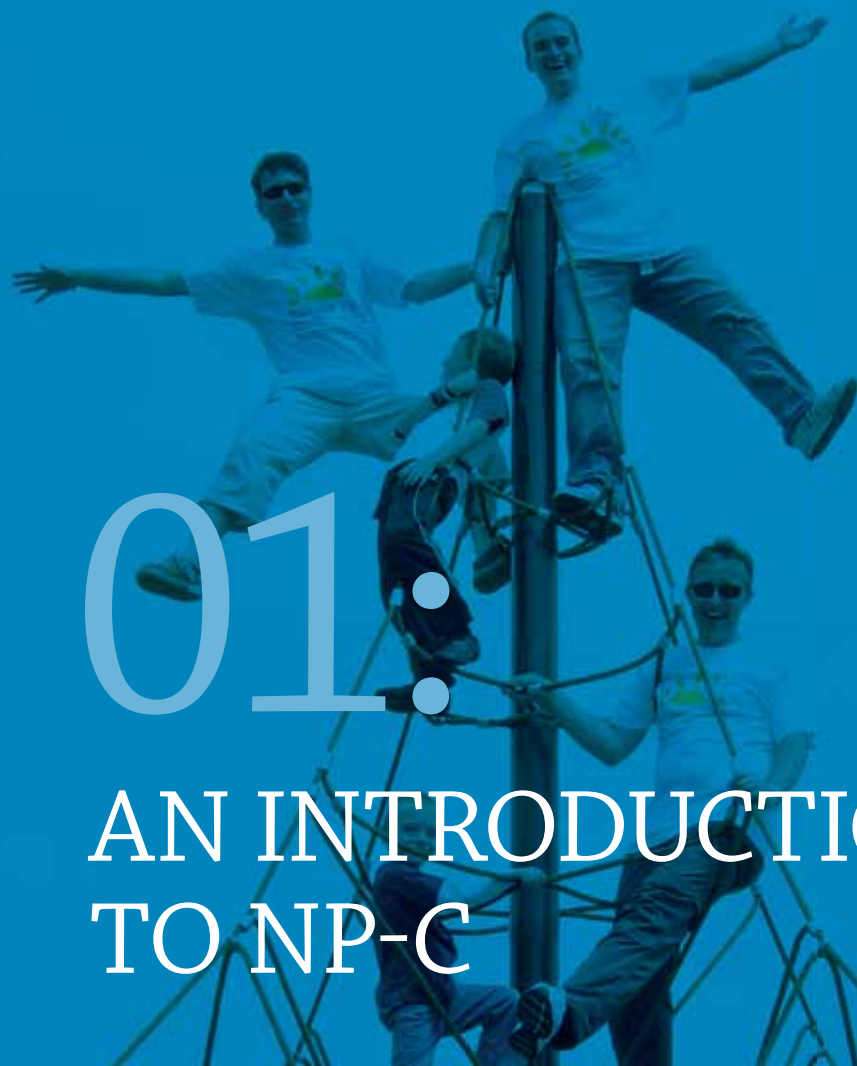


# Niemann-Pick type C disease

A practical guide for  
parents and carers



# 01.

## AN INTRODUCTION TO NP-C



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## Acknowledgements

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Susan and Jim Green, Marion Lee, Jon Lewis, William Owen, David Roberts, Ruth Robinson, Ian and Carolyn Sixsmith, David and Sally Wray, Susan Wright.

Grateful thanks go to all those who allowed us to include their precious photographs and anecdotes regarding NP-C. Special thanks to Sarah Holton, without whose help this guide may never have been realised.



# Introduction

**T**his guide has been developed with the help of parents and carers of children, young people and young adults affected by Niemann-Pick type C disease (NP-C). It aims to provide practical information, reassurance and support to those caring for an individual with NP-C.

The NPDG (UK) recognises the value of the knowledge, skills and experience gained by families caring for someone with NP-C. We hope that the information included here will assist all those caring for an individual with NP-C in dealing with the day-to-day challenges of the disease.

As Niemann-Pick type C is such a complex and variable condition, different information will be relevant to different people. The guide is modular and the NPDG (UK) will generally only provide those parts that are required on diagnosis and in the early stages of the disease. Extra sections can be requested as and when required. However, if you would prefer to receive the guide in its entirety, please let us know.

If at any time you wish to discuss the content of this guide, please contact the Niemann-Pick Disease Group (UK) by emailing [niemann-pick@zetnet.co.uk](mailto:niemann-pick@zetnet.co.uk) or phoning 0191 415 0693.

Toni Mathieson



Executive Director

The Niemann-Pick Disease Group (UK)

The content of this guide has been reviewed and approved by Professor Ed Wraith, medical adviser to the Niemann-Pick Disease Group (UK).

# My thoughts on living with Niemann-Pick type C disease

**A**ll parents can remember the moment when they were given the diagnosis that their child had Niemann-Pick type C. It is not something that is easily forgotten. As well as a feeling of shock, most felt an overwhelming sense of loss because, at a stroke, their hopes and aspirations for the future had gone, to be replaced by a cloud of uncertainty which wrapped itself around each member of the family, producing a sense of isolation and disorientation. At this time there seem to be no answers. Most would think, 'How will we cope?' We as families are called upon to meet this extraordinary challenge of life – in doing this we probably have to become extraordinary people.



Over time, the many parts to the jigsaw of care fit into place and a new perspective on life begins to emerge. Caring for your loved one increasingly becomes the focus for the whole family and everyday life is adjusted to fit in with this, often changing the dynamics within the family. However, although there can be difficulties in the hectic, everyday world of care, there will also be 'special moments' when the greyness of the world retreats and we seem to be on a higher plane, as if our senses, which were previously dulled, have suddenly developed an increased awareness of the world about us. Time suddenly becomes very important. Things seem to have a deeper meaning. We take less for granted. We appreciate the good things that happen to us. We are very aware of the kindness of others and may feel more inclined to do things for other people when time allows.

If we can remain strong and yet open-minded then often we will meet people who inspire us to see the world differently from the way we may have seen it before. These people may be professionals – nurses, doctors and care personnel – who by their personal qualities, dedication and skill win the admiration of both their colleagues and the families with whom they work. They may be family, friends, neighbours or members of the community who, by their actions, are inspirational in that they make us aware of just how much can be done, and even do what at first sight may seem to us to be impossible. Often the people who make the greatest contribution are those who do not realise how generous and skilful they are.

Many parents say that it is their loved one themselves who guides them through the experience. They display amazing personal qualities, which are an inspiration to everyone about them and give the whole family the courage to carry on, in the face of every challenge. Perhaps the focus is not the illness of the individual, but the celebration of their life. The family has the opportunity to be very close to their loved one and, as is often the case, the more you put into life the more you get out of it. Seen in this light, it is a remarkable opportunity for the family to do more: to give more time; to make more effort; to offer more love; to show more interest; and ... to do more living!



David Wray,  
Father of Andrew (NP-C)  
11/07/1991–29/08/2000

# The Niemann-Pick Disease Group (UK)

**T**he Niemann-Pick Disease Group (UK) is a support group consisting largely of the parents of those affected and their friends. The organisation was formed in 1991, as the 'Niemann-Pick Support Group' with assistance from Contact a Family and The Research Trust for Metabolic Disease in Children (now Climb). In 1996 the Group was granted charitable status as an independent charity and became 'The Niemann-Pick Disease Group (UK)'. All the trustees are volunteers and each takes on responsibilities within the Group to assist in the achievement of the aims and objectives of the organisation.

The Group employs an executive director and an information officer who have day-to-day responsibility for its central office in Washington, Tyne and Wear. They can be contacted via the 24 hour telephone helpline 0191 415 0693 or by email at [niemann-pick@zetnet.co.uk](mailto:niemann-pick@zetnet.co.uk).

The main aims and objectives of the NPDG (UK) are: to make a positive difference to the lives of those affected by Niemann-Pick diseases (NPD); relieve sickness and any distress which may arise from coping with the disease; and to advance the education and awareness of families, professionals and the general public in all matters concerning the disease.

The NPDG (UK) aims to provide effective support in the three main areas of care, information and research.

## **Care and support**

- provision of a 24-hour helpline – 0191 415 0693
- access to a clinical nurse specialist for NPD (based within the NHS) who can provide advice on all aspects of the disease
- provision of a families officer providing non-medical support and advocacy
- home visits from the clinical nurse specialist as required
- production of a family directory, encouraging the creation of family support networks



- organisation of an annual family conference, providing networking opportunities for families who are widely dispersed geographically
- organisation of clinic days for children and adults
- provision of counselling and advocacy services to families
- provision of an interactive family support service using video cameras, webcams and media links

The NPDG (UK) funds the post of a clinical nurse specialist (CNS) for Niemann-Pick disease, who is available to offer direct help to families and professionals, including:

- family counselling services, genetic counselling and advice on carrier testing
- advice on all aspects of the disease, including aids and adaptations, continence, nutrition, breathing, bathing, managing seizures, maximising movement, drug therapy, disease progression and palliative care
- home visits when required
- advocacy
- bereavement counselling

The role of clinical nurse specialist for NPD is to work alongside families and their local health and social care providers, to ensure those affected by the disease receive the optimum level of care. It is not always easy for families to recognise and express their needs; the CNS will ensure that the relevant local agencies respond to the changing needs of the family in a timely and appropriate manner.

The CNS is able to structure her work to suit families, making home visits around the UK when required, and is available to answer queries from families and professionals via the telephone helpline.

## Information

- provision of information packs
- regular newsletters and e-bulletins
- production and distribution of educational literature regarding NPD
- website – [www.niemannpick.org.uk](http://www.niemannpick.org.uk)
- telephone advice from the clinical nurse specialist and executive director
- collaboration with other relevant organisations, both nationally and internationally, to encourage the sharing of information and resources and to highlight best practice
- specialist information is also available for medical and social care professionals

The NPDG (UK) provides an information and advice service to families and carers as well as health and social care professionals. The Group is continually developing educational information that will contribute to a greater understanding of the Niemann-Pick diseases and assist in family support. We maintain active links, both nationally and internationally, with other support organisations, enabling us to share information and to stimulate interest in this group of diseases. The organisation of an annual family conference provides the opportunity for families, and professionals, to meet and share their experiences.

## Research

- the NPDG (UK) supports research in this area, enabling the collection of much-needed data regarding clinical aspects of the disease
- we maintain links with pharmaceutical companies and researchers regarding existing and future developments in possible palliative treatments for this group of diseases
- the Group provides a Trustee Memorial Award for scientific submissions by young professionals who are able to provide an original contribution to the scientific or public understanding of Niemann-Pick diseases
- the dissemination of current information regarding developments in research to families and other interested parties

# What is Niemann-Pick disease?

**T**here are two recognised forms of Niemann-Pick disease. Acid sphingomyelinase deficient (ASMD) Niemann-Pick disease (in which NP type A and NP type B represent the opposite ends of a spectrum of the same disease) and Niemann-Pick type C.

ASMD Niemann-Pick disease – or NP type A and type B – is caused by a deficiency of the enzyme, acid sphingomyelinase, causing a build-up of toxic materials in the body's cells.

Niemann-Pick type C is not caused by an enzyme deficiency, but the end result is the same; an accumulation of materials (cholesterol and other fatty acids) in the body's cells.

In ASMD Niemann-Pick type A, the accumulation of materials occurs very quickly, and life expectancy rarely exceeds five years of age.

ASMD Niemann-Pick type B does not usually affect the brain and, although growth may be slow, those affected will usually survive well into adulthood, with many being able to lead a full and normal life.



In Niemann-Pick type C, the brain and other organs are affected, leading to progressive intellectual decline, loss of motor skills, seizures and dementia. Speech can become slurred and swallowing problems may develop. The rate at which the disease progresses varies greatly between individual patients. Children who develop neurological symptoms in early childhood are thought to have a more aggressive form of the disease and may not survive to adolescence, while others may remain symptom-free for many years.

If you or someone you know has just been diagnosed as having Niemann-Pick disease, it is likely that you are feeling overwhelmed with emotion and greatly confused as to what the disease is and how it has been acquired. The information provided here is intended to help you and your family understand the disease. Hopefully, this will help, even in a small way, to deal with the distress that you inevitably feel.



# Why is it called Niemann-Pick?

**T**he Niemann-Pick diseases are quite separate in terms of their fundamental causes. However, they share many similarities in clinical presentation (the ways in which they affect the body). This has resulted in the diseases being grouped together as Niemann-Pick disease and named after two doctors who described the symptoms in the early part of the 20th century.

In 1914, a German paediatrician, Dr Albert Niemann, described the clinical presentation of children with the disease, but at that time little was known regarding what was happening inside the body's cells and molecules. Then, in the 1920s, the studies of Ludwig Pick provided evidence of a new disorder, one distinct from the storage disorders previously described. Further investigations using cells taken from the tissues of affected individuals in the mid and latter years of the century resulted in an improved understanding of the diseases and their cause. Since then there has been a considerable amount of research into these and other inherited diseases of metabolism. It was not until 1958 that the disease presentations were classified into types A, B and C. In 1966 types A and B were identified with a lysosomal enzyme, acid sphingomyelinase.

# What causes Niemann-Pick disease?



All types of Niemann-Pick disease are acquired through autosomal recessive inheritance; this means that both parents have to be carriers of the faulty gene (mutation). A mutation is a change or fault on a normal gene which means that it does not perform the function that it should do. Parents seldom know that they are carriers of the disease and have no control over whether the disease will be transmitted to their child. In each pregnancy of a carrier couple, there is a 25 per cent chance that they will both pass on this gene mutation to their child.

## What are autosomes?

Autosomes are the non-sex-related chromosomes. The term autosomal recessive means that the effects of possessing a single copy of a disease-causing gene are hidden. With a recessive condition, a person may be a carrier of a disease gene, but this may have no noticeable affect on their everyday lives and health.

A positive diagnosis of Niemann-Pick type C disease in a child means that each parent is a carrier of a disease-causing mutation on this gene.

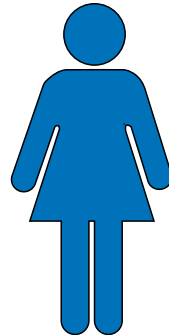
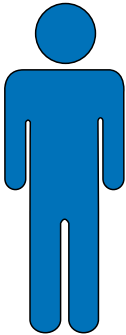
The child may inherit identical mutations from each parent and this would be referred to as **homozygous**. The homozygous condition may arise through intermarriage although this may not be obvious over many generations. In other instances the parental mutations may be different, but still disease-causing; this would be referred to as **heterozygous**.

Genes are found in pairs within the body. When a child is conceived each parent passes just one gene from every pair of genes to their child. The diagram opposite shows the combinations of a gene that may result if both parents are carriers of one copy of a faulty gene. In this condition each parent is described as being heterozygous for the disease gene.

# Autosomal recessive inheritance

Carrier father

Carrier mother



R r

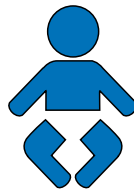
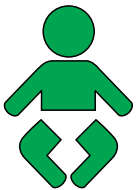
R r

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Normal child

Carrier child

Carrier child

Child with condition

# How is Niemann-Pick type C disease diagnosed?

**N**iemann-Pick type C is an extremely rare disease that affects multiple body systems. It has variable onset and progression over a course of years. In the past it was frequently misdiagnosed or even undetected. Even now that direct biochemical and genetic tests are available, diagnosis can be challenging. This highlights the need for increased awareness of the disease, and for effective referral to specialist care for patients who are suspected of having the condition. Niemann-Pick type C disease usually affects children of school age, but symptoms of the disease can present at any time from early infancy to adulthood.

Niemann-Pick type C is initially diagnosed by taking a small piece of skin (skin biopsy), then growing the cells (fibroblasts) from the biopsy in the laboratory, and studying their ability to transport and store cholesterol. The transport of cholesterol in the cells is studied by measuring conversion of the cholesterol from one form to another. This is called esterification. The storage of cholesterol is also assessed by staining the cells with a compound called filipin which glows under ultraviolet light.

It is important that both of these tests are performed, since reliance on one or the other may lead to the diagnosis being missed in some cases. Although cholesterol storage is present in Niemann-Pick type C, it must be stressed that this storage is not diet-related. Storage occurs in the body's cells due to the faulty gene (mutation), therefore the affected person's eating habits, or consumption of cholesterol will not affect the rate or level of storage.



*It wasn't until we met a doctor who had come across Niemann-Pick disease before, on a routine liver review at the beginning of 2007, that we were put on the road to a devastating diagnosis. By this time our daughter's spleen measured a huge 14.5cm on the scan and he felt a fresh investigation was required. She underwent further invasive testing, a second liver and bone marrow biopsy and a skin biopsy. The next ten weeks were the worst of our lives, as we waited for the results. I took it upon myself to search out more information and found the contact details for NPDG (UK). They kindly provided me with the support I needed and referred me to their clinical nurse specialist, who gave me and my husband a clearer picture of the disease and testing process. The definitive results came through in July but I think we had already accepted the fact it was NP-C long before that.*

Based on molecular genetic testing, NP-C is now divided into two subtypes – NP-C1 and NP-C2 – as each is caused by a different gene mutation. Approximately 95 per cent of Niemann-Pick type C cases are caused by genetic mutations in the NP-C1 gene, with the other five per cent caused by mutations in the NP-C2 gene.



The NP-C1 gene is located on chromosome 18. The gene provides instructions for producing a protein located mainly in the membranes of the lysosomes and endosomes. These are compartments in the cell that digest and recycle materials. While its exact function is not as yet completely understood, it is thought that this protein plays a role in the movement of cholesterol and other types of lipids (fats) across cell membranes.

The NP-C2 gene is located on chromosome 14. The gene provides instructions for producing a protein that is located mainly inside lysosomes, which are the compartments in the cell that digest and recycle materials. The NP-C2 protein binds to cholesterol, and researchers believe that it plays an important role in moving cholesterol and certain other lipids (fats) out of the lysosomes to other parts of the cell. At present the exact function of the NP-C2 protein is unknown.

In NP-C1, there is one common mutation and about 25 per cent of those affected carry one copy of this. Unfortunately there are over 250 other known mutations, often individual to families, and these may be difficult to find. There are fewer NP-C2 mutations, therefore analysis is more straightforward. Once the mutations have been found in the affected individual, it is then possible to perform carrier testing on other members of the extended family using a simple blood test. At present this service is only carried out in a few specialist centres.

Pre-natal testing is available for NP-C. Cells can be grown from samples taken at around 11 weeks of pregnancy (chorionic villus sampling – CVS) or an amniotic fluid specimen can be analysed during the 16th to 20th weeks of pregnancy. However, it may take several weeks for the cells to grow. If the DNA mutations are known, this process is much quicker.



# What are the signs and symptoms of Niemann-Pick type C disease?

**N**iemann-Pick type C disease (NP-C) is an extremely rare genetic disorder arising from the build-up of glycosphingolipids, particularly in the central nervous system (brain and spinal cord). These build up in toxic quantities as unesterified cholesterol, causing structural and functional damage in cells and tissues. In people without NP-C, glycosphingolipids are broken down naturally by the body's cells. NP-C is pan-ethnic and arises at irregular intervals across populations, regardless of race, although genetic clusters have been identified in Nova Scotia, Colorado, and New Mexico. It is believed that NP-C arises in one case per every 120,000 live births. It is considered highly likely, however, that this is an underestimate due to a mixture of factors – chiefly, in the failure to recognise the clinical characteristics and a previous lack of definitive diagnostic tests.



As mentioned above, NP-C is now divided into two subtypes – NP-C1 and NP-C2 – as each is caused by a different gene mutation. Niemann-Pick disease type D (NP-D), previously and still sometimes used to describe the genetic isolate from Nova Scotia, should no longer be considered as a separate condition as it is biochemically and clinically the same as NP-C, and is now known to result from mutations in the NP-C1 gene.

NP-C has an extremely varied clinical presentation, but is characterised by a range of progressive neurological problems that become severe and life-limiting in the later stages. It can present, either with or without associated hepatosplenomegaly (enlarged liver and spleen), in infants, children or adults. It is characterised by eye movement abnormalities (vertical supra-nuclear gaze palsy), dysphagia (difficulty in swallowing), dysarthria (slurred, irregular speech), ataxia (lack of muscle control) and progressive cognitive dysfunction (progressive intellectual decline) which can lead to dementia. In NP-C2, there may be increased respiratory involvement, resulting in frequent chest infections.



**What, typically, is the age when NP-C becomes apparent?**

NP-C is present in an individual from the moment of conception but is not necessarily apparent. The symptoms are often related to the age when the disease takes hold, and this is in itself an extremely variable factor ranging from birth to old age. Similarly, people with very late onset may be incorrectly diagnosed with a disease such as Alzheimer's disease. Since awareness of the disease has increased and diagnosis has improved, the age profile of the disease is beginning to look different to that of a few years ago. What was once considered to

be a childhood disease is now, equally, beginning to look like a disease of adults. Information on the numbers of people affected, age of onset and progression has been collected in a number of countries and this will help to provide a better picture in due course.

*We always knew from the moment she was diagnosed that our daughter had a life-limiting condition although what we hadn't expected was quite how 'limiting' it would be. Until the first signs of Niemann-Pick manifested themselves we always hoped that perhaps the diagnosis was wrong or that she might have only a mild form of this awful disease. Gradually she started to show symptoms of the progression of the disease. Then we began to notice she was losing some of the skills she had already learned and was finding it difficult to learn new ones.*

NP-C is a very variable disease. Symptoms may appear and then disappear. Some symptoms may never appear. The rate of progression of the disease is different from person to person. The rate of progression for an individual will change over time.

### **What is the life expectancy of a person diagnosed with Niemann-Pick type C?**

It is difficult to predict what the life expectancy will be for a person with NP-C. The age that neurological symptoms – symptoms that affect the working of the brain – first occur, and the rate of deterioration may be the only clues. By studying previous cases of the disease, it is thought that the earlier the onset of neurological symptoms, the faster the rate of subsequent deterioration. The NPDG (UK)'s clinical nurse specialist is currently researching and collating data related to life expectancy.

## **Prenatal testing and pre-implantation genetic diagnosis**

Once a child has been diagnosed with NP-C, it is usually possible to test future pregnancies at 11 weeks (chorionic villus sampling – CVS) or at around 13 weeks by amniocentesis. Ideally it is best to study the affected child's DNA to identify the mutations first, as this will enable the prenatal test results to be confirmed more quickly.

If none of the mutations have been identified, or only one has been found, skin biopsies are carried out on both parents. This gives a specific picture for the affected child and the parents, enabling the comparison of samples in future pregnancies. This method involves growing the sample taken from the placenta of the baby, which takes around six weeks from the date the sample is taken. A result will therefore not usually be available until 16–20 weeks into the pregnancy, when the decision on how to proceed has to be made.

Both CVS and amniocentesis carry a slight risk of miscarriage, so it is important for parents to discuss their options prior to having the test. If parents have decided they would not wish to terminate a pregnancy under any circumstances, they may then feel that putting that pregnancy at risk, however small the risk, would not be an option.

At the time of writing there are at least two centres in the UK that offer pre-implantation genetic diagnosis (PGD). This is based on in vitro fertilisation (IVF) and the genetic mutations from each parent need to be known. The principle behind the procedure is that very early embryos are checked for the known mutations soon after they begin making early divisions. Only an unaffected embryo (or possibly a carrier embryo) would then be implanted. This procedure is in its infancy in NP-C, and for current information on availability and success rates please contact the NPDG (UK).



The photographs used to illustrate this booklet show people with NPD and their families and friends. They have all been used with permission, but do not generally relate to the text they have been placed alongside.

**This booklet forms part of a resource pack published by the Niemann-Pick Disease Group (UK). It is intended to be read in conjunction with the other parts of the pack. If you do not have the other documents in the pack or would like further information, please contact us at the address below.**

Note: the information contained in the pack is not a substitute for professional medical care – it is meant to complement the advice and support you receive from your health and social care team.



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