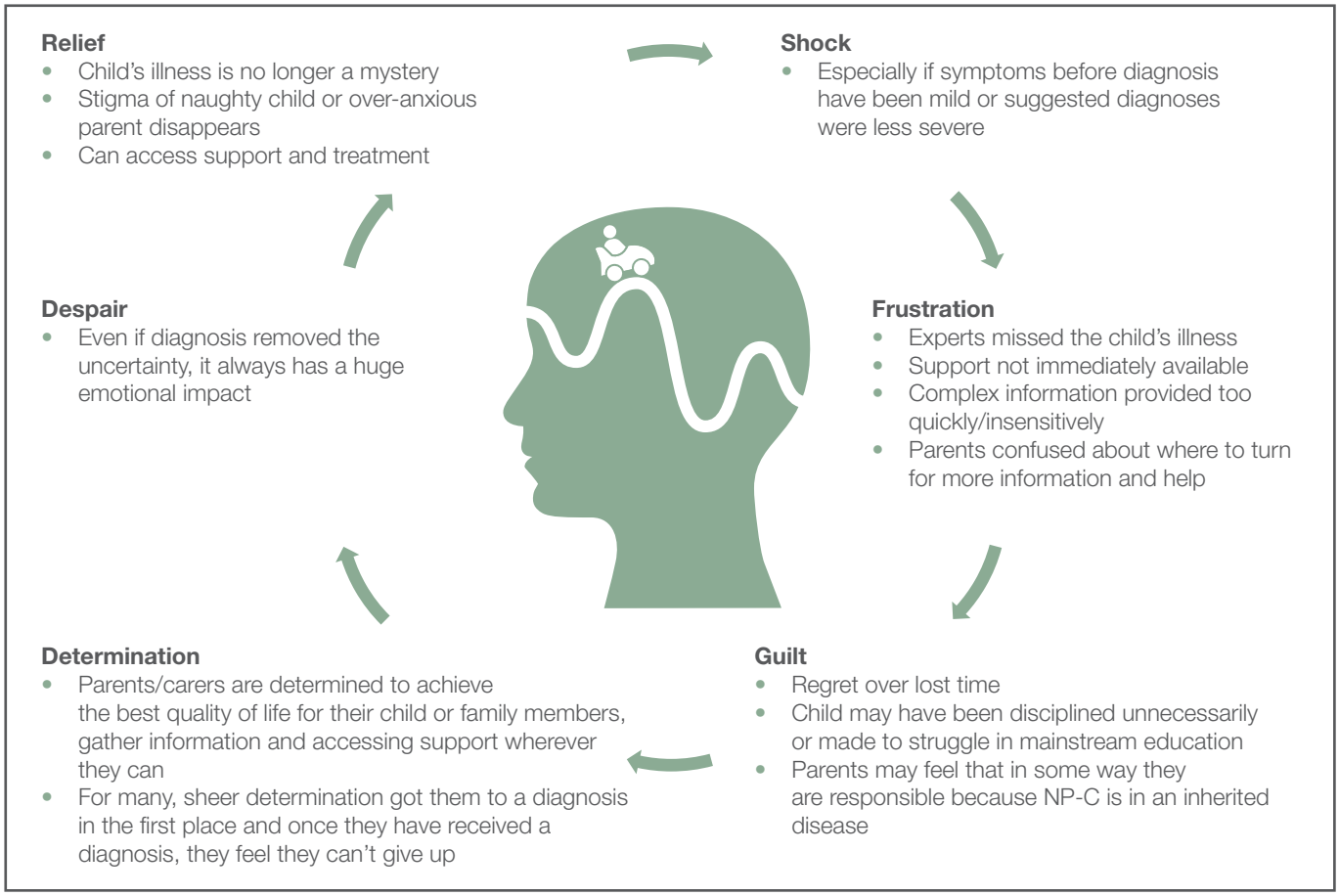

Figure 2: Parent and carer interviews provided insight into the range of strong emotions experienced at the time of diagnosis

Results: The value of having a diagnosis

All families interviewed, whether experiencing prompt or delayed diagnosis of NP-C, emphasised that early diagnosis not only helps families access support, advocacy and appropriate treatment earlier but also helps them to prepare emotionally and physically for their child's future. They can spend more quality time with their child before the disease progresses, for example, prioritise holidays and plan for the future.

The importance of support

Looking after a seriously ill child puts a great deal of physical and emotional strain on a family. There is the physical struggle of identifying available services, coordinating efforts across numerous healthcare teams and providing 24-hour care as symptoms become progressively worse. In addition, there is often the emotional struggle of balancing relationships with partners and other children.

An optimal support structure

Parents and carers interviewed have a clear idea of what an optimal support structure should comprise. They describe a model with the mother, or parents, at the centre surrounded by layers of support comprising social workers, healthcare practitioners, local government and charities (see Figure 3). In reality, this is rarely achieved. Access to day-to-day support varies significantly within countries, with availability of financial support for alterations to the home, respite care or counselling services for the family often depending on the child's age and local policies.

Most valuable forms of support

Even though the circumstances of the families interviewed differed extensively in terms of the support they receive, they were unanimous in their view of the most valuable elements of support:

- **A voice on the phone** – someone to talk to about a child's day-to-day symptoms
- **A central point of coordination for advocacy** – someone who knows what services and treatment are available and can help them prepare all the necessary documentation
- **Coordination of services** – a wider team that provides consistency of in-home services and supports the family in caring for the patient

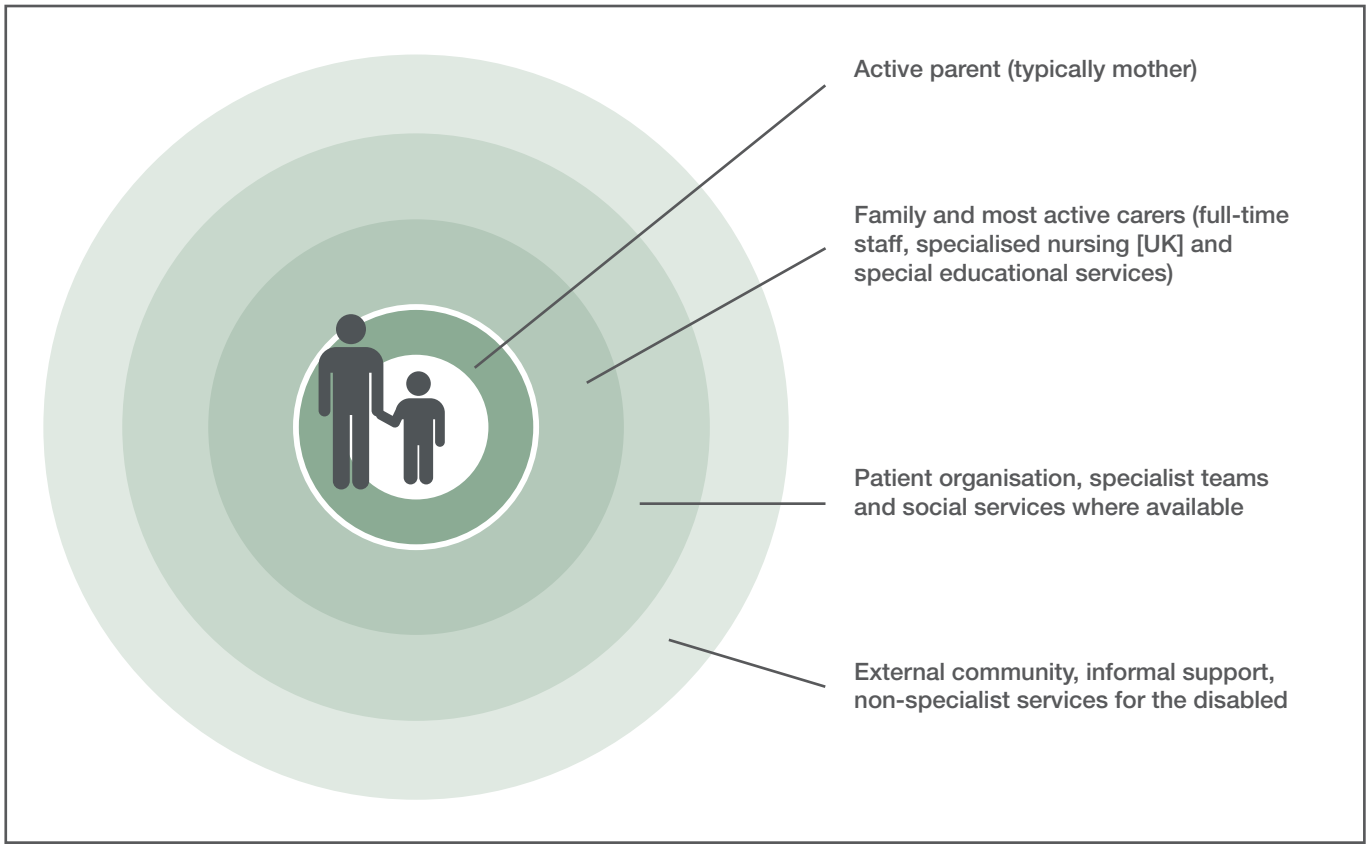

Figure 3: The optimal support structure for a family affected by NP-C

> *I think that patients definitively have this unmet need [for early diagnosis]. If you look at cases that are left without a diagnosis, family members will be wondering why their children are 'different', why can they no longer do certain things?... The patient is accused of being stubborn, lazy or uncooperative. Parents will be looking for all sorts of explanations – for the movement disorder as well as the mental deterioration. I think the family and the patient are relieved once they have the correct diagnosis. Finally, they have an explanation for the symptoms and know what is wrong.*
>
> ***Healthcare professional***

Paediatric NP-C case reports

The following two case reports have been provided by Professor Frits Wijburg. In the first report the patient was not diagnosed until the disease had progressed to a stage of severity where there were few treatment options available to help manage the disease. In the second case report recognition of symptoms suggestive of a diagnosis of NP-C led to further investigation and eventually a diagnosis of NP-C was confirmed at a stage in the course of the disease where it could still be treated.

Patient 1

A four year old boy presented to his healthcare clinician with symptoms that were diagnosed as ataxia and epilepsy. Over the subsequent years he experienced continuous progressive deterioration and went on to suffer from severe dystonia and eventually had to be fed artificially via a tube. After many years of continuous decline, he was eventually diagnosed with NP-C by a paediatric neurologist who recognised the symptom of vertical supranuclear gaze palsy (VSGP) and linked it with his other symptoms to get a confirmed diagnosis. The boy died soon after diagnosis. As he was diagnosed at such a late stage in the progression of the disease his family did not receive the support they needed and it was too late to start treatment.

Patient 2

A 19 year old girl experienced a sustained period of severe jaundice as a neonate. She nearly had a liver transplant but before this went ahead her liver improved and she was taken off the transplantation list. She then lived a normal life until about the age of seven years when she started to show difficulties in schooling. She was referred to a paediatrician who picked-up on the liver disease she had as a neonate and also saw that she was displaying the symptoms of ataxia. The paediatrician conducted literature search, which led to recognition that she may have NP-C. Indeed, repeated physical examination revealed that she was exhibiting VSGP. This allowed the paediatrician to link together the history of severe jaundice with the ataxia, the progressive learning disabilities and the VSGP leading to a confirmed diagnosis of NP-C. As the girl was diagnosed at a relatively early stage of disease progression she was started on treatment. She is now 19 years old, her NP-C disease progression is stable and she lives a relatively happy life at home with her parents despite her ataxia and intellectual disabilities.

What does this research mean?

The NP-C Patient and Healthcare Professional Survey highlights an overwhelming need for change. The lack of diagnosis of NP-C or common misdiagnosis is a great burden to patients and their families. There is low knowledge and awareness of metabolic storage diseases, such as NP-C, amongst GPs and paediatricians. Not only does this delay diagnosis but it can also lead to feelings of anger and frustration amongst parents whose instincts tell them there is a serious physical problem in their child, yet their concerns go unacknowledged.

As well as a combined effort to improve symptom recognition and creation of the opportunity for earlier diagnosis of NP-C, the survey also shows the desperate need for better provision of co-ordinated healthcare.

A centralised team approach where there is three-way communication between the carer/patient, healthcare team and patient advocacy/support group will not only enable families to access earlier treatment but also harness the social support that will enable them to achieve the best quality of life possible for their child.

Taking action

Earlier diagnosis of NP-C would allow families to access treatment. It would also provide healthcare professionals with an opportunity to advise and educate families about NP-C, direct them towards advocacy and support services and offer earlier genetic counselling.

So how can healthcare professionals help?

Firstly, there needs to be a greater focus on raising awareness of the visceral symptoms in infants which may be the first sign of NP-C. Proactive testing of neonates with enlarged spleens and ongoing severe jaundice before symptoms subside could result in earlier diagnosis in many patients. Secondly, for those patients whose first symptoms are that of developmental delay, specialists and paediatricians need to recognise when several specific symptoms are presenting and to be aware this could be pointing to NP-C as the cause. Sharing information amongst different specialists can help link together previously unrelated symptoms and reveal the wider picture. In patients with psychiatric symptoms, healthcare professionals need to look outside the familiar symptoms for others, usually somatic, that do not fit the current diagnosis.

The results of this study provides extensive insight into the huge emotional and social burden that families face when caring for a child with NP-C, emphasising that more needs to be done to help these families cope. It also highlights the need for the provision of fully co-ordinated healthcare teams around the family in order to provide a support structure that enables them to achieve the best quality of life they can for their child both in the early stages of NP-C and as the disease progresses.

So how can healthcare professionals help patients and carers?

They should direct parents and carers towards the information sources and patient associations that provide useful, unbiased disease information, social and psychological support and contact with other NP-C families. If possible, they should also refer parents and carers to `one point of contact,' preferably a specialist nurse, who can provide healthcare advice and act as an advocate for services and day-to-day needs.

A call to action for everyone affected by NP-C

1. Increase awareness of NP-C symptoms amongst healthcare professionals:

- Better healthcare professional knowledge of the visceral (classic) symptoms of NP-C would facilitate the earlier specialist care referral of infants and those children who present in early school years with visceral (classic) symptoms

2. Consider a diagnosis beyond the obvious:

- Specialists need to ensure that they are looking at all the symptoms a patient presents with and linking these symptoms together
- Specialists need to be informed about all the signs and symptoms of NP-C in order to enable them to link together seemingly unrelated features

3. Share information:

- Parents should be encouraged to share with their GP more background information and history about all the symptoms their child has ever had, if they continue to be concerned
- Both generalists and specialists need to ensure they share all disease history information with the specialist they are referring the patient on to so that specialists are able to recognise the wider picture
- Parents and carers could seek the support of teachers or other social networks to gain extra evidence when presenting concerns to healthcare professionals

4. Seek support:

- Parents and carers should be proactive in seeking support from patient organisations, social services and family networks to ease the emotional impact of receiving a diagnosis of NP-C and to help manage challenges in coping with the condition

Acknowledgements

We are grateful to all the families who took part in this educational research. The stories of their experiences will help both healthcare professionals understand the need for improved education and earlier diagnosis of NP-C and also help families to persist and seek the support and help they need.

The quotes used in this report are taken from individual face-to-face interviews carried out by Insight Research Group in January and February 2010.

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