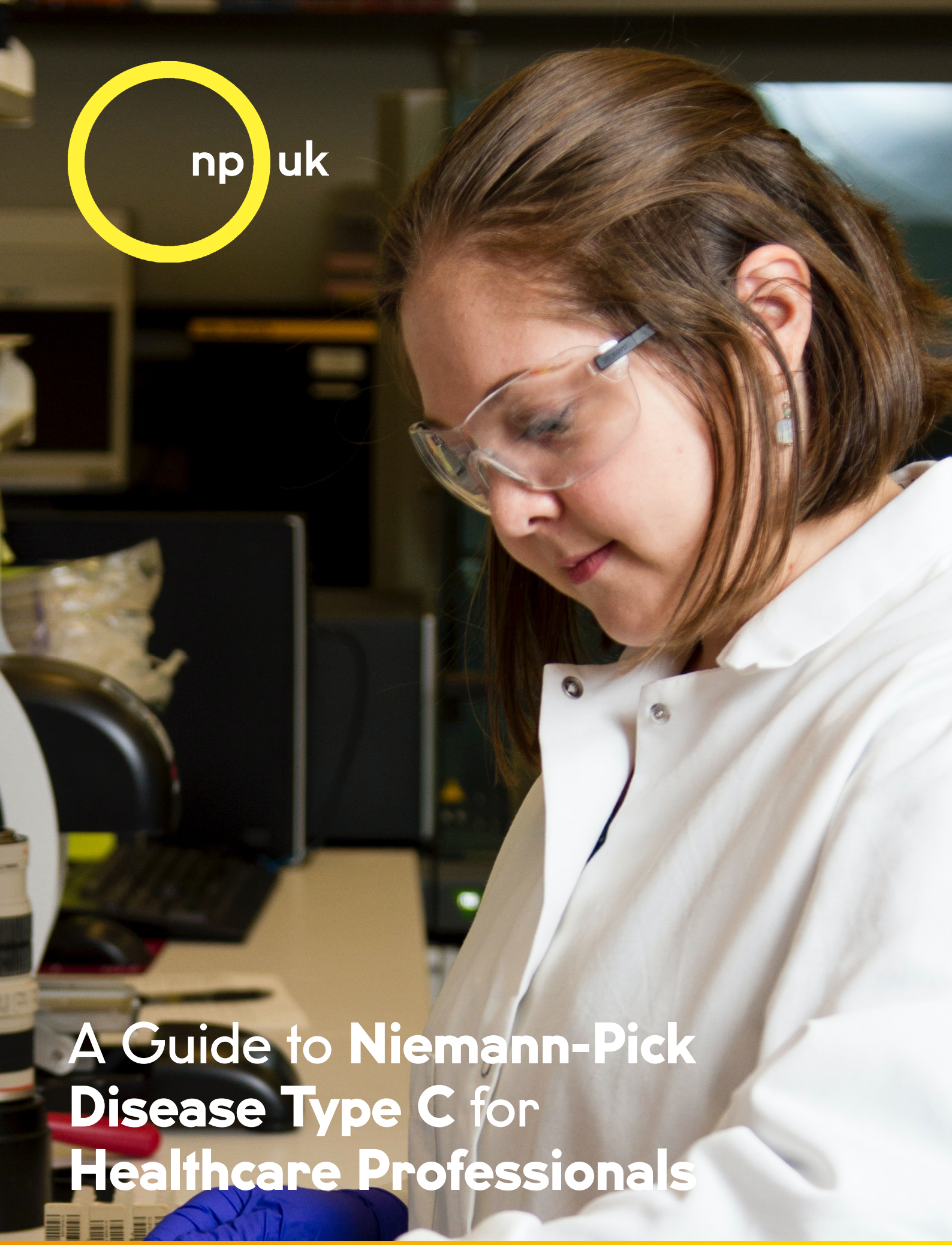

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A Guide to **Niemann-Pick Disease Type C** for **Healthcare Professionals**

Supporting those affected by Niemann-Pick

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Professor Marc C. Patterson, MD
Professor of Neurology, Pediatrics and Medical Genetics
Mayo Clinic Children's Center, Minnesota, USA

Dr Marie T. Vanier, MD, PhD
Honorary Director of Research at INSERM (National Institute of Health and Medical Research), Lyon, France

Dr Reena Sharma, MD
Consultant Adult Metabolic Medicine, Honorary Senior Lecturer
The Mark Holland Metabolic Unit, Salford Royal Foundation NHS Trust, Salford, UK

Professor Mark Walterfang, MBBS Hons PhD FRANZCP
Neuropsychiatry, Royal Melbourne Hospital, Australia

Dr Robin Lachmann PhD, FRCP
Consultant in Metabolic Medicine
National Hospital for Neurology, London, UK

Lydia Aston
Postdoctoral Researcher
Birmingham City University & Aston University, Birmingham, UK

Laura Bell
Clinical Nurse Specialist
Niemann-Pick UK (NPUK)

Jackie Imrie
Trustee
Niemann-Pick UK (NPUK)

Dr Will Evans
Chair and Trustee
Niemann-Pick UK (NPUK)

Toni Mathieson
Chief Executive
Niemann-Pick UK (NPUK)

GLOSSARY OF TERMS:

Allele	A particular form of gene. Alleles occur in pairs, one on each chromosome inherited from each parent
Amyloid precursor protein (APP)	Protein from which beta-amyloid (the main component of neuritic plaques in Alzheimer's disease) is derived by proteolysis
Ascites	Abnormal accumulation of fluid between tissues and organs in the abdom
Ataxia	Inability to coordinate voluntary muscular movements
Autophagy	Digestion of cellular constituents by enzymes of the same cell
Autosomes	Any chromosome other than the sex chromosomes
Cataplexy	Sudden loss of muscle control/tone while conscious, following emotional sti
Dysarthria	Difficulty in articulating words
Dysphagia	Difficulty in swallowing
Dystonia	Involuntary muscle contractions tha t cause slow repetitive movements or abnormal postures
Filipin	Antifungal agent used in fluorescent diagnostic staining of cultured NPC fibroblasts
Gelastic cataplexy	Cataplexy associated with laughter due to strong emotional stimulus
Glycosphingolipid	Carbohydrate-attached lipids (glycolipids) containing sphingosine
Hepatosplenomegaly	Enlarged liver and spleen
Homozygous	An individual is homozygous at a locus if (s)he has two identical alleles
Hypotonia	Decreased muscle tone
Lysosome	Sac-like intracellular organelle that contains various hydrolytic enzymes

Hypotonia	Decreased muscle tone
Lysosome	Sac-like intracellular organelle that contains various hydrolytic enzymes
Mutation	Change in the genetic material of an individual
Neurofibrillary tangles (NFTs)	Pathological protein aggregates found in neurones in neurological disease
ASMD NPA	ASMD Niemann-Pick disease type A
ASMD NPB	ASMD Niemann-Pick disease type B
NPC	Niemann-Pick disease type C
Organomegaly	Enlarged organs
Phenotype	The observable characteristics of an individual determined by interaction of genotype and environment
Phospholipids	Compound fat molecule in which there are two fatty acids and a phosphate group attached to glycerol
Saccades	Small, rapid movements of the eye as it jumps from one fixation point
Sphingomyelin	Phospholipid composed of a long chain base, sphingosine, a long chain fatty acid and phosphocholine
Splenomegaly	Enlargement of the spleen
Thrombocytopenia	A low platelet count
Vertical supranuclear gaze palsy (VSGP	Inability to look in a vertical direction because of cerebral impairment

Chapter 1: Niemann-Pick Disease Type C – A Clinical View

Niemann-Pick disease type C (NPC) is a rare, devastating, inherited neuro-degenerative disease characterised by severely impaired cellular lipid trafficking.[1] NPC is an autosomal recessive disease, requiring a patient to inherit a faulty gene from each parent.[1] It affects males and females equally and is pan-ethnic.[1] It is an entirely different disease to Niemann-Pick disease type A (NPA) and Niemann-Pick disease type B (NPB).

The exact prevalence of NPC is difficult to calculate as it is likely that some cases remain undiagnosed due to clinicians being unaware of the highly variable signs and symptoms of the disease and the complexity of diagnostic testing. However, prevalence has been estimated at 1 case per 100,000 live births.[1] This is likely to be an underestimate and significant improvements in clinical awareness and diagnostic methods in the past few years have led to a greater proportion of adult-onset cases being diagnosed since 2013.

Individuals with NPC have mutations in one of two genes, *NPC1* (95% of individuals) or *NPC2* (5% of individuals).[1] The diagnosis can be made at all ages, from before birth (NPC is a cause of stillbirth due to foetal ascites and liver disease) up to the sixth decade of life. On the whole, the presenting symptoms are less severe in older patients. Cases can also present to many different specialists, including hepatology, paediatrics, haematology, adult neurology and psychiatry. Increased awareness of this devastating condition is required at all levels of care to support the quick diagnosis for individuals and ensure the provision of appropriate treatment and adequate counselling.

The impact of NPC on social and health care is huge: optimal disease management involves a multi-disciplinary, multi-professional team based in a specialist centre, closely liaising with community providers. With continued efforts, it is hoped that future research will lead to a cure for the disease. In the meantime, international research is progressing toward the development of effective disease-modifying treatments and investigational therapies that could play an enormous role in the fight against NPC.

Dr Simon Jones
Consultant in Paediatric Inherited Metabolic Disease
The Manchester Centre for Genomic Medicine, Manchester, UK

Jackie Imrie
Trustee
Niemann-Pick UK (NPUK)

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Chapter 2: A Call to Action – The Patient Association View

Due to the rarity and variable nature of NPC, the path to diagnosis can be slow and challenging. It can have a profound effect on all aspects of a patient's life and severely impact their entire family. Following a diagnosis, patients and their families require sensitive and coordinated support, as well as clear and accurate information to assist them in navigating essential services as they prepare for the future.

Endless rounds of appointments and screening tests, plus progressing or complex symptoms can affect a patient's ability to work or to attend school, which can place a significant emotional and financial strain on patients and their families.

As health and social care services vary in each local area, families can feel bewildered and isolated due to conflicting advice or a lack of disease-specific information. As NPC progresses and patients develop more complex needs, symptoms can change rapidly, leading to a range of emotional and practical issues.

However, dedicated patient advocacy groups can provide extensive and expert support for patients and their families as they adjust to diagnosis and begin to understand the impact that NPC will have on their lives.

Like our counterparts around the world, Niemann-Pick UK (NPUK) can help patients and families to access essential health and social services or equipment to support daily living. Our expert advocates can also provide emotional support to build resilience, strengthen family relationships and reduce crisis points. Through our community networks and condition-specific events, we can connect patients and families, and help to reduce feelings of isolation and increase opportunities for mutual support.

Working in collaboration with global advocacy groups, NPUK aims to highlight the unmet need that exists in NPC and many other rare conditions. Through the provision of information, advice and encouragement, advocacy communities support and empower patients and their families. Together, our shared voice can facilitate improvements in care and services and influence therapy development.

To increase the knowledge and understanding of rare conditions such as NPC it is critical to support research; NPUK actively supports and funds research to improve the lives of those affected by NPC.

The International Niemann-Pick Disease Registry (INDPR) was established to collect much-needed clinician and patient-reported data on a global scale, providing extensive insight into patient impact and experience. This comprehensive, international data resource, specific to Niemann-Pick diseases, encourages efficient and timely diagnosis, enables progress in research and facilitates the development of therapeutic interventions.

Increasing interest and activity in the NPC field brings much hope and encouragement for the future. NPUK will continue to encourage innovative research and advocate for equal access to coordinated care and the latest therapies, to ensure that all patients can achieve the best possible quality of life.

Dr Will Evans
Chair and Trustee
Niemann-Pick UK (NPUK)

Toni Mathieson
Chief Executive
Niemann-Pick UK (NPUK)

Chapter 3: Overview

Niemann-Pick diseases are a group of rare, autosomal recessive, lysosomal lipid storage disorders, affecting both children and adults.[1] These can be further divided into two distinct subgroups: acid sphingomyelinase deficiency (ASMD), caused by mutations of the SMPD1 gene, which includes Niemann-Pick disease types A and B, and Niemann-Pick disease type C (NPC), a cellular lipid trafficking disorder, caused by *NPC1* or *NPC2* mutations.[1]

The prevalence of NPC is estimated to be 1 case per 100,000 live births.[2] This is likely to be an underestimate due to considerable challenges in diagnosis, primarily caused by its highly heterogeneous and non-specific presentation.[3] It affects people of all races, sex, ethnicities and nationalities across the globe, although genetic isolates have been identified in Nova Scotia, Colorado, and New Mexico.[4]

Symptoms of NPC develop as multiple tissue lipids accumulate in toxic quantities in the parenchymal organs and the central nervous system (CNS), causing irreversible cellular damage and sadly leading to the premature death of affected individuals.[4,5]

NPC's extremely heterogeneous clinical presentation is characterised by visceral, neurological and psychiatric manifestations that are not specific to the disease, and can appear either alone or in combination.[3] Understanding common symptom combinations in the context of NPC and its age of onset, can greatly aid suspicion of NPC and subsequent diagnosis.[3,6,7] Leading manifestations that, in combination, are highly suggestive of NPC include splenomegaly, ataxia, psychosis and cognitive decline, leading to dementia.[6] Eye movement abnormalities and specifically, vertical supranuclear gaze palsy (VSGP), can be seen as the hallmark of the disease and greatly increase the likelihood of a NPC diagnosis when seen in combination with any other symptoms.[3,6,7] The burden of disease is perhaps best demonstrated by the patient journey in the 'classical' phenotype of NPC, as described below.

Although the time to diagnosis remains a significant barrier to care and support access for patients and their families, the outlook for people affected by this lifechanging disease compared to previous decades is increasingly positive. This is primarily driven by substantial advances in diagnostics and screening algorithms, identification of new biomarkers, a widely-approved treatment option and multiple clinical trials investigating potential new and effective therapies.[2,7,8]

Classical NPC: the patient journey

New-borns with 'classical NPC' often present with unexplained cholestatic jaundice. Despite being present for two weeks or more, this type of jaundice resolves spontaneously and does not require phototherapy treatment. Therefore, it may be missed out by parents when later asked to recall their child's medical history.

Early childhood development is typically normal, though they may experience some problems at nursery or school, such as lack of attention or poor handwriting. Over the years, they may experience increasing problems at school, such as being teased for being clumsy or struggling to integrate socially, before signs of progressive dementia and overt ataxia become apparent. At this point, difficulty with eye movement may be noticed, with eye blinking or head thrusting on attempted vertical gaze, as well as gelastic cataplexy (limited or generalised atonia triggered by strong emotion, typically by laughter).

Increasing educational and relationship problems may develop as dysarthria, dysphagia and drooling hinders communication. This may be accompanied by dystonia, which slowly graduates from initial spasms of the hand and foot to presence in most body parts. Hepatosplenomegaly is often first detected in early childhood, though it remains undetected in some cases.

Feeding tubes are required as dysphagia progresses, and spasticity or rigidity add to the complex care needs of the child or young adult. Tragically, many patients die before adulthood, with aspiration pneumonia being the most common cause of death.

As cognition and physical ability declines through late childhood and adolescence, the child is unable to continue at regular school and becomes wheelchair bound. Schizophrenic-like periods of psychosis may occur around puberty.

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Chapter 4: History

Niemann-Pick Disease Types and Nomenclature

Niemann-Pick disease is named after the pioneering work of German paediatrician, Albert Niemann (1880-1921) and German pathologist, Ludwig Pick (1868-1944),[1,2] who were the first to recognise a new and distinct type of lipid storage disorder in infants.[2]

Further classification of the disease did not take place until 1958, when Crocker and Farber published a case series on patients demonstrating a wide variability in disease presentation.[3] Variations such as age of onset, clinical expression, presence of neurological symptoms and extent of sphingomyelin storage in the tissues prompted Crocker to classify Niemann-Pick disease into four subgroups (A to D) based on biochemical and clinical criteria.[4]

Categories of Niemann-Pick disorders as classified by Crocker[2–4]

Group A (ASMD-NPA) characterised by classic neurodegenerative disease, involving extensive visceral and cerebral sphingomyelin storage and leading to mortality in early childhood

Group B (ASMD-NPB) included patients with marked visceral symptoms but no involvement of the nervous system

Group C (NPC) manifested as a gradually progressive neurologic disease

Group D (previously known as NPD) was virtually identical to NPC, except that it was limited to a genetic isolate from Nova Scotia

Most notably, non-neural tissues in those affected by type C and D showed relatively less sphingomyelin and greater cholesterol storage compared to types A and B. This highlighted the critical differences in the fundamental biochemical fault and pathophysiology of NPC, compared to NPA and NPB.

Further differences between the subgroups were identified a few years later. In 1966, Brady et al discovered that the main biochemical fault in type A and B was a severe generalised acid sphingomyelinase deficiency, which was not the case for type C and D. This finding, alongside the detected build-up of multiple complex glycosphingolipids in NPC (i.e. not just sphingomyelin), suggested that NPC should be considered a distinct subtype from NPA and NPB. This decision was subsequently formalised by expert consensus in 1982.[5]

Niemann-Pick disease is still classified according to Crocker's subtypes; however, there have been noteworthy progressions in knowledge regarding the genetic origins and fundamental pathophysiological mechanisms. Specifically, the characterisation of the gene mutation causing each subtype has proven that NPC is not only distinct from NPA and NPB clinically but also different at the molecular and biochemical level (see Pathophysiology, page 17). NPA and NPB are now referred to as acid sphingomyelinase deficient Niemann-Pick disease (ASMD) to distinguish these diseases from NPC.

In recent years, it has become apparent that there is a broad clinical spectrum of ASMD, and patients with intermediate phenotypes have also been described (NPA/B). To better recognise this broad spectrum of disease, ASMD has recently been re-classified into three subtypes that more accurately describe their clinical presentations: acute neuropathic form (NPA), chronic neurovisceral form (NPA/B), and chronic visceral form (NPB). The various subgroups of Niemann-Pick disease are summarised in Table 1.

Table 1: Niemann-Pick disease subgroups[6,7]

Disease type	Differentiating characteristic	Main pathophysiology	Genetic origin
Niemann-Pick disease type A (NPA) or infantile neurovisceral ASMD	Presentation in infancy, very poor disease prognosis	Acid sphingomyelinase deficiency	*SMPD1* gene mutation
Niemann-Pick disease type A/B (NPA/B) or chronic neurovisceral ASMD	Slower progression of neurological symptoms and prolonged survival compared to NPA	Acid sphingomyelinase deficiency	*SMPD1* gene mutation
Niemann-Pick disease type B (NPB) or chronic visceral ASMD	Juvenile presentation involving the lungs	Acid sphingomyelinase deficiency	*SMPD1* gene mutation
Niemann-Pick disease type C (NPC)	Pan-ethnic, occurring in all ages with brain complications	Fault in cellular cholesterol trafficking	*NPC1* or *NPC2* gene mutation
Niemann-Pick disease type D (NPD)*	As for type C, but with Nova Scotian descent	Fault in cellular cholesterol trafficking	*NPC1* gene mutation

Type D should no longer be considered as a distinct subtype; it is biochemically and clinically identical to type C.

Use of molecular genetic testing has led to NPC being split into two further types – *NPC1* and *NPC2*, based on the specific gene mutation (see Genetics, page 14). Similarly, NPD is no longer considered a separate condition, as it is biochemically and clinically identical to NPC and now understood to develop from an *NPC1* gene mutation.[8,9] Subsequent studies by Pentchev et al[10] demonstrated that the underlying defect in NPC was not acid sphingomyelinase deficiency but, instead, the faulty esterification of endogenous and exogenous cholesterol. Development of diagnostic procedures for the recognition of cholesterol trafficking faults have enabled earlier recognition of NPC patients and allowed researchers to map the gene now understood to be accountable for the majority of NPC cases.[11,12]

This clinical guide focuses on NPC; however, NPA and NPB are mentioned where relevant to provide context and maintain completeness.

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Chapter 5: Genetics

Major advances in the 1990s led to the description of two genetic complementation groups[1,2] and the isolation of the underlying genes associated with NPC.[3,4] It was discovered that mutations in either the *NPC1* gene or the *NPC2* gene resulted in a similar cellular phenotype, including a unique impairment in the processing and utilisation of endocytosed cholesterol (see Pathophysiology, page 17). The *NPC1* gene is mutated in at least 95% of the families affected,[2] including those historically categorised as type D.[5] Localised at chromosome 18q11-q12, it spans 56 kb, contains 25 coding regions (exons), and encodes NPC1, a large late endosomal/lysosomal multipass membrane protein. Conversely, the *NPC2* gene is only involved in approximately 5% of NPC families. Localised at chromosome 14q24.3, it contains five exons and encodes a small soluble late endosomal/lysosomal protein named NPC2.

Mutational Patterns – Genotype/Phenotype Correlations

Over 700 *NPC1* genetic variants have already been reported, among which, close to 500 are considered pathogenic.[6] About 70% are missense mutations, but all types have been described, including deep intronic mutations and large deletions. There are only a few common or recurrent mutations and a geographical/ethnic variation of mutational patterns. Globally, the most frequent mutant allele is p.I1061T,[7] constituting about 27% of alleles in the United Kingdom,[8] 15% in Germany, 13% in France, and 9% in Spain. It is, however, much less frequent in Italy (4%)[6] and the Czech Republic (4%), and it has not been reported in East Asian countries. Conversely, p.P1007A, the second most frequent mutation, is more prevalent in patients from Germany (13%), the Czech Republic (10%) and Brazil than within Italy, Spain, or France (with only 3 to 4% of alleles). Studies in large national cohorts may reveal a high prevalence of specific mutations, e.g. p.F284Lfs26* (6%) in Italy or p.R1186H (18%) in the Czech Republic.

Only 26 pathogenic *NPC2* mutations have been described to date, with many of the described patients originating from Italy, North Africa, Turkey, and Iran. Most mutations lead to a functionally null allele. One single large deletion (covering exons 2 and 3) has been reported, and a missense mutation affecting the cholesterol-binding site of NPC2 was identified in several families.

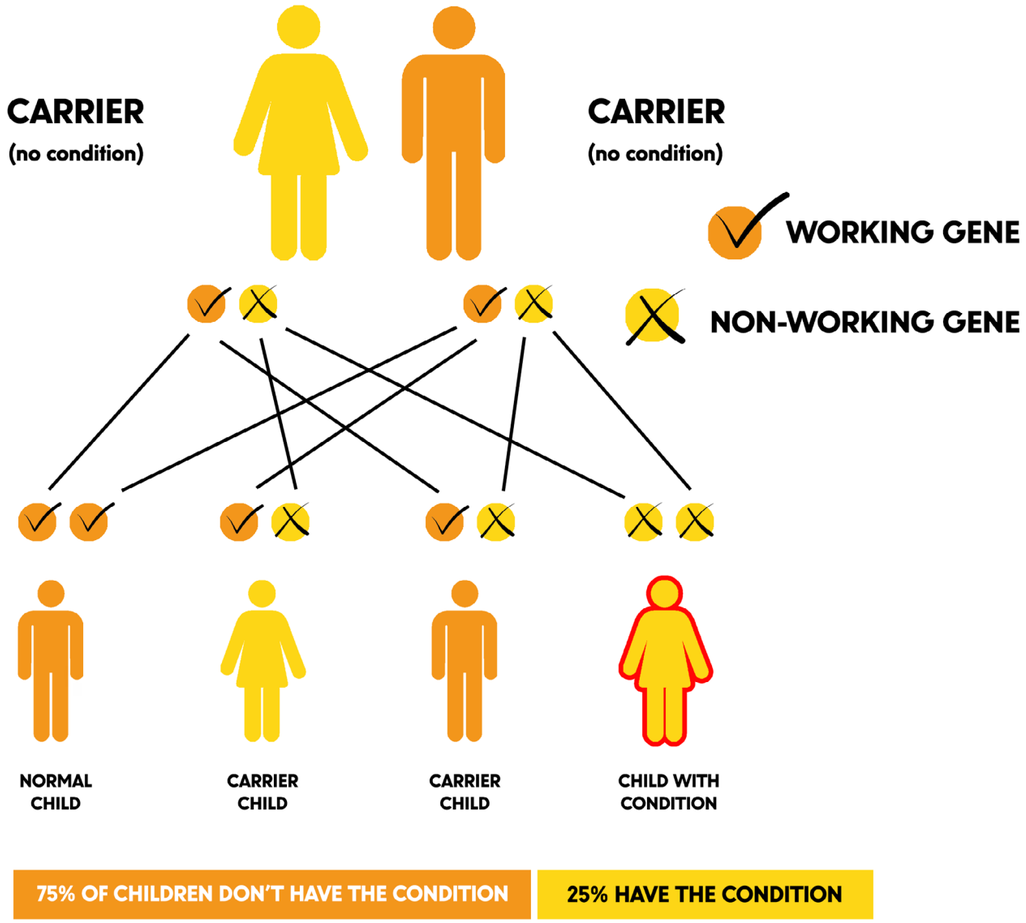
Genotype-phenotype studies in homoallelic patients have generally shown a good correlation between two alleles with stop, nonsense or frameshift mutations and the most severe neurologic course. At the other end of the clinical spectrum, some *NPC1* mutations appear to be associated with an adult-onset form, even when combined to a null allele. From observations in multiplex families, it can be concluded that mutations show correlations with the global subtype of neurologic disease. Greater differences between siblings are seen in the adolescent/adult-onset forms. Registries associating clinical histories and molecular data should significantly improve our knowledge on the genotype/phenotype correlations and their limitations.

Patterns of Inheritance

NPC is inherited in an autosomal recessive manner, i.e., two copies of a gene mutation at a particular locus on one of the 22 pairs of autosomes (non-sex chromosomes) must be present for the disease phenotype to manifest.

In each pregnancy of a carrier couple, there is a 25% chance that they will both pass on their disease-causing NPC gene to a child, who would then be affected. There is a 50% chance that only one of them would pass on a disease-causing NPC gene, making the child a heterozygote carrier like the parents. There is a 25% chance that both functional genes would be passed on, and the child would neither be a carrier nor affected. Overall, unaffected children have a two in three risk of carrying one abnormal *NPC1* or *NPC2* allele. Furthermore, each sibling of an affected individual's parents is at a 50% risk of being a carrier.

Figure 1: Autosomal recessive inheritance



Genetic Counselling – Carrier Testing – Prenatal Testing

Genetic counselling provides individuals and families affected by NPC with information on the nature, inheritance, and implications of this genetic disorder in order to help them make informed medical and personal decisions. It is particularly relevant with regard to family planning.

For optimal genetic counselling, the two pathogenic alleles should have been identified in the family index case. A complementary parental study is especially important as it will ensure allele segregation and identify the respective paternal or maternal mutation (which is often different, but it can also be the same).

Carrier testing in blood relatives (also for future generations) will then be reliable and easy, by searching for the family mutation. The optimal time to determine genetic risk, clarify carrier status, and discuss the availability of prenatal testing is before pregnancy. Too often, however, the first consultation occurs at the beginning of a pregnancy, and time matters. It is therefore useful to genotype historical patients in retrospect, whenever feasible. And it can be advisable for the family to keep a copy of the result. Of note, carrier testing in a partner from the general population would require full sequencing of the gene and incurs the risk of not being able to interpret the finding of the eventual VUS (variants of unknown significance).

Prenatal testing is offered when both parents are carriers of the disease-causing NPC gene, and there is a subsequent 25% risk that the foetus is affected by NPC. It is currently only performed by molecular genetic analysis (on foetal material obtained by chorionic villus sampling (CVS) at 10-12 week's gestation, or by amniocentesis at 15-18 weeks of gestation). The procedure is therefore only applicable when the disease-causing mutations have been identified in the proband and/or the couple.

Preimplantation genetic diagnosis (PGD) is possible dependent on local commissioning agreements and approvals. It involves in vitro fertilisation (IVF) and embryo selection.

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Chapter 6: Pathophysiology

NPC Defects in Lipid Trafficking

In NPC, the endosomal-lysosomal trafficking of lipids is disrupted, resulting in the accumulation of cholesterol and other lipids within the lysosomes.[1] Homeostasis of cholesterol is important for the functional integrity of cells. However, in NPC, the abnormal lipid trafficking leads to the sequestering of endocytosed LDL-cholesterol in lysosomes surrounding the cell nucleus. In addition, movement from these lysosomes to the cell membrane and endoplasmic reticulum is impeded, resulting in excessive accumulation of unesterified cholesterol.[2,3,4]

Diagnosis

Until recently, the main diagnostic test for NPC disease was filipin staining of unesterified cholesterol in cultured fibroblasts taken from a skin biopsy and cholesterol esterification analysis. Although this approach is applicable in the diagnosis of the 'classic biochemical phenotype' disease, it is not so useful in 'variant biochemical phenotypes' where there are relatively mild changes in intracellular cholesterol transport.[5,6] Over the past few years, research efforts have led to the development and use of several NPC disease biomarkers.[1] The combination of these biomarkers and genetic testing has replaced filipin staining as the first-line assessment to confirm a clinical suspicion of NPC.[1]

NPC causes complications in intracellular lipid storage; both the lipid profile and level of accumulation vary across the different tissues. For example, in the liver and spleen, NPC leads to storage of high levels of unesterified cholesterol, sphingomyelin, phospholipids, and glycosphingolipids.[2] There is a tendency towards a greater build-up of lipids in the spleen than in the liver.[7]

In brain tissue, neither cholesterol nor sphingomyelin accumulates in excess, but there are notable changes (10- to 20-fold increase) in the storage of glycosphingolipids, particularly gangliosides GM2 and GM3.[5]

From a histopathological perspective, there are two principal pathologic features in all clinical forms of NPC: the presence of foamy storage cells (lipid-laden macrophages) in the visceral organs and the build-up of storage materials in the neurons and glial cells. Foamy cells and sea-blue histiocytes are present in the liver, spleen, lung, lymph nodes and bone marrow preparations.[2] Histopathologic evaluation shows only slight pathologic involvement of the skin, skeletal muscle, and eyes.

Neuropathology

There are two neuropathologic changes linked to glycosphingolipid build-up: deformities in neurone shape (meganeurite formation) and the substantial growth of new, ectopic dendrites that can impact on the larger basal ganglia and thalamic neurons.[8,9]

Differential storage of excess GM2 and GM3 gangliosides and unesterified cholesterol in neurons leads to recognisable ultrastructural changes and atrophy in the brain.

Prolonged disease commonly leads to the formation of neurofibrillary tangles (NFTs) in the CNS that are similar to those seen in Alzheimer's disease and possibly related to the dysregulation of cholesterol metabolism (see Other possible pathogenic mechanisms, page 19).[10] However, unlike in Alzheimer's disease, where NFTs are mainly found in areas of the cerebral cortex, NFTs in NPC are concentrated in the basal ganglia, hypothalamus, brain stem and spinal cord.[2,11]

Neuroaxonal dystrophy can be seen in some patients with NPC and, as the disease progresses, selective neurodegeneration involving the Purkinje fibres in the cerebellum (but not cerebral white matter) can be observed.[9]

Visceral Pathology

There is considerable variability in the extent and severity of visceral pathologic manifestations in patients with NPC. The presence of splenomegaly (abnormal enlargement of the spleen), with or without associated hepatomegaly (abnormal enlargement of the liver), is the strongest visceral indicator of NPC and seen in the majority of patients.[12] It presents along a continuum – from slight to severe enlargement – even in young children.[12] Hepatomegaly may manifest in early life and may be indicated by the presence of transient conjugated hyperbilirubinaemia or severe cholestatic hepatopathy. However, along with lymphadenopathy, it is rarely seen in juvenile and adult cases.[12]

Severe pulmonary involvement can develop in both *NPC1* and *NPC2* disease. It is typically associated with more severe disease and can result in death due to respiratory failure.[12]

Role of NPC Gene Products in Pathogenesis

Approximately 95% of patients have mutations in the *NPC1* gene, while the remainder have mutations in the *NPC2* gene.[5] Mutations in either of these two genes causes an impairment in the processing and export of endocytosed cholesterol.[5,10]

The *NPC1* gene is responsible for producing a 1278 amino acid protein with 13 transmembrane domains.[2,13] The protein occupies the late-endosomal compartment from which it is ferried to the plasma membrane and other intracellular sites.[13,14] Although the exact function of this protein is uncertain, it plays a role in the movement of cholesterol and glycosphingolipids within cells and across cell membranes.[13,15,16,17,18]

The *NPC2* gene product is a soluble 132 amino acid glycoprotein found in all tissues, but the highest concentrations are located in the epididymal fluid. The protein is located in late-endosome/lysosome lumen, where it binds to cholesterol and promotes its transport.[10,14,19,20]

Other Possible Pathogenic Mechanisms

NPC involves some disease-related molecular pathways that are similar to those present in Alzheimer's disease, including changes in lysosomal function.[10] In vitro studies suggest that endosomal abnormalities linked to diminished lipid trafficking in NPC may play a part in the abnormal processing of amyloid precursor protein (APP) and aggregation of amyloidogenic protein fragments (e.g. beta-amyloid), including an increased deposition of amyloid plaques, in the brain.[10,21,22]

Multiple genes involved in the trafficking and processing of APP and the microtubule-associated protein, tau, as well as in the membrane trafficking, intracellular regulation of calcium and metal ion levels and antioxidant capacity, were expressed to a greater extent in *NPC1* cells.[23] Alzheimer-associated protein aggregation is thought to be a likely contributor to NPC neurodegeneration. Although the precise relationship is unclear, there is a connection between late-endosomal cholesterol accumulation and amyloid protein aggregation.[24]

In common with other lysosomal diseases, autophagy is thought to be a pertinent neurodegenerative process in NPC.[25] In vitro research shows that cellular autophagy is increased in NPC.[26] In *NPC1* deficiency, an increase in the steady state levels of autophagosomes and late endosomes has been observed, and there is also research showing defective amphisome formation.[25] Similarly, evidence of autophagy has been identified in *NPC2* mutant cells, as well as cells from Sandhoff disease mice.[26,27]

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Chapter 7: Epidemiology

Incidence and Prevalence

Published data regarding the incidence of NPC have historically been underestimated due to a number of factors, including the use of confusing terminology, lack of specific biochemical or genetic tests, mixed pathology, and the different clinical manifestations of the disease.[1] However, retrospective studies from expert centres in several countries have reported an annual incidence ranging between 0.25 and 2.20 per 100,000 live births.[1]

Although the data is limited, the prevalence of NPC is thought to be 1 case per 100,000 live births.[1] This is also likely to be an underestimate, as improvements in awareness and diagnostic methods in recent years have led to an increase in the number of adult-onset cases diagnosed since 2013.[1] In addition, the frequency of NPC in early life is thought to be underestimated due to its non-specific presentation and high infant fatality rate.[2,3]

NPC shows autosomal recessive inheritance. It affects males and females equally and is pan-ethnic.[2,4] However, there are three distinct populations showing a 'founder effect', i.e. a mutation traceable back to a sole ancestor or small group of ancestors.[2,4] These populations include those of French Acadian descent in Nova Scotia (originally classified as having NPD), those of Hispanic descent in parts of Colorado and New Mexico, and a Bedouin group in Israel.[2,4,5]

The Importance of Disease Registries

Disease registries that collect data on disease epidemiology, symptomatology and disease management of rare diseases such as NPC are critical to the development of regional health policy and infrastructure as well as making decisions about the allocation of funding. Further, disease registries encourage understanding, help to target research and share data to help show the effectiveness and safety of disease interventions.

The International Niemann-Pick Disease Registry

The International Niemann-Pick Disease Registry (INPDR) was established by a collaboration of patients, health professionals and medical researchers with the shared vision of an improved and more supportive healthcare environment for patients affected by Niemann-Pick diseases, encouraging efficient and timely diagnosis, access to expert care and treatment and facilitating research to improve the patient experience.

The INPDR includes both clinical reported data and patient reported data for ASMD Niemann-Pick disease and NPC. It provides access to a singular resource for use by advocacy organisations, industry, academia, policy makers and healthcare professionals, enabling effective cross-sectoral collaboration.

This comprehensive, international data resource, specific to Niemann-Pick diseases, benefits patients by increasing understanding of these rare conditions, facilitating progress in therapeutic development and monitoring care standards. Find out more here: www.inpdr.org.

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Chapter 8: Clinical Manifestations

Signs and Symptoms

NPC is a complex disease that primarily affects the spleen, liver and brain. The presentation of a combination of visceral, neurological and psychiatric symptoms is highly suggestive of the presence of NPC.[1] These combinations are commonly classified according to the age of onset of neurological symptoms (see Table 2).

Table 2. Clinical presentation of NPC at various ages of disease onset *(adapted from Patterson et al 2001,[2] Geberhiwot et al 2018[3])*

Age of Onset	Clinical Presentation
Pre-/Perinatal period (< 2 months)	• Foetal ascites/hydrops • Hepatosplenomegaly • Cholestatic jaundice (benign, self-limiting or rapidly fatal) • Thrombocytopenia • Pulmonary disease • Liver failure • Failure to thrive • VSGP usually absent
Early infantile period (2 months < 2 years)	• Hypotonia • Delated developmental motor milestones, speech delay • Hepatosplenomegaly or splenomegaly (isolated or with neurological manifestations) • Prolonged neonatal jaundice • Dysphagia, spasticity • VSGP usually absent
Late infantile period (2 years < 6 years)	• Hepatosplenomegaly or splenomegaly (isolated or with neurological manifestations) • History of prolonged neonatal cholestatic jaundice • VSGP may be present • Developmental delay/regression, speech delay • Clumsiness, frequent falls • VSGP may be present • Hearing loss • Cataplexy • Seizures (partial/generalised) • Progressive ataxia, dystonia, dysarthria, dysphagia

Juvenile (classical) **(6 years to 15 years)**	• Hepatosplenomegaly or splenomegaly (isolated or with neurological manifestations; often not present) • Poor school performance, learning disability • Loss of language skill • Frequent falls, clumsiness • Progressive ataxia, dystonia, dysarthria, dysphagia, dysmetria, dyskinesia • VSGP may be present • Gelastic cataplexy • Seizures (partial and/or generalised) • Behavioural problems
Adolescent and adult **(>15 years)**	• Cognitive decline, dementia, learning disability • Psychiatric signs: Schizophrenia (psychosis), depression • Clumsiness, progressive motor symptoms, tremor, ataxia, dystonia/dyskinesia, dysarthria, dysphagia • VSGP may be present • Splenomegaly (often not present; isolated in very rare cases)
VSGP, vertical supranuclear gaze palsy, growing latency in the initiation of vertical saccades with progressive slowing and ultimate loss of saccadic velocity.	

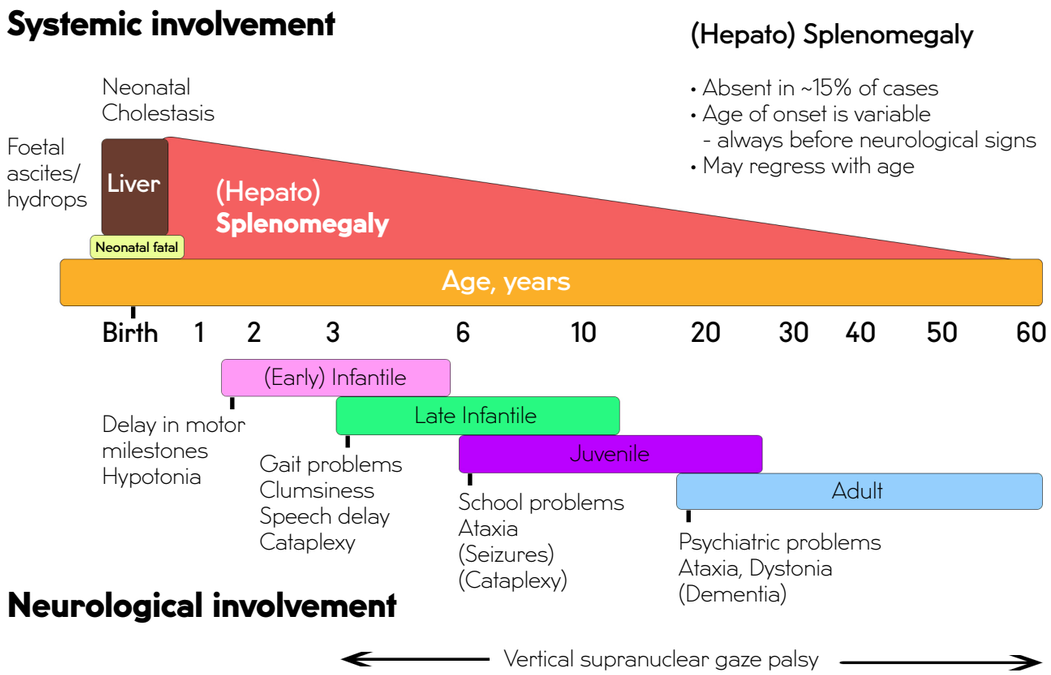

Figure 2. Schematic representation of the main forms of the disease, with particular emphasis on type and age of onset of first neurological symptoms *(reproduced from Vanier et al 2010[4])*

Neonatal and Infantile Presentations

Neonatal and infantile presentations of NPC are generally non-specific and, as a result, may go undetected. In severe disease, ultrasound examination can detect foetal ascites in utero.[5] These infants also tend to have severe neonatal liver disease with hepatosplenomegaly, jaundice and persistent ascites.[6] Organomegaly is not always present at the neonatal stage; but, its absence does not rule out a diagnosis of NPC.[6] In infants with NPC2, the primary presenting feature may be extensive and fatal foam cell accumulation in the lungs.

Respiratory and hepatic dysfunction can be minimal or even absent in some infants. Where hepatic dysfunction resolves without indication, it may only be when neurological disease manifests at a later stage that hepatic signs will be remembered. In some cases, there may be early signs of hypotonia and some delay in psychomotor development. VSGP is not always seen at this age but usually develops by adulthood.

Childhood Presentations

Classic symptoms of NPC presenting in middle-to-late childhood include gait disturbance and clumsiness that ultimately advances to overt ataxia and impaired vertical gaze. An estimated 20-50% of children with NPC present with gelastic cataplexy, ranging from head nods to total collapse induced by strong emotional stimuli, such as laughing,[6,7,8] and 33-54% have partial and/or generalised seizures.[7,8,9] In some cases, children may have disturbed sleep, indicating an effect on hypocretin-secreting cells of the hypothalamus.[10,11]

Progressive disease leads to the development of dystonia, initially manifesting as dystonia in one limb, before progressing to all limbs and axial muscles. Speech slowly declines, with mixed dysarthria and dysphonia. Dysphagia progresses in tandem with the dysarthria, and oral feeding becomes impossible due to frequent aspiration of food. Cognition problems and signs of progressive dementia become increasingly apparent.

Adolescent and Adult Presentations

Adolescent and adult presentations of NPC are primarily characterised by more subtle physical symptoms, for example, presence of neurological disease that progresses at a slower rate compared to infantile NPC,[12] and psychiatric illnesses such as depression, psychosis, and schizophreniform pathology.[13,14] Visceral symptoms are rare in adult-onset patients.[6]

Data on the frequency of medical and developmental manifestations of NPC are limited. However, two UK natural history studies have explored data on patients' clinical presentations and confirmed the wide phenotypic variability of the disease.[15,16] A large-scale, US survey of patients conducted in 2007 with NPC1 showed the most common medical and developmental problems associated with the disease were clumsiness, learning difficulties, ataxia, VSGP, and dysphagia.[7]

Disease detection should be dependent on finding a combination of signs and symptoms, as opposed to isolated findings.[1] Table 3 lists NPC symptoms according to visceral, neurological and psychiatric manifestations. However, the combined presentation of these manifestations should lead to the consideration of NPC in the differential diagnosis of this symptomology (Table 4).[1]

Table 3. Classification of signs and symptoms in NPC *(from Mengel at al 2013[1])*

Visceral	• Isolated unexplained splenomegaly • Hepatomegaly/splenomegaly • Prolonged neonatal cholestatic jaundice • Hydrops foetalis or foetal ascites • Pneumopathologies (aspiration pneumonia, alveolar lipidosis, interstitial lung involvement) • Mild thrombocytopenia
Neurological	• Vertical supranuclear gaze palsy • Gelastic cataplexy • Dystonia • Dysarthria • Dysphagiaw • Hypotonia • Clumsiness • Delayed developmental milestones • Seizures • Hearing loss • Developmental delay and pre-senile cognitive decline
Psychiatric	• Organic psychosis • Disruptive/aggressive behaviour • Progressive development of treatment-resistant psychiatric symptoms

Table 4. Sign and symptom combinations strongly suggestive of NPC *(from Mengel at al 2013[1])*

Splenomegaly	**+**	• Vertical supranuclear gaze palsy • Hypotonia • Schizophrenia-like psychosis • Gelastic cataplexia • Delayed developmental milestones • Mild thrombocytopenia
Ataxia	**+**	• Dystonia • Dysarthria/dysphagia • Cognitive decline
Psychotic symptoms	**+**	• Cognitive decline

The combination of one of the symptoms on the left with at least one of those on the right is strongly suggestive of NPC.

The Suspicion Index (SI) tool can then be used to recognise patients suspected of having NPC, based on manifestations within and across the visceral, neurological and psychiatric domains.[17]

Prognosis

Life expectancy with NPC varies widely but, in general, correlates with the age at onset of neurological symptoms. Patients with the early-onset disease tend to progress faster, and death occurs most often between 3 and 5 years of age; those with a late infantile neurologic onset typically die between 7 and 12 years.[18] Analysis of data for 338 individuals with NPC who died between 1968 and 2018 found the median age of death to be 13 years (range 0.1-69 years) (see Figure 3).[19]

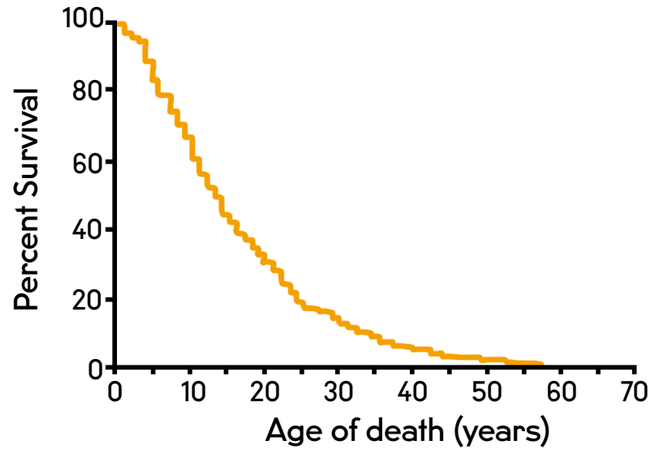

Figure 3. Survival curve from data of 338 individuals with NPC *(reprinted from Bianconi 2019 with permission from Elsevier[19])*

There is no cure for NPC. Historically, treatment has focused on the management of clinical symptoms to improve quality of life.[18] However, the outlook for people affected by this life-changing disease is increasingly positive. This is primarily driven by substantial advances in diagnostics and screening algorithms, identification of new biomarkers, a disease-specific treatment option (miglustat) and multiple clinical trials investigating potential new and effective therapies.[3,20,21]

Miglustat has been found to halt or attenuate disease progression by blocking the production of glycosphingolipids and is the only licensed disease-modifying medicine in the EU for the treatment of neurological manifestations of NPC disease.[3,6,20]

A recent study by Patterson et al[22] evaluated the effect of miglustat on long-term survival with NPC. The study found that treatment with miglustat was associated with stabilisation of neurological manifestations in most patients. The safety and tolerability of miglustat therapy was consistent with previous studies.[22]

Several further therapies have been studied or are currently being evaluated to assess their long-term safety and effectiveness as possible treatments for patients with NPC. These include arimoclomol, 2-hydroxypropyl-cyclodextrin (HPBCD), and vorinostat.[23]

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Chapter 9: Diagnosis

Laboratory Diagnosis

Historically, and until recently, the demonstration in cultured cells (usually skin fibroblasts) of an accumulation of unesterified cholesterol in perinuclear vesicles, visualised by fluorescence microscopy after staining with filipin, was considered as the first-line and gold standard diagnostic test. Since the early 2000s, this has been used in combination with gene mutation analysis whenever possible.[1] In expert hands, the "filipin test" remains a particularly useful tool, but it has never been suited for general use in metabolic/lysosomal laboratories, which often have less expertise in cell biology studies. Further drawbacks of filipin staining are the need for a skin biopsy and the lengthy turn-around time from sampling to result.[2]

Fortunately, during the past decade, alongside the extraordinary progress in gene sequencing technology, several plasma metabolites have emerged as sensitive NPC biomarkers. This has led to a paradigm shift in laboratory diagnosis through new diagnostic algorithms.[3,4]

Currently, upon clinical suspicion of NPC, first-line testing will involve the measurement of one, or several, biomarkers in plasma in the majority of cases. The most widely used biomarker tests (including in the UK[5]) include the two oxysterols cholestane-3ß-5–6ß-triol and 7-ketocholesterol, followed by N-palmitoyl-O-phosphocholine-serine [PPCS], the correct structure and new name of the so-called "lysosphingomyelin-509".
All three biomarkers show a good sensitivity, i.e. they are elevated in the plasma of almost all patients with NPC (although there is the chance of false negatives), but they are not entirely specific to NPC as an elevation also occurs in ASMD. The simultaneous measurement and ratio identification of PPCS and lysosphingomyelin (lysoSM) should solve this problem as lysoSM is only strikingly elevated in ASMD. For oxysterols, the lack of specificity includes a few additional diseases such as acid lipase deficiency. In the future, a further compound, the bile acid 3,5,6-trihydroxy-cholanoyl-glycine, may replace cholestane-triol (see Geberhiwot et al 2018[4] for review). The identification of elevated values for one or preferably several biomarkers is a strong argument in favour of the diagnosis of NPC, but the definitive diagnosis will require molecular analysis of the *NPC1* and the *NPC2* genes.

Sanger sequencing, next-generation sequencing technologies, and gene panels can now provide accurate and sensitive methods for genetic analysis. But some mutations may be overlooked in gDNA sequencing, and complementary tests may be necessary to assess copy number variation, large deletions and intronic mutations.[3] With the current technology, the proportion of mutated *NPC1* alleles that have remained unidentified in proven patients is very small (1.6% of alleles in a recent large survey of a historical Italian cohort).[6] Whenever sequencing or a more refined study identifies two alleles with mutations recognised as clearly pathogenic in either the *NPC1* or the *NPC2* gene, the diagnosis is certain.

To ensure the segregation of alleles, it is important that at least one of the parents (or both, in the case of an apparent homozygous mutation) has also been studied.[3,4] In practice, interpretation of the data may remain uncertain, mostly due to the finding of variants of unknown significance (VUSs). At this stage, when genetic testing remains inconclusive, the filipin test regains ground as the best functional approach.

The Role of Neuroimaging in Niemann-Pick Disease Type C

Structural neuroimaging is an important part of the initial laboratory workup of patients with NPC, as often patients will be imaged as part of working through the differential diagnoses for ataxia, cognitive impairment or gaze palsy, as a number of disorders may present with specific neuroimaging changes that warrant neuroimaging. There is a long history of variable neuroimaging changes being reported in NPC patients.[7] Most clinicians will opt for magnetic resonance imaging (MRI) in the first instance, as this can exclude other pathology, but also may demonstrate some of the suggestive features of NPC, such as white matter hyperintensities and cerebellar volume loss in children, and cortical and subcortical grey matter volume loss in adults.[8] These particular changes are relatively non-specific; however, the neuroimaging changes are also quite variable, with a number of patients showing very minor changes on routine MRI. It is important to distinguish clinically significant changes on imaging, where the deviation of signal intensity or volume from expected norms is obvious to the reporting radiologist, from findings that are seen in research studies, where a range of abnormalities in diffuse white matter, subcortical grey matter structures and other brain regions have been reported at a group level,[8-12] but are not pronounced enough to be routinely detectable in a clinical setting.

Some research has suggested that some of these measures – such as volume of the cerebellum, or the integrity of white matter – may be useful biomarkers to monitor changes with treatment occurring across the brain, particularly with the disease-modifying drug miglustat,[13,14] but generally, these measures have not yet supplanted symptom-based illness measures in routine clinical practice.[15] They do, however, hold great promise as objective and very sensitive ways to document illness progression and response to future treatments.[15]

As in all neurodegenerative disorders, modern imaging techniques that allow binding of ligands to specific cellular substrates using positron-emission tomography (PET) imaging show promise in demonstrating specific molecular pathological processes, such as the formation of neurofibrillary tangles[16] and the presence of neuroinflammation.[17] These also show promise as future illness biomarkers but remain some way off routine clinical use for cost and logistical reasons.

Patient A

Patient A, a female infant, was diagnosed at 9 months old. She was born at 36 weeks, weighing 1.75kg. The initial diagnoses were prolonged jaundice since birth and progressive abdominal distension from 8 weeks. Developmental delay and history of poor weight gain was also present. On examination, the child was severely underweight, the liver was palpable and the spleen enlarged by 10cm. The cardiovascular and respiratory systems were unremarkable. Ophthalmic examination was normal with no cherry red spot. Diagnosis of NPC was made and confirmed by molecular genetic testing. Over the next 3 months, the child's weight was managed with dietetic input and naso-gastric tube feeding.

The child and family were referred to the specialist team including a nurse specialist, consultant, physiotherapist and speech and language therapist. The nurse specialist carried out a home visit to determine which local healthcare services were involved and to ensure the child and family had all the support they required at the time and for moving forwards. Understandably, during this visit, the parents had many questions they wanted to ask around the child's diagnosis and the disease itself.

At 12 months, a gastrostomy was fitted to ensure the child was receiving adequate nutrition and to allow medications to be administered via the gastrostomy. Following this procedure the child's weight increased, remained stable and miglustat was also started.

At a further clinical review at 18 months, the parents reported that the child was developing well, had learnt to hold things in her hand, sit up unaided, and could bear weight while holding onto furniture.

Think Again. Think NPC disease awareness campaign

Think Again. Think NPC is an international awareness campaign led by the International Niemann-Pick Disease Alliance (INPDA), an umbrella group of non-profit Niemann-Pick disease patient support organisations from across the world. The campaign aims to reduce the time to diagnosis of NPC, by raising awareness of the key signs and symptoms of the disease amongst healthcare professionals who may be unfamiliar with the condition. By increasing awareness, and encouraging those healthcare professionals to Think Again. Think NPC, the hope is to help patients by speeding up diagnosis and subsequent access to treatment and support. Find out more at www.think-npc.com.

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Chapter 10: Social Impact

NPC is a highly variable disease, and the age of onset and exact symptoms can vary between patients. Although NPC affects children, adolescents and adults in different ways, the disease has a substantial impact on each patient's everyday life. From issues with schooling and employment, to the need for their wider family members to become carers and the multitude of healthcare considerations, NPC has a devastating effect on the lives of patients and their families.

Effects on schooling and work

Patients affected by NPC typically experience progressive intellectual, movement and behavioural problems that can severely hinder their performance, whether at school or work. Children with NPC may face many challenges in the classroom, so annual psychometric testing may be helpful in arranging appropriate school support. An example of the schooling challenges experienced in NPC are shown in the case history of 'Patient B', below.

Patient B

Patient B was diagnosed with NPC at the age of 9 years after experiencing unsteadiness and frequent falls, and following a neurological consultation, ataxia and VSGP were noted. Parents reported a difficult, traumatic birth, several delayed developmental milestones including, learning to walk, talk and difficulties with academic achievements at school and 'keeping' up with his peers. The family were put in touch with the clinical nurse specialist following the diagnosis as the family were keen to expedite as much support as possible for their son, particularly around educational support.

A meeting was arranged with the child's school, parent's and clinical nurse specialist to discuss what support the child would need in school following their diagnosis and ensure they received the optimum level of care and support within the education setting. It had become very apparent that Patient B was really struggling with the academic work at school and it was causing him a great deal of distress both in and out of the classroom. His parents felt that the gap between his son and his peers had very much widened and was having a detrimental effect on their son's wellbeing both at school and at home.

Many children with NPC are able to access mainstream education, however, after 12 months within the mainstream setting and the difficulties the child encountered, it was decided, along with the parent's agreement, that placement within special educational needs (SEN) would be more appropriate to meet the needs of their son. Transition to the SEN school was successfully completed within six months, and the child is settled and very happy in their new school.

In adulthood, the progressive memory loss and/or psychiatric features, characteristic of adult-onset NPC can place severe limits on a patient's ability to work.

Impact on Family Members

Impact on parents: The parents of children with NPC face some of the greatest possible challenges associated with a severe and chronic disease. Parents or other caregivers must learn to provide complex treatment regimens and often have to consult with numerous medical specialists. Many parents experience financial difficulties or struggle to access financial support, not to mention that their energies may be almost entirely consumed in coping with the effect of their child's severe disability on everyday living, education and work opportunities.

Impact on siblings: While there can be benefits for some non-affected siblings of children with NPC, such as the strengthening of parent-child and child-child relationships, adverse effects can also arise. There can be excessive sibling concern about the ill child's condition, jealousy of the attention the ill child attracts, and disappointment around the restriction of family events. A child's chronic illness affects their entire family. It can be disruptive and stressful for non-affected siblings, and in some cases, can contribute to an increased risk of psychological/emotional disturbance. Helping to improve parental awareness and increase their confidence in managing their child's illness is essential to support the optimal development of both the child with NPC and any non-affected siblings.[1,2]

Impact on partners and/or children: Adult NPC patients may have a partner and children caring for them. Sometimes young children may have to become a carer for their ill parent. The impact of this must be recognised and help provided where appropriate. Niemann-Pick specific patient associations can offer support and signposting to assist carers and extended family members of all ages.

Power of Attorney and Advance Care Planning

Deteriorating memory loss can affect the decision-making abilities in adult patients as the disease progresses. Appointing a lasting power of attorney with a trusted family member who can assist in decisions about financial and end of life scenarios as well as support the participation in future clinical trials is therefore advisable. Advanced care planning with the support of an NPC specialist nurse can ensure that an adult patient's wishes are fulfilled at a time when they are unable to make decisions for themselves.

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Chapter 11: Holistic Support

Holistic Care and Quality of Life

Living with a rare disease generates unique challenges for both the person diagnosed and their carers. An individual's sense of self, social interactions and daily life can be disrupted when diagnosed and living with an illness, particularly NPC. The complexity of living with illness goes much further than the disease itself, and in order to offer tailored support, we need to understand more of the impact that it has on a person's Quality of Life (QoL). The concept of QoL is a well-established and highly valued focus in both research and clinical practice. The World Health Organisation defines QoL as being: "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[1] It is multi-dimensional in its outworking and is affected in a complex way by a person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment.[2]

In a recent study by Aston, Shaw and Knibb (2019)[3], interviews were conducted with NPC patients and their carers which have helped shape the wider understanding about the many ways NPC impacts QoL. An in-depth analysis of these interviews showed that, for children with NPC, the experience of living with NPC, both in terms of the physical manifestations of NPC and the subjective feelings of contentment in their body, played a part in how they felt about their QoL[3]. For example, whether the child could play with their toys or take part in activities, engage with friends and family and the extent to which NPC had affected these encounters was shown to be important. For adults who were diagnosed with NPC in adulthood, a change in identity was communicated, as were the repercussions that this had on their social relationships and their sense of security.[3] The adults spoke of the past and the life they knew before their diagnosis. The changes their diagnosis brought to many aspects of their life affected their relationships and connectedness to others, as well as the impact on their mood, with some experiencing periods of anxiety and depression.[3]

The items included on the QoL scales within Aston, Shaw and Knibb's study represent the subjective experiences of people's worlds when living with NPC.[3] These items could be used as a dialogue aid for healthcare professionals to have a more in-depth understanding of the impact of living with NPC on a person's QoL, especially as this is an under-researched area. In order for care to be holistic, the subjective experiences of living with NPC included in these scales should be discussed to enable services to deliver support that focuses on meaningful person-centred care.

Holistic Care Planning

NPC is a devastating condition that affects a patient's entire family. Healthcare providers, therefore, play a very important role in managing the different challenges that NPC presents. This role extends beyond the provision of medical care to directing patients and their families towards information on NPC and its treatment, offering access to local patient organisations, social networks with other families affected by NPC, and psychological support.

Specialist Care Centres

Optimal management of NPC involves a multidisciplinary, multi-professional team approach; one that is based in a specialist centre but liaises closely with community providers.[4] These specialist care centres can offer comprehensive, integrated, multidisciplinary care for patients, alongside information and support for family members.

Specialist centre care providers, physicians/paediatricians, and local palliative care services should develop close working relationships to support patients and families with NPC through the disease lifespan. Key elements of this relationship include:[4]
a) Advance care planning with regular updates.
b) Assured lines of communication and information for patients and their families.
c) A designated point of contact for each stage in the care pathway.

Physiotherapists, speech therapists, occupational therapists and disease counsellors can all play a role in supportive care for patients. For those patients nearing the end-of-life, ongoing assistance involving palliative care services for symptom control, respite care, and psychological and spiritual support may all be beneficial.[4]

'Patient C' below highlights the kind of coordinated, team-based support necessary for the care of an adolescent with NPC.

Patient C

Patient C was diagnosed with NPC at the age of 16. At diagnosis he had impaired speech, was ataxic and had problems with looking down. However, on review he had problems since the age of four but with slow progression of disease, and he had received good support from local services. At the age of 18, Patient C experienced greater problems with swallowing, and the speech and language team and a dietitian became involved. He also received physiotherapy at this time for dystonia that was now affecting his limb positioning and walking. Unfortunately, six months later he was non-ambulant and dependent upon a wheelchair.

When Patient C was aged just over 19, his mother contacted the nurse specialist as things seemed to be falling apart. An emergency home visit concluded that his problems were now very complex but he was no longer covered by paediatric services and had not been allocated another consultant. He was attending a day care centre with inpatient facilities during the day but his mother felt he was not receiving enough stimulation. In absence of a lead consultant, the nurse specialist spoke with both the social worker and centre staff and the first of many meetings were set up to coordinate the care team for Patient C and his mother...

His feeding was assessed and gastrotomy sited for additional fluid and food supplementation. He was provided with facilities in the home for hoisting as well as a hospital bed. A member of staff at the day centre acted as key worker to ensure his needs were addressed and that everyone was aware of any changes. For the last year of his life, Patient C lived in his own flat with 24-hour carers, in line with his wishes at the time.

There were times when Patient C's mother found it difficult to talk directly to the team. In these situations, the nurse specialists often liaised on the family's behalf.

To find a specialist centre in your country, please visit the *Resources* section (see page 47).

Patient Associations

Patient associations can provide educational material, plus practical and counselling support to patients and families affected by NPC. A centralised team approach that enables three-way communication between the carer/patient, healthcare providers and patient advocacy/support groups may generate opportunities for earlier access to treatment and the essential social support that can help to improve quality of life.[4]

Patient associations are also often engaged in activities to raise money for NPC research. A list of support organisations is provided in the *Resources* section (see page 47).

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Chapter 12: Treatment Strategies

There is no definitive therapy or cure for NPC. While progress is being made in identifying effective disease modifying treatments, symptomatic treatment remains central to disease management.

Symptomatic Therapies

Current, non-specific treatments for NPC concentrate on supportive care intended to manage disease symptoms. Therefore, these treatments are not expected to slow disease progression, although it is possible that, for example, improved control of infections and ensuring adequate nutrition, could result in positive effects on long-term outcomes. Common symptoms of NPC and the relevant supportive therapies are listed in Table 5.

Table 5. General symptomatic therapies provided in supportive care

Symptom	Definition	Treatment
Feeding problems	Difficulty swallowing (dysphagia) can get progressively worse and lead to problems with feeding.	Most children with NPC ultimately require gastrostomy feeding, with observation in case of aspiration or nutritional compromise.
Cataplexy	A sudden loss of muscle tone, resulting in a range of symptoms from head drops to complete collapse in response to strong stimulus. Any symptom perceived by the patient to be humorous may evoke this response, hence the term gelastic cataplexy.	Tricyclic antidepressants or CNS stimulants, such as modafinil, can be useful in controlling cataplexy.
Dystonia and tremor	Dystonia is a movement disorder in which muscles with opposing actions are simultaneously activated. It results from a dysfunction in the basal ganglia. The loss of coordination of agonist and antagonist muscles is characteristic of NPC.	Some patients respond to anticholinergic medication such as trihexyphenidyl. Treatment for tremors depends on their characteristics, but it may include the use of agents such as propranolol or trihexyphenidyl.
	Tremor refers to an alternating movement of a limb or body part that can be observed in the chin, or the lower and upper extremities, which reflects dysfunction in either the basal ganglia, the mid-brain, or the cerebellum, or a combination of these.	
Spasticity	Unlike dystonia, where resistance to movement of a limb is uniform regardless of the speed of movement, spasticity is an increase in muscle tone that is proportionate to the rate of movement of the body part. So, if a patient moves more rapidly, they will experience more resistance. However, a spastic limb reaches a point, called the 'clasp-knife' phenomenon, whereby there is a sudden reduction in muscle tone and the limb can then move freely through the rest of the range of a movement.	Physical therapy and stretching exercises are recommended to sustain mobility for as long as possible. This may be supple-mented with medications such as baclofen and a benzodiazepine, or focused therapy with botulinum toxin injections.
Seizures	Epileptic seizures are the clinical manifestations of exces-sive. electrical discharges arising from the cortex "surface" of the brain. These may take the form of impaired consciousness, jerking, twitching (which may be focal and involve one limb or one side of the body), or generalised seizures that involve both sides of the body. The diagnosis is supported by findings on the EEG, but so metimes prolonged monitoring is required to capture episodes and accurately classify seizures.	Anti-seizure drugs can control or reduce the frequency of seizures. The medication choice depends on the electrical and clinical characteristics of the seizures. In some young children with difficult-to-treat seizures, a ketogenic diet may be recommended.
Sleep disorders	Dysfunction of the hypothalamus is frequent in NPC. Manifestations include sleep inversion (where the patient prefers to sleep during the day and awake at night), which	Sleep disorders should be treated by ensuring the best possible environment for sleep; a cool, quiet, dark room, regular sleep hours, and where necessary,

	can be very disruptive to family life, and narcolepsy, in which patients have an irresistible urge to sleep throughout the day. Cataplexy can also be regarded as a sleep disorder when a form of REM sleep intrudes into consciousness and causes sudden, diminished muscle tone.	assisted by agents such as melatonin or modafinil. In some cases, consultation with a sleep specialist and an overnight sleep study, especially where there is sleep apnoea, may be helpful.
Bowel management	Patients with NPC, particularly those that are less mobile, are subject to diminished frequency of bowel movements. However, it is worth noting that miglustat therapy has been associated with gastrointestinal disturbances such as diarrhoea, flatulence and abdominal pain/discomfort.	In order to prevent severe constipation, it is important to ensure adequate fluid and fibre intake. Fruit and vegetables are important sources of both water and fibre and should be an integral part of the diet. Laxatives may be required but should always be administered under the supervision of a physician.
Lung disease	Due to problems with muscle tone and coordination of movement, as well as impaired swallowing and the difficulty of generating a forceful cough, NPC patients have an impaired ability to protect their airway. As a result, patients with NPC are at increased risk of chest infections such as bronchitis and pneumonia.	It is crucial to work with therapists to preserve the safety of the airway, including management of an appropriate diet. Where aspiration is a problem, physical therapy and the use of drugs to dilate the airways and suppress inflammation are appropriate. Antibiotics may be useful in the case of intercurrent pulmonary infection.
Ataxia	Ataxia is the incoordination of movement and accompanying imbalance. It may manifest as unsteadiness of the trunk, when attempting to sit or stand still, or a tendency to sway or fall when walking. Patients may also present with a tremor and inaccurate movement of the limbs when reaching or performing other activities.	Physiotherapy may help patients with ataxia. Traditionally, the use of weights inserted in clothing on the limbs or trunk may restrict tremor and inaccuracy of movement in the limbs, but it is generally poorly tolerated. Several drugs may alleviate this symptom, but an experimental agent, N-acetyl-L-leucine, is currently under investigation for the treatment of
		ataxia in NPC (as well as GM2-gangliosidosis and ataxia-telangiectasia).

Disease-Modifying Therapies

Several therapies that target different aspects of the pathophysiology of NPC are under investigation. As of December 2020, one treatment, miglustat, approved in the EU in 2009, is recommended for the neurological manifestation of NPC, while several others are currently being studied. There are a number of rational approaches to disease-modifying therapy, including gene repair or replacement, and downstream interventions such as substrate depletion and inhibition of substrate synthesis.

Gene Repair or Replacement

Because NPC is a genetic disease resulting from mutations in the *NPC1* or *NPC2* gene, a rational approach would be to either repair the mutated gene copies or replace the mutated copies of the gene with a normal copy.

Newly available technology such as CRISPR-Caspase gene editing is the first of a new generation of molecular tools that, in theory, would permit editing and the repair of mutated genes. This technology has been used in tissue cultures and some animal models of disease, but it is not yet ready for clinical trials in neurological disorders such as NPC.

The replacement of a mutated gene with a normal copy, or gene 'transfer', has been successfully performed in several animal models of NPC. Several groups of researchers are currently working towards the clinical trials of gene therapy for this disease.

The NPC1 protein, which is abnormal in the majority of patients with NPC, is a very large protein embedded in the membrane surrounding the late endosome and the lysosome of the cell. Many experiments over the past 30 years have shown that this protein cannot be replaced. However, many patients with NPC have mutations that cause an abnormal folding of the protein, so that it is destroyed by the quality control system of the endoplasmic reticulum before it reaches its target in the lysosome. Strategies directed at ensuring the correct folding of the mutated protein, which could lead to its delivery in the lysosome, would, therefore, represent a rational approach to treatment.

Arimoclomol enhances the expression of heat shock protein 70, which improves the folding of the NPC1 protein. This agent has shown evidence of clinical benefit in a trial of patients with NPC1.[1] It is currently being reviewed for approval for the treatment of this disease by regulatory agencies in the US and Europe.[2]

The NPC2 protein, in contrast to the NPC1 protein, is a small, soluble protein, which theoretically can be transferred from a donor to a host cell. Because of this, stem cell transplantation is a rational alternative for patients with NPC2.

Downstream Interventions

Substrate Depletion

As there is an accumulation of several larger molecules within the lysosome present in NPC patients, the depletion of these accumulating molecules would be a rational approach to treating the disease. A block randomised study of cholesterol lowering agents, including statins, in 25 patients with NPC was published in 1993.[3] The study found that the amount of cholesterol in the liver could be reduced but this had no benefit on patient survival in the subsequent follow-up.

More recent studies of cyclodextrin have shown that the agent can mobilise cholesterol from lysosomes and redistribute it within the cell.[4] Studies in NPC mouse[5] and cat models[6] have shown substantial increases in survival, and uncontrolled studies in humans provide supporting evidence of a benefit.[7] A controlled clinical trial showed no evidence of benefit, but flaws in the study design likely accounted for the outcome.[8] Further trials are currently planned.

In the trials described above, cyclodextrin was administered via lumbar puncture to ensure the most direct access to the brain and spinal cord. Additional studies are underway to investigate the effects of IV cyclodextrin and the combination of IV and intrathecal cyclodextrin.

Inhibition of Substrate Synthesis

Glycosphingolipids, including GM2-ganglioside and glucosylceramide, accumulate in excess in NPC lysosomes. The accumulation of GM2-ganglioside correlates with ectopic dendritogenesis (the development of a connection between neurones in inappropriate places) and the formation of abnormal structures called axonal spheroids (swellings within the axons of nerve cells). If the accumulation of glycosphingolipids could be reduced by inhibiting their synthesis, it may improve the outcome in NPC.

Studies of the NPC mice model show that an inhibitor of glucosylceramide, miglustat, delayed the onset of disease and increased the survival of affected mice.[9] Subsequent human trials led to the approval of this drug for the treatment of neurological manifestations of this drug in the EU and many other countries in 2009, except the US.[10,11] More recent long-term studies support the effects of miglustat in stabilising swallowing and increasing the lifespan in patients with NPC taking this drug.[12,13]

Evaluating Clinical Treatment Effects

The goal of research into potential treatments for NPC is to develop drugs that are safe, effective and accessible to all members of the community. This typically requires extensive animal studies, followed by controlled clinical trials conducted in cooperation with national regulation authorities.

Because NPC is an ultra-rare disease, designing and executing clinical trials can be challenging. In contrast to common diseases such as hypertension or hypercholesterolaemia, where many thousands are affected and could potentially participate in clinical trials, there are relatively few patients with NPC, and each one may have different clinical manifestations and rate of disease progression. As a result, recruiting participants for traditional, controlled clinical trials for a relatively large number of patients, who would normally receive a placebo alongside a similar group of patients who receive an active drug, may not be feasible. National regulators are now starting to accept non-traditional trial designs that use different methodology but are still able to provide evidence that the drug is safe and effective.[14]

Outcome Measures

Demonstration of treatment efficacy requires the use of outcome measures that are meaningful to both patients and clinicians and can be measured in a reliable and reproducible fashion.

There are several laboratory tests and examinations that can be performed in NPC. However, these are not generally regarded as acceptable outcome measures by regulatory authorities unless they can be shown to correlate with symptoms or signs that are meaningful to patients. Because of the large variability in NPC, there is likely to be no single measurement that can reflect the outcomes for the disease. As a result, so-called 'composite outcomes' scales have become the preferred primary outcomes measure for clinical studies. These involve the measurement of symptoms or signs in different domains or function, such as coordination, balance, speech or swallowing.

Several scales have been developed and published over the past two decades, but essentially all of them are based on a four-domain scale originally developed in Spain.[15] A widely adopted version of this four-domain scale is the NPC Clinical Severity Score (NPCCSS), developed by the US National Institutes for Health, which contains 17 domains. The NPCCSS provides a comprehensive evaluation of the disease, but it is quite time-intensive to perform, and several domains may show variability due to symptomatic treatment, which presents challenges when used in clinical trials.

A refinement of the NPCCSS scale, a five-domain simplification, has been shown to correlate strongly with the 17-domain scale and reflects the most meaningful domains identified by clinicians and patients and their families.[16] This five-domain scale was used in the recent successful trial of arimoclomol.[17]

Table 6. Overview of NPC severity scales

Scale Name	List of Domains Measured
5-Domain NPCCSS[18]	The 5-domain NPCCSS measures ambulation, cognition, fine motor, speech and swallowing. Five domains, selected by NPC individuals, their caregivers and NPC experts as the most clinically relevant, reduce variability and increase the suitability for use in clinical trials.
Functional Disability Scale[19]	Modified from Pineda et al,[20] this clinical severity assessment measures seven domains: ambulation, manipulation, language, swallowing, eye movements, seizure and neurocognitive development (for patients under 12 years of age). However, it has not been formally validated for treatment monitoring.

NPC-cdb Scale[21]	Unlike previous scales, the NPC-cdb scale represents the sum of all past and current symptoms present in a patient at any given time, with each symptom contributing a severity-weighted summand.
NPC Clinical Severity Score (NPCCSS)[22]	Comprises 17 domains based on a cohort of 18 NPC patients and 19 historical cases from the National Institutes of Health. The NPCCSS measures: • Nine major domains: ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, swallowing • Eight minor domains: auditory brainstem response, behaviour, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, respiratory problems.
Disease-specific Disability Scale[29]	In an adaption of the scale developed by Iturriaga et al,[15] the Disease-specific Disability Scale assigns weighted scores for each parameter. It measures four domains: ambulation, manipulation, language and swallowing.
Disability Scale[15]	The Disability Scale was developed via a cohort of 30 NPC patients. It measures four domains: ambulation, manipulation, language and swallowing.

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Chapter 13: Conclusions

NPC is a rare, devastating genetic condition originating from a biochemical defect that impedes cellular lipid trafficking. As a result, cholesterol and glycolipids accumulate within the endosomal/lysosomal system, causing a diverse number of symptoms depending on the patient's age at onset.

Although the classic presentation of NPC occurs in middle-to-late childhood, featuring chronic progression and death typically by the early teens, NPC can be diagnosed much later with some individuals surviving into early adulthood. In exceptionally rare circumstances, patients can live well into middle age.

The exact prevalence of NPC disease is difficult to calculate due to insufficient clinical awareness as well as the relative complexity of biochemical testing. However, it has been estimated at 1 case per 100,000 live births.[1] The extreme disabilities caused by NPC, particularly during the later stages of the disease, affect a patient's entire family and optimal disease management requires highly specialised healthcare within a multidisciplinary, managed-care setting.

Even though NPC is not yet curable, knowledge on its pathogenesis has increased several-fold since the characterisation of the *NPC1* and *NPC2* genes. The mainstay of therapy remains symptom management, while progress is made in identifying effective disease-modifying treatments and investigational therapies.

As of December 2020, one treatment, miglustat, is approved in the EU (approved in 2009) for the neurological manifestation of NPC, while several others are currently being studied. A centralised team approach that enables three-way communication between the carer/patient, healthcare providers and patient advocacy/support groups may create opportunities for earlier access to treatment and the essential social support that can improve quality of life for an NPC patient.

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RESOURCES:

Patient Organisations

Niemann-Pick UK (NPUK)

Niemann-Pick UK (NPUK) is a small charity based in the UK who are dedicated to making a positive difference to the lives of those affected by Niemann-Pick diseases and their families, from diagnosis to bereavement and beyond. They provide a specialist care, support and advocacy service, aiming to minimise the burden of living with NPD. This includes practical advice, emotional support and expert information, and the active support of research that will lead to progress in care and treatment.

Website: www.npuk.org

Email: info@npuk.org

International Niemann-Pick Disease Alliance (INPDA)

The INPDA is a global network of non-profit organisations working in the field of Niemann-Pick diseases. It provides a collaborative forum for the sharing of information and experience regarding all aspects of Niemann-Pick disease, including best practice in patient advocacy, the provision and distribution of information and the furtherance of research.

Website: www.inpda.org

Email: info@inpda.org

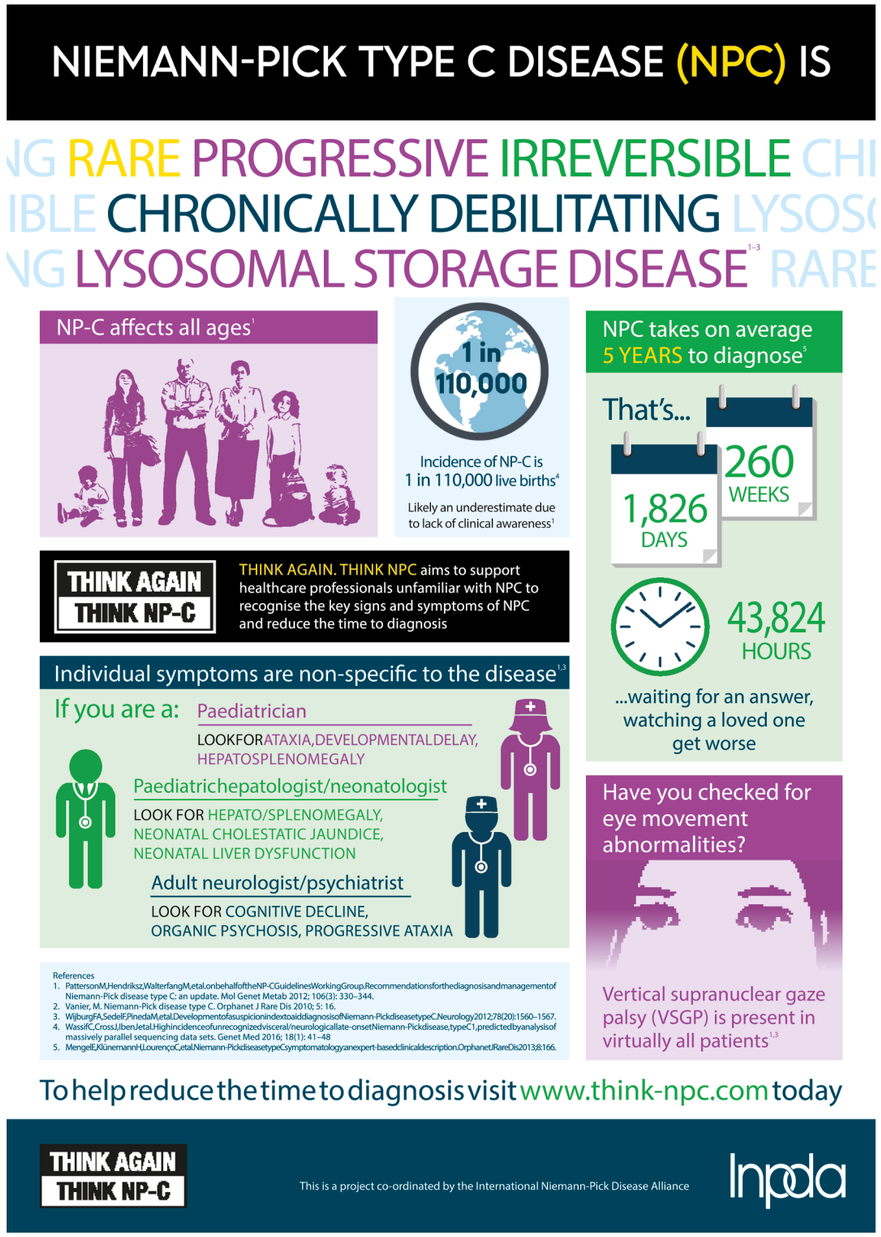
The INPDA currently has 23 member groups in 17 countries (correct March 2021):

Specialist Centres

Specialist centres can offer comprehensive, integrated, multidisciplinary care for patients, alongside information and support for family members. To find a specialist centre in your country, please visit the Orphanet website here: www.orpha.net

Think Again. Think NPC

Think Again. Think NPC is an international awareness campaign led by the INPDA. It aims to reduce the time to diagnosis of NPC, by raising awareness of the key signs and symptoms of the disease amongst healthcare professionals unfamiliar with the condition. By increasing awareness, and encouraging healthcare professionals to Think Again. Think NPC, the hope is to help patients by speeding up diagnosis and subsequent access to treatment and support. Find out more at www.think-npc.com.



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To help reduce the time to diagnosis visit www.think-npc.com today

THINK AGAIN THINK NP-C

This is a project co-ordinated by the International Niemann-Pick Disease Alliance

Inpda

Niemann-Pick UK (NPUK)
Suite 2 Vermont House, Washington,
Tyne & Wear, United Kingdom, NE37 2SQ
Contact: info@npuk.org / 0191 415 06 93

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