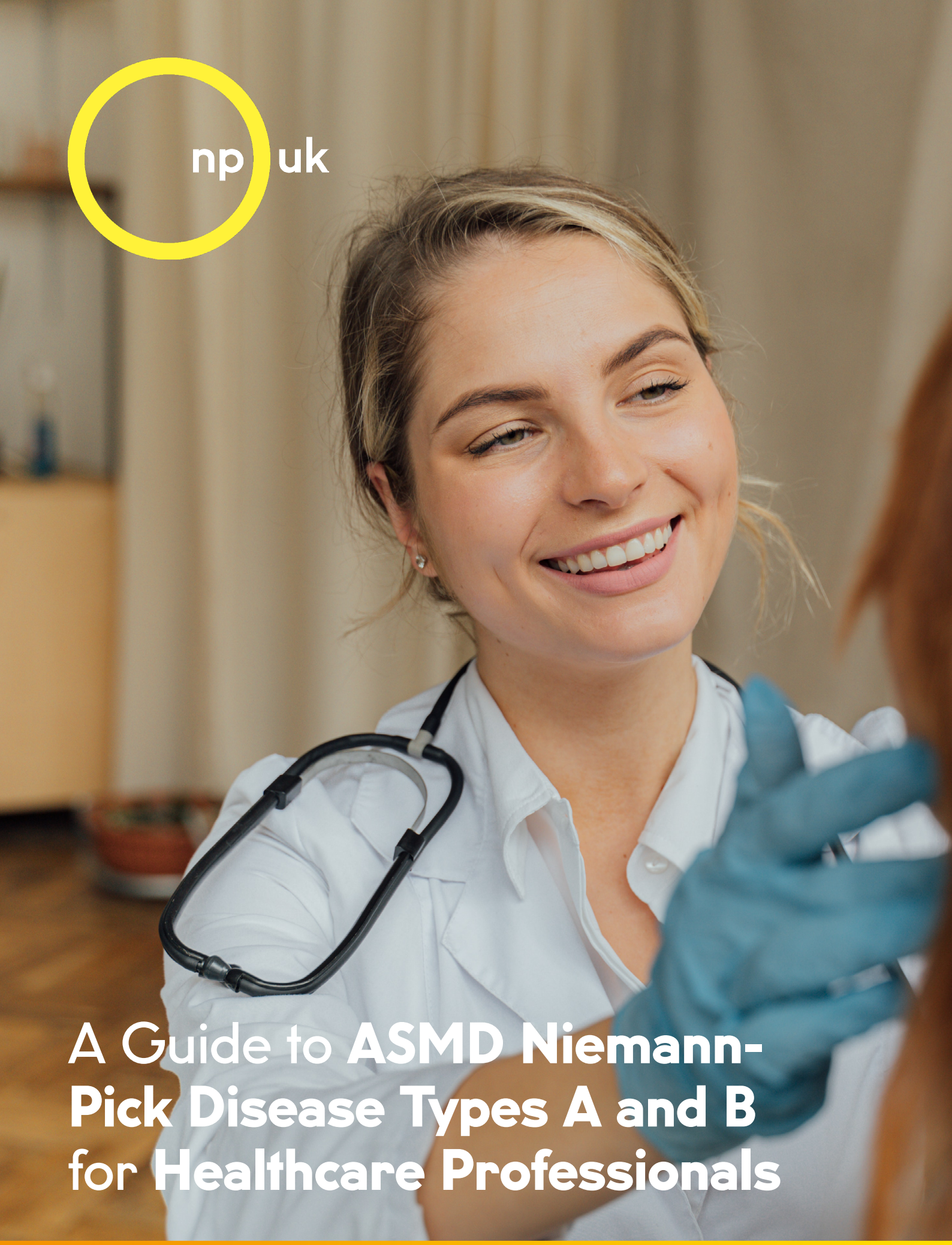

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A Guide to **ASMD Niemann-Pick Disease Types A and B** for **Healthcare Professionals**

Supporting those affected by Niemann-Pick

CONTENTS

ACKNOWLEDGEMENTS:

Thank you to the following experts who contributed to the content of this guide:

Andrea Dardis, PhD
Regional Coordinator Centre for Rare Diseases
University Hospital "Santa Maria della Misericordia", Udine, Italy

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

Margaret McGovern, MD, PhD
Professor of Pediatrics, Dean for Clinical Affairs & Vice President Health System Clinical Programs
Stony Brook Children's Hospital, New York, USA

Dr Edward Schuchman
Genetic Disease Foundation - Francis Crick Professor & Vice Chair for Research
Icahn School of Medicine at Mount Sinai, New York, USA

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:

Acid sphingomyelinase (ASM)	Lysosomal enzyme that breaks down a substance called sphingomyelin. This enzyme is defective to a greater or lesser extent in ASMD Niemann-Pick disease
ASMD	Acid sphingomyelinase deficiency Niemann-Pick disease (includes Niemann-Pick disease types A and B)
Allele	A particular form of gene. Alleles occur in pairs, one on each chromosome inherited from each parent
Autosomes	Any chromosome other than the sex chromosomes
Cation	The ion in an electrolyte which carries a positive charge
Dyslipidaemia	Abnormal amount of lipids in the blood
Hepatosplenomegaly	Enlarged liver and spleen
Heterozygous	An individual is heterozygous at a locus if (s)he has two different alleles at that locus
Homozygous	An individual is homozygous at a locus if (s)he has two identical alleles at that locus
Knockout mouse model	Niemann-Pick mouse created by destroying the Niemann-Pick gene
Lysosome	Sac-like intracellular organelle that contains various hydrolytic enzymes
Mutation	Small yellow area seen on examination of the retina
NPA	ASMD Niemann-Pick disease type A
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
Polymorphisms	The occurrence in a population (or among populations) of several phenotypic forms associated with alleles of one gene or homologues of one chromosome
Reticuloendothelial system (RES)	Mammalian defence system against foreign bodies, consisting of macrophage cells located in the lymph nodes, liver, spleen and bone marrow
Sphingomyelin	Phospholipid composed of a long chain base, sphingosine, a long-chain fatty acid and phosphocholine
Splenectomy	The removal of the spleen
Splenomegaly	Enlargement of the spleen
Thrombocytopenia	A low platelet count

Introduction to this booklet

Acid sphingomyelinase deficient (ASMD) Niemann-Pick disease is an extremely rare disorder resulting in potentially life-limiting illnesses in children and young adults. It covers a spectrum of conditions and this booklet provides information on ASMD Niemann-Pick disease types A and B, which are two forms of the disease associated with a deficiency in the body of the enzyme acid sphingomyelinase.

The booklet brings together a wide range of information which should be useful to everyone involved in the treatment of patients with ASMD Niemann-Pick disease types A and B. It is intended to help patients, their families, doctors and scientists gain a better understanding of the disease and how to manage it.

ASMD families meeting together at the NPUK Annual Family Conference & Interactive Workshop on Niemann-Pick Disease 2019

Chapter 1: ASMD Niemann-Pick Disease – A Clinical View

The first cases of types A and B Niemann-Pick disease (NPA and NPB) were described in the early 20th century. However, their association with the deficiency of the lysosomal enzyme acid sphingomyelinase (ASM) was made later, in the 1960s. Currently, this disease is referred to as acid sphingomyelinase deficient (ASMD) Niemann-Pick disease to distinguish it from Niemann-Pick disease type C (NPC), a related but genetically and biologically distinct disorder. Historically, only two types of ASMD were recognised, NPA and NPB.

However, in recent years, it has become apparent that there is a broad clinical spectrum of the disease caused by ASM deficiency, 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 types that more accurately describe their clinical presentations: acute neuropathic form (NPA), chronic neurovisceral form (NPA/B), and chronic visceral form (NPB).

Patients at the severe end of the spectrum (NPA) have a very rapidly progressive neuro-degenerative disease, usually resulting in death before the age of four years. In contrast, patients at the other end of the spectrum (NPB), have a phenotypically variable disorder that is usually diagnosed in childhood because of hepatosplenomegaly. The majority of NPB patients survive well into adulthood, with little or no neurological involvement. Progressive pulmonary infiltration is a common disease-related complication for most patients, whilst the haematological effects of hypersplenism and liver-related illness can be severe. ASMD is inherited in an autosomal recessive manner, with more than 266 mutations identified in the *SMPD1* gene.[1] Currently, there is no specific therapy for ASMD, but clinical trials of enzyme replacement therapy are ongoing throughout the world for those with the NPB phenotype.

Because of the severity and complexity of ASMD, patients should be managed at specialist centres for inborn errors of metabolism, wherever possible, where interdisciplinary care can be offered. The social and healthcare impact of ASMD cannot be overestimated, and patient organisations and support groups play a vital role in improving the quality of life of a patient. With continued efforts, it is hoped that future research will lead to treatments and perhaps even a cure. International research into the development of such therapies is in progress and it is hoped that they will play a huge part in fighting this disease.

Dr. Edward Schuchman
Genetic Disease Foundation - Francis Crick Professor & Vice Chair for Research
Icahn School of Medicine at Mount Sinai, New York, USA

Jackie Imrie
Trustee
Niemann-Pick UK (NPUK)

References:

1. Stenson PD, Ball EV, Mort M, et al. Human Gene Mutation Database (HGMD®): 2003 update. *Hum Mutat.* 2003;21:577-581. doi: 10.1002/humu.10212

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

Due to the rarity and variable nature of ASMD, the path to diagnosis can be slow and challenging for patients and it can have a profound effect on all aspects of family life. During this time, they 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 can vary in local areas, families may feel bewildered and isolated due to conflicting advice or a lack of information specific to ASMD. Extensive support in coping with the practical and financial implications of ASMD may also be required.

The support of dedicated patient advocacy groups can help patients and families as they adjust to a diagnosis and begin to understand the impact of living with ASMD.

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 to increase opportunities for mutual support.

Working in collaboration with global advocacy groups, NPUK aims to highlight the unmet need that exists in ASMD 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 ASMD it is critical to support research; NPUK actively supports and funds research to improve the lives of those affected by ASMD.

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 ASMD 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

ASMD is a rare autosomal recessive inherited metabolic disease that leads to the accumulation of sphingomyelin in cells and tissues.[1]

Meikle (1999) estimates the incidence in newborns to be between 0.4 in 100,000 to 0.6 in 100,000,[2] although this is likely to vary widely among different populations. Although all patients with ASMD share the same metabolic defect, the severity of ASMD ranges from a rapidly progressive infantile neurovisceral disease, that is uniformly fatal in early childhood, to more slowly progressive chronic neurovisceral and chronic visceral forms. The phenotypic variability of ASMD has led to the categorisation of subtypes based on severity and the degree of neurological involvement.

Historically, two distinct subtypes have been described based on their phenotypes (types A and B).

Type A disease is a severe neurodegenerative disease of infancy, characterised by progressive psychomotor retardation, failure to thrive, hepatosplenomegaly, cherry-red macula, and death by three to four years of age.

In contrast, type B is characterised by hepatosplenomegaly, thrombocytopenia, interstitial lung disease and dyslipidaemia, with most patients having little or no neurological involvement.[3] The diagnosis of Niemann-Pick disease type B is usually made in childhood after organomegaly is noted, and it is common for individuals to survive well into adulthood.

Recent studies suggest that there is a spectrum of disease, related to the amount of enzyme activity and presenting as an intermediate phenotype characterised by different levels of neurological involvement.[4]

There is currently no treatment for ASMD. However, clinical trials of enzyme replacement therapy for type B have shown remarkable improvements in the disease.[5] Gene therapy may also be a potential route for treatment.[6]

The following classifications have been described by Dr Margaret McGovern's presentation at the NPUK conference in 2007.

Infantile neurovisceral ASMD: Niemann-Pick disease type A
Consistent clinical findings and a stereotypical course

- Massive organomegaly
- Cherry red spot on eye exam
- Lung disease and infections
- Cholesterol abnormalities
- Rapid, progressive, neurologic disease
- Failure to thrive
- Death by the age of four years

Chronic visceral ASMD: Niemann-Pick disease type B
ASM deficient patients surviving early childhood: more variability

- Variable age of onset, ranging from infancy to adulthood, with a slowly progressive multisystem disease
- Manifestations without neurodegeneration
- Hepatosplenomegaly, interstitial lung disease and cholesterol abnormalities are common evidence of neurological involvement in 28% of patients
- Progressive neurologic disease in less than 10% of patients
- Most common findings are hypersplenism and dyslipidaemia
- Progressive lung disease occurs in most patients biochemical and clinical criteria[4]

Chronic neurovisceral ASMD: Variant patients

- Disease symptoms range from severe to moderate
- Initial development is normal
- Neurological difficulties begin between 18 months to seven years of age
- Ataxia, gross motor delays, and learning disabilities are commonly seen
- Progressive multisystem disease manifestations are similar to, or more severe than, those observed in chronic visceral ASMD

References:

1. Schuchman EH, Desnick RJ. Niemann Pick disease types A and B: acid sphingomyelinase deficiencies. In Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease.* 2001;8: 3589–3610

2. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA.* 1999;281(3):249-254. doi:10.1001/jama.281.3.249

3. McGovern MM, Wasserstein MP, Giugliani R, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. *Pediatrics.* 2008;122(2):e341-e349. doi:10.1542/peds.2007-3016

4. Pittis MG, Ricci V, Guerci VI, et al. Acid sphingomyelinase: identification of nine novel mutations among Italian Niemann Pick type B patients and characterization of in vivo functional in-frame start codon. *Hum Mutat.* 2004;24(2):186-187. doi:10.1002/humu.9263

5. Miranda SR, He X, Simonaro CM, et al. Infusion of recombinant human acid sphingomyelinase into niemann-pick disease mice leads to visceral, but not neurological, correction of the pathophysiology. *FASEB J.* 2000;14(13):1988-1995. doi:10.1096/fj.00-0014com

6. Passini MA, Bu J, Fidler JA, et al. Combination brain and systemic injections of AAV provide maximal functional and survival benefits in the Niemann-Pick mouse. *Proc Natl Acad Sci U S A.* 2007;104(22):9505-9510. doi:10.1073/pnas.0703509104

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.

References:

1. Niemann A. Ein unbekanntes Krankheitsbild. Jahrb. Kinderheillkd. 1914;79:1-10

2. Vanier MT. Niemann-Pick disease type C. *Orphanet J Rare Dis.* 2010;5:16., doi:10.1186/1750-1172-5-16

3. Crocker AC, Farber S. Niemann-Pick disease: a review of eighteen patients. Medicine (Baltimore). 1958;37(1):1-95. doi:10.1097/00005792-195802000-00001

4. Crocker AC. The cerebral defect in Tay-Sachs disease and Niemann-Pick disease. *J Neurochem.* 1961;7:69-80. doi:10.1111/j.1471-4159.1961.tb13499.x

5. Elleder M, Jirásek A. Niemann-Pick Disease. Report on a symposium held in Hlava's Institute of Pathology, Charles University, Prague 2nd-3rd September, 1982. *Acta Univ Carol Med (Praha).* 1983;29(3-4):259-267

6. Patterson M. Niemann-Pick Disease Type C. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; January 26, 2000

7. National Institute of Neurological Disorders and Stroke (NINDS). Niemann-Pick disease. Accessed July 20, 2007. www.ninds.nih.gov/disorders/niemann/niemann.htm

Chapter 5: Genetics

The Molecular Genetics of ASM

In 1991, researchers attributed a single locus for the gene encoding ASM to the chromosomal region 11p15.1 to p15. 4. Indeed, no homologous coding sequences or pseudogenes were identified elsewhere in the genome.[1]

The *SMPD1* gene (GenBank#NC_000011.10), encoding the ASM enzyme, spans ~5 kb and consists of six exons (Table 1).[1,2,3,4] Two in-frame start codons were identified in the *SMPD1* coding region, at codon 1 and 33.[5]

Table 1. Intron-exon junctions in the human *SMPD1* gene (based on NM_000543.5)

Exon number	Exon size (NT)	Codons	5′ donor splice site	Intron size (NT)	3′ acceptor splice site
1	443 (the first 125 non-coding)	1-106	AG gtgagc(D1)	467	cag A (AI)
2	773	107-364	AG gtactt(D2)	1059	cag A (A2)
3	172	364-421	**AA** gtgagg(D3	229	tag G (A3)
4	77	422-447	AG gtagga(D4)	202	cag G (A4)
5	146	447-496	TG gtgagt(D5)	156	cag G (A5)
6	799 (the last 389 non-coding)	496-631 (last TAG excluded)			

The underlined residues represent divergences from the 5′ donor or 3′ acceptor splice site consensus sequences; the bold AA indicates a change from the invariant AG dinucleotide in the 5′ donor splice site (D3) at the junction of intron 2 and exon 3.[1]

As of June 2020, 266 variants in the SMPD1 gene have been reported in the Human Gene Mutation Database,[6] including 195 missense/nonsense, 47 small deletions, 14 small insertions/duplications, 4 indels, 5 splicing substitutions and 1 gross insertion/duplication. A locus-specific database providing a more comprehensive analysis of SMPD1 mutations can be accessed at https://inpdr.org/smpd1/.

Four SNPs within the *SMPD1* coding sequence have been identified; the most frequent being p.V36A and p.G508R. Besides these SNPs, a polymorphic region coding for the signal peptide of ASM, characterised by a three- to an eight-fold repeat of the hexanucleotide GCTGGC (p.L37_A38[3_8]),[7] has been described. Recently, the p.A487V substitution, previously reported as a disease-causing mutation, has been characterised as a polymorphic variant.[8]

SMPD1 variants have been identified worldwide. The spectrum of *SMPD1* mutations is heterogeneous, and most mutations are private. However, the most frequently reported mutation worldwide is a 3-base deletion, first described by Levran et al,[9] leading to the loss of the arginine residue Arg610del (p.R610del). This mutation has been consistently identified in patients with the non-neuronopathic NPB phenotype. Few mutations are more frequently represented among individuals of a particular ethnic group. Indeed, the frameshift mutation p.F333SfsX52 and the missense mutations p.L304P and p.R498L, account for more than 90% of alleles in NPA patients of Ashkenazi Jewish origin.[10,11,12] The p.H423Y represents 75% of NPB alleles in Saudi Arabian patients[13] and mutations p.R3AfsX76 and p.H284SfsX7 are frequent in NPA/B patients from China.[14] The missense mutation p.W393G is present in 100% of the alleles associated with the intermediate phenotype in the Gypsy population.[15] Even though the p.Q294K mutation has been found in patients from different populations, it is most commonly identified in patients from Czech and Slovak heritage.[16]

Patterns of Inheritance

ASMD is inherited in an autosomal recessive manner. For most inherited metabolic diseases, the phenotype of a particular inherited mutation (i.e. age of onset and the profile/severity of symptoms) usually runs consistently within families.[17]

In each pregnancy of a carrier couple, there is a 25% chance that they will both pass on their disease-causing *SMPD1* 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 *SMPD1* 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 *SMPD1* allele. Furthermore, each sibling of an affected individual's parents is at a 50% risk of being a carrier.

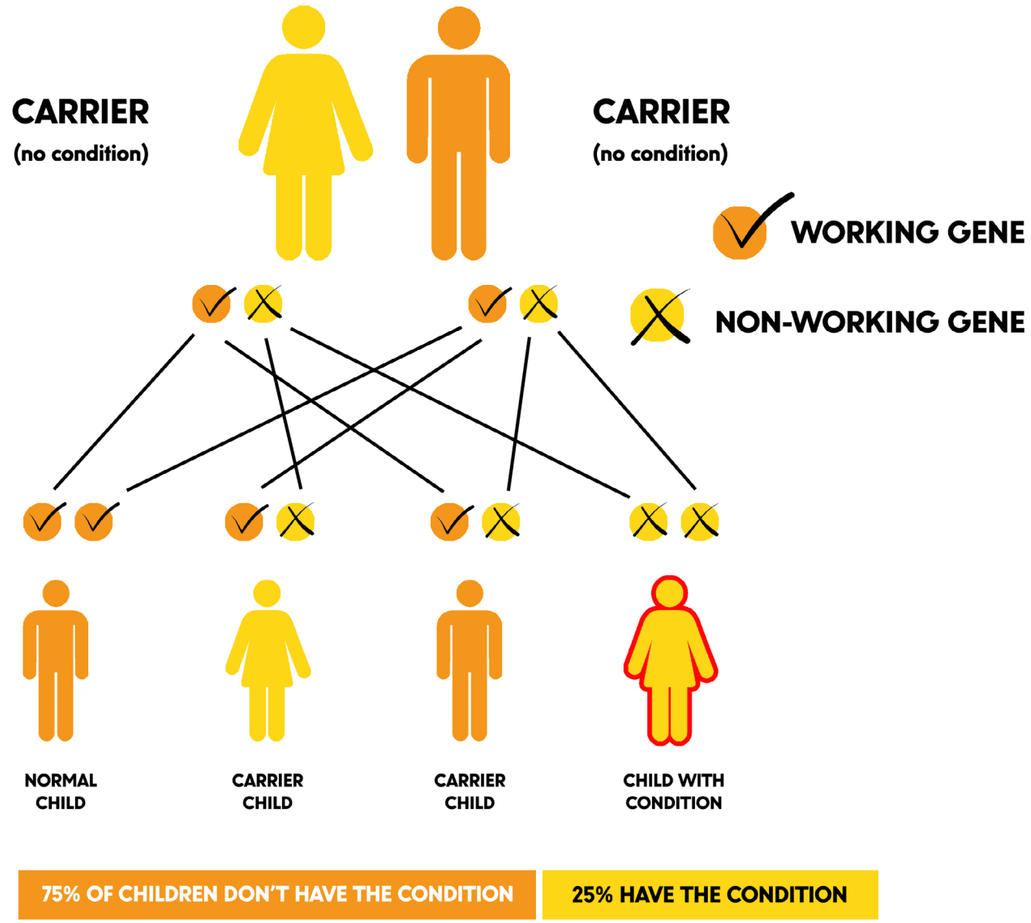


Figure 1: Autosomal recessive inheritance

Carrier Detection and Genetic Counselling

Biochemical testing cannot be relied upon to identify individuals who are heterozygous for *SMPD1* mutations (carriers), because the enzymatic activity results are similar to the activity seen in healthy controls. Therefore, genetic testing of *SMPD1* familial mutations must be used to identify carriers among relatives of affected individuals.

Genetic counselling must be offered to all newly diagnosed patients and family members to provide information about the genetic testing, mode of inheritance and the risk of recurrence of the disease, to promote informed choices. In terms of family planning, it is particularly relevant to discuss the availability of prenatal testing.

Genetic Prenatal Testing

Prenatal testing is offered when both parents are carriers of *SMPD1* mutations, and there is a subsequent 25% risk that the foetus is affected by ASMD. Although the analysis of the foetal cells for the *SMPD1* mutations identified in the parents is the preferred test, prenatal assessment of ASM enzymatic activity is also possible.

Genotype/phenotype Correlation

As most *SMPD1* mutations have been found in single families and in compound heterozygosity, it is challenging to correlate the genotype and phenotype. However, some general assumptions can be made for recurrent mutations found in homozygosis. This is the case for mutations p.F333SfsX52, p.L304P and p.R498L, which are associated with the severe type A phenotype, the p.R610del and p.H423Y, which have been consistently identified in patients with the non-neuronopathic NPB phenotype;[13] and the p.Q292K, associated with an intermediate neurological phenotype.[18]

Frameshift and nonsense mutations can be considered as severe alterations, except for p.W32X. When present in homozygosis, this variant is associated with the NPB phenotype. This is likely due to the initiation of translation at ATG33, resulting in the synthesis of a partially active protein, which is missing the first 32 residues of the predicted signal peptide.[19]

In general, patients who carry at least one *SMPD1* mutant allele, leading to the synthesis of a partially active ASM protein, present with the NPB phenotype. However, patients carrying severe mutations in both alleles may display a wider spectrum of clinical presentations.[20]

References:

1. da Veiga Pereira L, Desnick RJ, Adler DA, Disteche CM, Schuchman EH. Regional assignment of the human acid sphingomyelinase gene (SMPD1) by PCR analysis of somatic cell hybrids and in situ hybridization to 11p15.1----p15.4. *Genomics*. 1991;9(2):229-234. doi:10.1016/0888-7543(91)90246-b

2. Quintern LE, Schuchman EH, Levran O, et al. Isolation of cDNA clones encoding human acid sphingomyelinase: occurrence of alternatively processed transcripts. *EMBO J*. 1989;8(9):2469-2473

3. Schuchman EH, Suchi M, Takahashi T, Sandhoff K, Desnick RJ. Human acid sphingomyelinase. Isolation, nucleotide sequence and expression of the full-length and alternatively spliced cDNAs. *J Biol Chem*. 1991;266(13):8531-8539

4. Schuchman EH, Levran O, Pereira LV, Desnick RJ. Structural organization and complete nucleotide sequence of the gene encoding human acid sphingomyelinase (SMPD1). *Genomics*. 1992;12(2):197-205. doi:10.1016/0888-7543(92)90366-z

5. Schuchman EH, Desnick RJ. Niemann Pick disease types A and B: acid sphingomyelinase deficiencies. In Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 2001;8: 3589–3610

6. Stenson PD, Ball EV, Mort M, et al. Human Gene Mutation Database (HGMD®): 2003 update. *Hum Mutat*. 2003;21:577-581. doi: 10.1002/humu.10212

7. Wan Q, Schuchman EH. A novel polymorphism in the human acid sphingomyelinase gene due to size variation of the signal peptide region. *Biochim Biophys Acta*. 1995;1270(2-3):207-210. doi:10.1016/0925-4439(95)00050-e

8. Rhein C, Naumann J, Mühle C, et al. The Acid Sphingomyelinase Sequence Variant p.A487V Is Not Associated With Decreased Levels of Enzymatic Activity. *JIMD Rep*. 2013;8:1-6. doi:10.1007/8904_2012_147

9. Levran O, Desnick RJ, Schuchman EH. Niemann-Pick type B disease. Identification of a single codon deletion in the acid sphingomyelinase gene and genotype/phenotype correlations in type A and B patients. *J Clin Invest*. 1991;88(3):806-810. doi:10.1172/JCI115380

10. Levran O, Desnick RJ, Schuchman EH. Niemann-Pick disease: a frequent missense mutation in the acid sphingomyelinase gene of Ashkenazi Jewish type A and B patients. *Proc Natl Acad Sci U S A*. 1991;88(9):3748-3752. doi:10.1073/pnas.88.9.3748

11. Levran O, Desnick RJ, Schuchman EH. Identification and expression of a common missense mutation (L302P) in the acid sphingomyelinase gene of Ashkenazi Jewish type A Niemann-Pick disease patients. *Blood*. 1992;80(8):2081-2087

12. Levran O, Desnick RJ, Schuchman EH. Type A Niemann-Pick disease: a frameshift mutation in the acid sphingomyelinase gene (fsP330) occurs in Ashkenazi Jewish patients. *Hum Mutat*. 1993;2(4):317-319. doi:10.1002/humu.1380020414

13. Simonaro CM, Desnick RJ, McGovern MM, Wasserstein MP, Schuchman EH. The demographics and distribution of type B Niemann-Pick disease: novel mutations lead to new genotype/phenotype correlations. *Am J Hum Genet*. 2002;71(6):1413-1419. doi:10.1086/345074

14. Zhang H, Wang Y, Gong Z, et al. Identification of a distinct mutation spectrum in the SMPD1 gene of Chinese patients with acid sphingomyelinase-deficient Niemann-Pick disease. *Orphanet J Rare Dis*. 2013;8:15. Published 2013 Jan 28. doi:10.1186/1750-1172-8-15

15. Mihaylova V, Hantke J, Sinigerska I, et al. Highly variable neural involvement in sphingomyelinase-deficient Niemann-Pick disease caused by an ancestral Gypsy mutation. *Brain*. 2007;130(Pt 4):1050-1061. doi:10.1093/brain/awm026

16. Pavlů-Pereira H, Asfaw B, Poupctová H, et al. Acid sphingomyelinase deficiency. Phenotype variability with prevalence of intermediate phenotype in a series of twenty-five Czech and Slovak patients. A multi-approach study. *J Inherit Metab Dis*. 2005;28(2):203-227. doi:10.1007/s10545-005-5671-5

17. Imrie J, Dasgupta S, Besley GT, et al. The natural history of Niemann-Pick disease type C in the UK [published correction appears in J Inherit Metab Dis. 2007 Oct;30(5):833]. *J Inherit Metab Dis*. 2007;30(1):51-59. doi:10.1007/s10545-006-0384-7

18. Wasserstein MP, Aron A, Brodie SE, Simonaro C, Desnick RJ, McGovern MM. Acid sphingomyelinase deficiency: prevalence and characterization of an intermediate phenotype of Niemann-Pick disease. *J Pediatr*. 2006;149(4):554-559. doi:10.1016/j.jpeds.2006.06.034

19. Dardis A, Zampieri S, Filocamo M, Burlina A, Bembi B, Pittis MG. Functional in vitro characterization of 14 SMPD1 mutations identified in Italian patients affected by Niemann Pick Type B disease. *Hum Mutat*. 2005;26(2):164. doi:10.1002/humu.9353

20. Zampieri S, Filocamo M, Pianta A, et al. SMPD1 Mutation Update: Database and Comprehensive Analysis of Published and Novel Variants. *Hum Mutat*. 2016;37(2):139-147. doi:10.1002/humu.22923

Chapter 6: Diagnosis

Clinical Diagnosis

Enzymatic diagnosis
ASMD is diagnosed by the markedly deficient activity of acid sphingomyelinase in peripheral leukocytes or cultured skin fibroblasts.

In general, residual ASMD activity in type A and type B ranges from <1% to around 10% of normal levels. Type B patients generally have higher levels, but this is not a reliable predictor of phenotypic severity. There is also significant overlap between normal and heterozygote enzyme activity levels, therefore enzymatic studies alone are not reliable for carrier detection.

It is worth noting that patients carrying the p.Q292K mutation can be misdiagnosed if tested for ASM activity using the fluorometric substrate 6-Hexadecanoylamino-4-methylumbelliferylphosphorylcholine, since the mutant is active against this substrate but inactive against the natural sphingomyelin. Assays that allow the identification of this particular mutant have been developed.[1,2]

Molecular diagnosis
Molecular testing approaches can include single-gene testing or the use of a multi-gene panel.

Since the vast majority of pathogenetic alleles are due to point mutations or small delete/insertions, and the mutational spectrum of *SMPD1* gene in ASMD patients is heterogeneous, the analysis of the exons and exon/intron junctions by Sanger Sequencing or Next-Generation Sequence (NGS) is recommended.

Targeted analysis for pathogenic variants can be considered for individuals of Ashkenazi Jewish ancestry in which three mutations (see the previous chapter) account for around 90% of the alleles.

Copy number variations are identified in a small percentage of patients and can be detected by multiplex ligation-probe amplification (MLPA).

References:

1. van Diggelen OP, Voznyi YV, Keulemans JL, et al. A new fluorimetric enzyme assay for the diagnosis of Niemann-Pick A/B, with specificity of natural sphingomyelinase substrate. *J Inherit Metab Dis*. 2005;28(5):733-741. doi:10.1007/s10545-005-0105-y

2. Ghomashchi F, Barcenas M, Turecek F, Scott CR, Gelb MH. Reliable Assay of Acid Sphingomyelinase Deficiency with the Mutation Q292K by Tandem Mass Spectrometry. *Clin Chem*. 2015;61(5):771-772. doi:10.1373/clinchem.2014.236448

Chapter 7: Pathophysiology

Acid Sphingomyelinase

Under normal conditions, ASM is mainly found in lysosomes, where its function is to participate in membrane degradation and turnover. Within this organelle, the enzyme exists in a complex with other lipid hydrolases, including acid ceramidase. Trafficking of ASM to lysosomes follows a path similar to that of most other lysosomal hydrolases and is due primarily to the presence of mannose-6 phosphate residues on N-linked oligosaccharide side chains. Small amounts of the enzyme are released from cells into the circulation, but importantly, ASM needs zinc for full activity. Inside the lysosome, the enzyme is fully saturated with this cation. The secreted form is not fully saturated with zinc, but it can be activated in vitro by addition of the cation to the assay mixture.

Sphingomyelin, the substrate for ASM, is a structural component of most cell membranes, and together with cholesterol, it is a significant constituent of membrane raft structures.[1]

Hepatosplenomegaly

A common clinical presentation for patients with all forms of ASMD is hepatosplenomegaly. In a cross-sectional study of 59 patients with NPB, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated in 51% of patients, and total bilirubin was elevated in 33% of patients.[2] In some patients, liver fibrosis and development of cirrhosis are major morbidities. Similarly, the spleen is enlarged in most patients with ASMD.

In a healthy adult, the spleen is about 11cm long and weighs about 150g. In one study, a cross-sectional analysis of growth was performed on 23 children and adolescents with enzymatically and genotypically confirmed ASMD. The mean liver and spleen volumes were 2.06 and 13.46 times the normal levels for weight, respectively.[3]

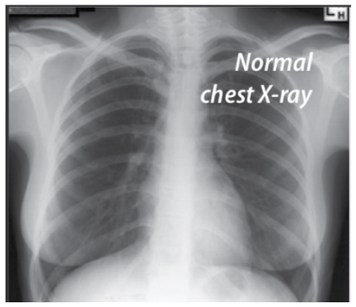
The enlargement of the spleen results from infiltration by lipid-laden macrophages and can be substantial. Large spleen size is associated with an increased incidence of bleeding and bruising and can have an impact on digestion and breathing, which can cause considerable discomfort.

Pulmonary Disease in ASMD

Most patients with ASMD have evidence of interstitial lung disease (ILD) by chest radiography and high-resolution computed tomography. However, some patients with significant radiographic evidence of lung disease do not have severe clinical symptoms.

Therefore, imaging studies are not sufficient for evaluating pulmonary disease in ASMD and must be interpreted alongside pulmonary function testing and the clinical status of the patient. In general, there is a slow progression of pulmonary disease, even though it remains the leading cause of death in patients with NPB.

a)



b)

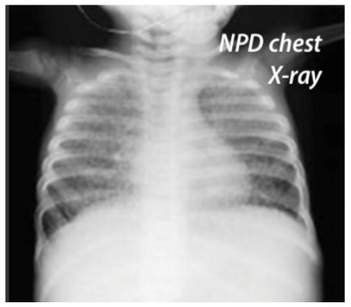


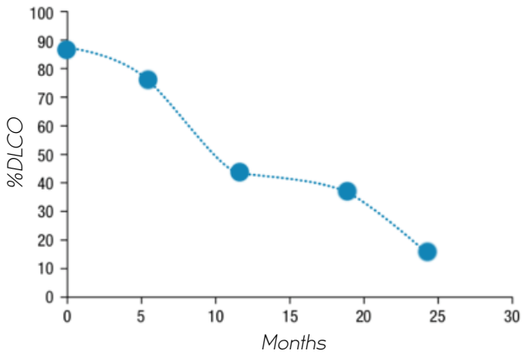
Figure 2. The chest x-ray in a) shows a healthy lung and b) shows a patient with NPA with sphingomyelin storage causing ILD

Lung Function and Respiratory Symptoms

In 2004, Wasserstein, McGovern et al carried out a longitudinal study into the natural history of NPB.[4] This study featured 53 patients aged between seven and 65. The patients all had chest X-rays, high-resolution chest CT scans (HRCT) and were then assigned a score for ILD. Pulmonary function tests were also performed. ILD was present in all but one patient, and some patients also had pulmonary nodules. There was no association of ILD score with age or DLCO (diffusion lung capacity for carbon monoxide), which is the extent to which oxygen passes from the air sacs of the lungs into the blood. All patients reported shortness of breath, fatigue and recurrent infections.

The graph on the left shows the decline in pulmonary function over time in one patient who had undergone splenectomy. The graph on the right compares the lung function in splenectomised versus non-splenectomised patients.[5] Splenectomy is generally contraindicated due to risk of progressing respiratory insufficiency and exacerbating liver disease.[6]

a)



b)

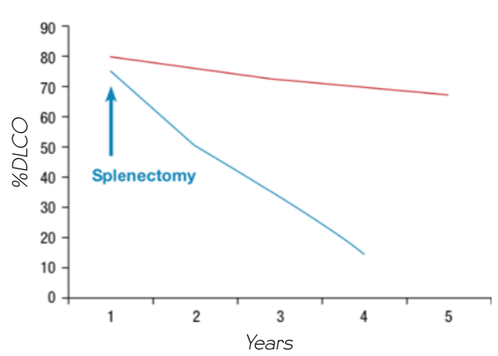


Figure 3. a) lung function in a splenectomised patient and b) lung function over time: splenectomised vs non-splenectomised patients

Treatment of ILD

- Home oxygen therapy
  Breathing supplemental oxygen increases the amount of oxygen in the blood. This may help reduce shortness of breath and prevent other complications.
- Pulmonary rehabilitation
  Aerobic training sessions
- Smoking cessation
- Lung transplantation for severe ILD

Effects on Lipid Profile

In a cross-sectional study,[7] most patients were found to have atherogenic lipid profiles. Low high-density lipoprotein (HDL) was the most characteristic lipid abnormality, affecting 74% of the patients studied. In addition, 41% had high total cholesterol levels, 62% had high triglycerides, 46% had high low-density lipoprotein (LDL), and 62% had high very-low-density lipoprotein levels. All of these levels were age-matched and gender-matched in the control subjects. The mean cholesterol/HDL ratio was more than twice as high (2:3) as the upper range of normal. Patients who had undergone splenectomy had a mean cholesterol/HDL ratio almost twice as high as those with intact spleens. McGovern et al[7] concluded that lipid abnormalities are part of the phenotype in types A and B Niemann-Pick disease and may be associated with early atherosclerotic heart disease.

Table 2. Mean lipid values for male and female patients with NPA & NPB

		Male, mean (mg/dL)/(SD)	Female, mean (mg/dL)/(SD)	Desirable[8] (mg/dL)	Abnormal[8] (mg/dL)
Cholesterol	Type A	253 (65)	241 (47)	<170	>200
	Type B	237 (71)	213 (52)		
HDL-C	Type A	16 (5)	23 (12)	>45	<35
	Type B	20 (7)	24 (11)		
LDL-C	Type A	156 (57)	164 (54)	<110	>130
	Type B	169 (62)	145 (49)		
Triglycerides	Type A	207 (79)	198 (87)	<125	>125
	Type B	235 (96)	169 (90)		

Haematological Problems

Bleeding is a frequent problem in patients with ASMD. In the study carried out by McGovern et al,[8] 49% of the patients had evidence of bleeding problems. Most (29%) were related to epistaxis or nose bleeds. In two patients, these required repeated cauterisations and the case study on page 34 describes a young woman with this problem. Other reported bleeding events included bleeding into the brain, lung, tonsil and uterus. Anecdotally, most patients with ASMD do report a higher incidence of bruising compared to their peers.

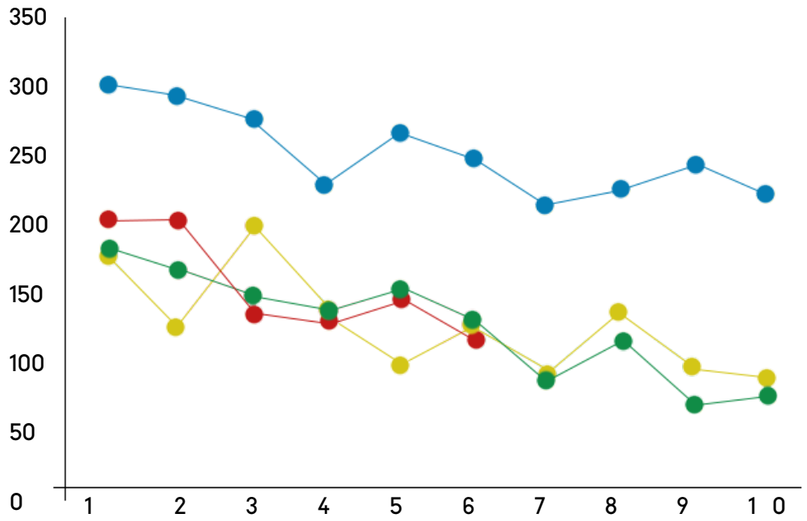


Figure 3. Platelet counts over time in four patients (normal range 150–450)

Bone Problems

Skeletal involvement is a common feature of ASMD. By medical history, 19% of the patients in one study had suffered one or more bone fractures.[8] Subsequent examinations of the skeleton in 20 paediatric and 26 adult patients with NPB, using dual X-ray absorptiometry scans to measure bone mineral content (BMC) and bone mineral density (BMD), showed that paediatric patients had significant decreases in adjusted mean BMC and BMD at the lumbar spine, hip and femoral neck compared with a cohort of healthy age-matched subjects. In addition, most adults with NPB had osteopenia or osteoporosis at one or more sites, according to the World Health Organization classification of BMD.[7]

Bone problems can lead to an increased disability, as well as pain and decreased mobility. Therefore, it is very important to recognise it and take steps to minimise any related problems.

Growth

Most children with ASMD have delayed growth. This is particularly noticeable in adolescence, and it can be the problem that causes the most anxiety for children with ASMD. In one study, a cross-sectional analysis of growth was performed on 23 children and adolescents with enzymatically and genotypically confirmed ASMD. The mean Z scores for height and weight were –1.24 (29th percentile) and –0.75 (34th percentile). The mean liver and spleen volumes were 2.06 and 13.46 times the normal levels for weight, respectively. Skeletal age was delayed by an average of 2.5 years, and serum IGF-1 level was at or below the 2nd percentile in eight of 12 patients. Short stature and low weight were significantly correlated with large organ volumes, delayed bone age, and low IGF-1 levels. In contrast to patients with other mutations, individuals homozygous for the ΔR608 mutation had normal height and weight, markedly less hepatosplenomegaly and bone age delay, and normal IGF-1 level.[3]

The experience in the UK is that, although growth is delayed in their early teens, most adolescents continue growing well into early adulthood and do attain a normal height by their mid-twenties. This information may be reassuring for many children with ASMD.

References:

1. Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. *J Inherit Metab Dis.* 2007;30(5):654-663. doi:10.1007/s10545-007-0632-9

2. Henderson SL, Packman W, Packman S. Psychosocial aspects of patients with Niemann-Pick disease, type B. Am *J Med Genet A.* 2009;149A(11):2430-2436. doi:10.1002/ajmg.a.33077

3. Wasserstein MP, Larkin AE, Glass RB, Schuchman EH, Desnick RJ, McGovern MM. Growth restriction in children with type B Niemann-Pick disease. *J Pediatr.* 2003;142(4):424-428. doi:10.1067/mpd.2003.113

4. Wasserstein MP, Desnick RJ, Schuchman EH, et al. The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. *Pediatrics.* 2004;114(6):e672-e677. doi:10.1542/peds.2004-0887

5. Mendelson DS, Wasserstein MP, Desnick RJ, et al. Type B Niemann-Pick disease: findings at chest radiography, thin-section CT, and pulmonary function testing. *Radiology.* 2006;238(1):339-345. doi:10.1148/radiol.2381041696

7. Niemann A.1914. Ein unbekanntes krankheitsbild. Jahrb Kinderheilkd;79:1

8. McGovern MM, Wasserstein MP, Giugliani R, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. *Pediatrics.* 2008;122(2):e341-e349. doi:10.1542/peds.2007-3016

Chapter 8: Epidemiology

Incidence and Prevalence

ASMD is pan-ethnic and affects males and females in equal numbers.[1] However, the exact incidence and prevalence of the disorder are unknown, as no population-based screening programs have been undertaken for this disorder.

The birth prevalence of ASMD type A has been estimated at 1 in 400,000.[2] However, ASMD type A occurs more frequently among those of Ashkenazi Jewish origin.

Among non-Jewish ASMD patients, the type B form is more prevalent. The prevalence of ASMD type B has been estimated at 1 in 250,000 people.[2]

The Importance of Disease Registries

Disease registries that collect data on disease epidemiology, symptomatology and disease management of rare diseases such as ASMD diseases 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: https://inpdr.org/.

References:

1. Acid Sphingomyelinase Deficiency - NORD (National Organization for Rare Disorders). NORD (National Organization for Rare Disorders). https://rarediseases.org/rare-diseases/acid-sphingomyelinase-deficiency/. Published 2020. Accessed December 8, 2020

2. Orphanet Report Series. Prevalence of rare diseases: Bibliographic data – January 2021. Accessed March 15, 2021. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_diseases.pdf

Chapter 9: Potential Therapies

Haematopoietic Stem Cell Transplantation (HSCT)

HSCT using bone marrow as the donor cell source has been performed in several ASMD patients. Reduction in liver and spleen size was noted in at least one case, but severe transplantation-related complications were seen in this patient and others. Another case demonstrated resolution of respiratory disease.[1] No impact on the neurological phenotype of type A patients has been shown. Transplantation in the knockout mouse model resulted in high engraftment levels and positive effects on the reticuloendothelial system (RES) organs, but intermediate effects on neurological disease. As a result of these and other studies, it is thought that HSCT may benefit those patients with no neurological involvement, but potential severe transplant-related complications are of concern.

Liver Transplantation

Liver transplants could be a safe and effective treatment for patients with NPB suffering from severe liver and pulmonary dysfunction, and it may become an increasingly preferred therapy in the future.[2] One study following seven children with NPB after receiving a liver transplant demonstrated that the transplant restored the liver and pulmonary function, with catch- up growth and improved psychomotor ability detected during the long-term follow up.[2]

Splenectomy

Another approach has been a partial or full splenectomy. However, post-splenectomy there seems to be increased pulmonary storage and a faster progression and severity of pulmonary disease. Also following splenectomy in patients with severe disease, the disease burden in other organs can increase dramatically, so splenectomy should be avoided in these instances.

There is no documented rationale for a partial or full splenectomy, but it is possibly to reduce pain and/or the risk of splenic rupture and to treat hypersplenism and improve blood counts. In addition, the increased energy demand of the enlarged spleen may contribute to the observed poor growth and failure to thrive. Other factors associated with hypersplenism include anaemia, low white blood cell count and the risk of haemorrhage from thrombocytopaenia.

Pulmonary Lavage

This is discussed on page 23, but the general opinion is that these procedures only seem to have a temporary effect on pulmonary function. In the absence of a systemic study exploring this therapy, the evidence is limited to case reports. Over time, inflammatory cells are likely to repopulate the airways and symptoms can become as severe or even worse than before the procedure.

Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) is seen as the gold standard for achieving widespread delivery of enzymes to clinically affected organs. Olipudase alfa, an investigational recombinant human acid sphingomyelinase, has been used in two separate clinical trials, in both adult and paediatric patients, with positive results. Long-term data from the phase I study has shown remarkable improvements in organomegaly, lung function and lipid profile. Further, a large phase III double-blinded randomised placebo-controlled trial has been completed in adults, and an open-label trial completed in children, the results of which suggest that, similar to Gaucher disease, ERT can reverse the disease process.[3]

Future Potential Therapies

Gene therapy

Gene therapy approaches have been studied extensively in trials carried out on knockout mice. One example is the use of retroviral vectors containing the full-length *SMPD1* cDNA. These were used to transduce knockout bone marrow cells and then transplanted into partially irradiated littermates. The effects of the procedure showed the same level of improvement as ERT on the organs, but no effect on neurological symptoms. The potential advantage of gene therapy over HSCT is that the patient's own bone marrow might be used and could potentially make toxic preconditioning unnecessary.

Recent research suggests that cerebellomedullary (CM) cistern injection of adeno-associated viral vector serotype nine encoding human ASM (AAV9-hASM) in non-human primates results in widespread transgene expression within the brain and spinal cord cells without signs of toxicity. The study supports CM injections for future AAV9-based clinical trials in NPA, as well as other lysosomal storage brain disorders.[4]

References:

1. Shah AJ, Kapoor N, Crooks GM, et al. Successful hematopoietic stem cell transplantation for Niemann-Pick disease type B. Pediatrics 2005; 116:1022

2. Liu Y, Luo Y, Xia L, et al. The Effects of Liver Transplantation in Children With Niemann-Pick Disease Type B. *Liver Transpl.* 2019;25(8):1233-1240. doi:10.1002/lt.25457

3. GlobeNewswire News Room. 2020. Sanofi : Positive Topline Results Demonstrated By Olipudase Alfa, *First And Only Investigational Therapy In Late-Stage Development For Acid Sphingomyelinase Deficiency.* [online] Available at: <https://www.globenewswire.com/news-release/2020/01/30/1977201/0/en/Sanofi-Positive-topline-results-demonstrated-by-olipudase-alfa-first-and-only-investigational-therapy-in-late-stage-development-for-acid-sphingomyelinase-deficiency.html> [Accessed 8 December 2020]

4. Samaranch L, Pérez-Cañamás A, Soto-Huelin B, et al. Adeno-associated viral vector serotype 9–based gene therapy for Niemann-Pick disease type A. *Science Translational Medicine.* 2019;11(506)

Chapter 10: Social and Psychological Impact

Patients living with ASMD often feel like they are living with a 'hidden disability' or an 'invisible illness', particularly if they are regularly told by others that they 'look well'. They often struggle to continuously repeat their story and explain their illness to others, which can be both upsetting and stressful.

Case study A:

One young gentleman has learnt to manage this extremely well after having to explain to his colleagues why he attends the hospital for a clinical trial every fortnight. To help him cope with this, he has rehearsed what he says, and pre-empts their reaction by warning them he is going to use some big words like saying "I have a Lysosomal Storage Disorder, so this means I am deficient in an enzyme called sphingomyelinase which means I attend a trial to replace the enzyme with an artificial version".

Very little research has been undertaken into the social and psychological impact of ASMD. However, Dr Shelly Henderson, Assistant Professor and Director of Behavior Medicine at UC Davis in California, chose the social and psychological impact of ASMD for her PhD dissertation at the Pacific Graduate School of Psychology in 2006 and has shared this information with the British and American Niemann-Pick patient advocacy groups. The following draws on the excellent work she has produced in covering this topic.[1]

Extract from Psychological aspects of patients with Niemann-Pick disease (Henderson, 2009)[1]

Acknowledging that patients with Niemann-Pick disease face numerous psychological stressors, Henderson set out to explore the experiences of patients and families living with NPB. Stressors include extensive medical input, uncertainty around diagnosis, living and coping with chronic illness and grief and bereavement. Seventeen patients over the age of 13 were interviewed.

It was acknowledged that each family had its own unique set of circumstances but that there were some areas of consensus.

o All participants identified limited physical activity, social isolation and peer rejection as significant stressors.

o These stressors had a specific impact during the age span of 10-16 years.

o Parents and adult patients expressed significant frustration regarding the lack of information and treatment available.

o Patients described relying on close family relationships as a way of coping with the illness.

o Adult patients identified early medical experiences as having a considerable psychological impact.

Looking at these responses, it is clear that there are often discrepancies in how an adolescent feels and how the parent thinks they feel.

Several parents did not realise how much their daughters had been hurt when they were teased about looking pregnant. Similarly, although most parents recognise that their teenage child may have concerns about their height, this survey highlights the substantial impact on children. It is an age when most children are sensitive about their appearance and may experience bullying or name-calling due to delayed puberty and short stature.

Many of the children also mentioned that, when they were younger, they felt isolated and often pushed out of society. Their illness meant that they had to avoid contact sports and could not take part in team games and so lost the opportunity to learn group and social skills.

Case Study B:

This lady explains the difficulties she has encountered. Because I 'look well on the outside', it is really difficult for people to understand why I need a break or a rest after a short while, or why I am unable to take part in contact sports. Often, people are quite shocked and don't understand why I unable to keep up with their pace of walking. I have also spent the majority of my life trying to keep up with others, so I don't stand out from my peers and appear 'different'.

Those affected with ASMD often feel fuller quicker and so need to eat little and often. For children in school, this may cause difficulties as they may need to snack during the day or in class, and some schools and classmates may not always be understanding of this.

ASMD patients may have limited energy, so go to bed earlier and miss out on evening socialisation or struggle with homework after school. Also, they find they may have to be selective about how they choose to spend their time, so may not socialise as much as they would like, which can have a big impact on their quality of life and mental well-being. Further, patients might need to rest during the day and are unable to mobilise for long distances and so would need to stop for regular rest or require a buggy or mobility scooter.

References:

1. Henderson SL, Packman W, Packman S. Psychosocial aspects of patients with Niemann-Pick disease, type B. *Am J Med Genet A.* 2009;149A(11):2430-2436. doi:10.1002/ajmg.a.33077

Chapter 11: Support

Patient Associations

ASMD can be a devastating condition that impacts the entire family. Patient associations can provide educational material, plus practical and counselling support to patients and families affected by ASMD. Many patient associations also actively participate in fundraising for the support of medical therapy and ASMD research. A list of patient associations is provided in the Resources section on page 36.

Specialist Care Centres

Specialist care centres (see Resources, page 38) can provide comprehensive, integrated, multidisciplinary care for patients, as well as information and support for family members, as they aim to incorporate networks of all relevant medical disciplines within the core team. They have effective links with national networks of testing laboratories and other care centres at the national and international level and play an important role in disease auditing and the maintenance of geographical coverage. Metabolic nurse specialists are integral to the day-to-day running of clinics and deal with many of the familial aspects of work with patients and family members. Physiotherapists and occupational therapists should also all be involved in supportive care for patients.

Chapter 12: The Family Perspective

For parents and relatives of patients with Niemann-Pick disease, the progression of the disease and its symptoms and side-effects can be extremely stressful and worrying. Telling the story of how their child has been affected by ASMD is often harrowing, but sharing these experiences can be very beneficial. Here, the relatives of patients with NPA and NPB describe their experiences of the disease and the effects that it's had on their children.

Case study C: a girl, two and a half-years-old

I am the grandparent of a child who passed away. She was only two and a half years old. I don't even know where to begin telling you her life story.

She was born weighing 5lb 8oz, just a few days early. Pregnancy for mom was normal, and she was their first and only child. From the outset, she never could eat much. At three months old, the doctor said her liver was enlarged, and after months of many tests, liver surgery was performed.

One month after that, we were told she had Niemann-Pick disease, but they didn't know whether it was type A or B. They ran DNA tests, and still, no type could be determined. So, all we could go by was that she was meeting her milestones at the time.

But, at about 13 months, she stopped developing. She managed to walk by holding onto things, and she was able to hold a cup and feed herself. The only word she could say was 'Hi'. Throughout this time, she would get colds, and terrible constipation. She would take Miralax, but that would cause stomach pains and bad gas. In March, she caught pneumonia, and that was the start of her downfall. They say it "triggered the button". She was unable to do anything in the coming months; she couldn't even sit up. There was never a time that she could go more than three to four hours without eating, even at night.

By October she was hospitalised with mono [glandular fever] and was in horrific pain. She was in the hospital for five weeks, and during that time, she also developed RSV [respiratory syncytial virus, a major cause of respiratory illness in young children] and C difficile infection. She went through surgery to insert a gastrostomy tube.

After five weeks, we knew it was near the end and the hospice helped us to get her home. After that, she stopped being able to digest any food, and after six days, she tragically passed away. There is so much more to her life that I would love to tell you about.

Case study D: a four-year-old boy

Our son was diagnosed at six months with Niemann-Pick type A/B. He will turn four years old soon. He has an unusually large liver and spleen, even for Niemann-Pick disease. Unfortunately, I don't have any recent measurements. We haven't noticed any bleeding issues or bruising, but based on his platelet counts, we know the potential for problems exists.

He had sleep apnoea issues when he was two years old. After removing his adenoids and tonsils, he now has only slight apnoea problems. His lungs don't look healthy on an X-ray, but they appear to be functioning OK.

His bones are very weak, and his muscle tone is poor so he struggles walking. About five minutes is the maximum time that he is able to stay on his feet.

His height and weight are below normal, but only slightly. He eats frequently and doesn't have any digestive problems. He is an extremely picky eater though. We don't have any firm evidence of neurological involvement, but there may be some minor issues. We are anxiously awaiting phase two of the enzyme replacement trial.

Case study E: a teenager

This young lady is in her mid-teens. For the whole of her life, she has had a massive abdomen and gets teased at school as other children suggest she is pregnant. For the last few years, she has been in the hospital several times a year because of severe nosebleeds. She is much shorter than her peers, but she is a very intelligent young lady and copes very well with her problems. She is desperate for enzyme replacement therapy to start.

Chapter 13: Conclusions

ASMD is a rare, progressive genetic disease that results from a deficiency of the enzyme ASM, which is required to break down sphingomyelin. As a result, sphingomyelin and other substances accumulate in the tissues of the body. It is a highly variable disease, and the age of onset, symptoms and severity can vary drastically between patients.

Although all patients with ASMD share the same metabolic defect, the severity of ASMD ranges from a rapidly progressive infantile neurovisceral disease, that is uniformly fatal in early childhood, to more slowly progressive chronic neurovisceral and chronic visceral forms. The phenotypic variability of ASMD has led to the categorisation of subtypes based on severity and the degree of neurological involvement. Increased awareness of ASMD is required at all levels of care to support the quick diagnosis for individuals and ensure the provision of appropriate treatment and adequate counselling.

Until enzyme replacement therapy becomes a reality, there is no curative treatment. A number of interventions such as HSCT, liver transplantation, pulmonary lavage and splenectomy can alter the progression of the disease but are often associated with a high incidence of unwanted side-effects.

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, essential information and practical support. Patient groups can also facilitate access to others in a similar position, enabling mutual support and community interaction which, can improve quality of life for an ASMD patient.

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. Here we've provided information about specialist centres in the UK and the US. For information about specialist centres in other countries, please visit the Orphanet website here: www.orpha.net

Specialist Centres in the UK

Most patients with ASMD NPA and B are seen at one of the nationally funded specialist centres for lysosomal storage diseases.

BIRMINGHAM

Birmingham Children's Hospital *(paediatrics)*
Steelhouse Way,
Queensway, Birmingham B4 6NH

T: 0121 333 9999
W: https://bwc.nhs.uk/

Definition University Hospitals Birmingham NHS Foundation Trust *(adults)*,
Queen Elizabeth Hospital
Birmingham, Mindelsohn Way, Edgbaston,
Birmingham B15 2GW

T: 0121 371 2000
W: https://www.uhb.nhs.uk/home.htm

CAMBRIDGE

Addenbrooke's Hospital *(adults)*,
Cambridge University Hospitals NHS Foundation Trust, Hills Road,
Cambridge CB2 0QQ

T: 01223 245151
W: https://www.cuh.nhs.uk/uk/

LONDON

Great Ormond Street Hospital *(paediatrics)*,

UCL Institute of Child Health, 40 Bernard Street,
London WC1N 1LE

T: 020 7242 9789
W: www.ich.ucl.ac.uk

The Royal Free Hospital *(adults)*,
Pond Street, London
NW3 2QG

T: 020 7794 0500
W: www.royalfree.nhs.uk

National Hospital for Neurology and Neurosurgery *(adults)*,
Queen Square, London
WC1N 3BG

T: 020 3456 7890
W: www.uclh.nhs.uk

MANCHESTER & SALFORD

St Mary's Hospital *(paediatrics)*,
Department of Genetic Medicine,
Oxford Road, Manchester M13 9WL

T: 0161 276 1234
W: https://mft.nhs.uk/rmch/

Salford Royal Hospital NHS Foundation Trust *(adults)*,
Stott Lane, Manchester
M6 8HD

T: 0161 789 7373
W: https://www.srft.nhs.uk/

Additional Centres of Excellence

Evelina London Children's Hospital
St Thomas' Hospital
Westminster Bridge Road
London SE1 7EH

T: 020 7188 7188
W: https://www.evelinalondon.nhs.uk/

University Hospitals Bristol
Trust Headquarters,
Marlborough St, Bristol BS1 3NU

T: 0117 923 0000
W: http://www.uhbristol.nhs.uk/

Key Specialist Centres in the US

Icahn School of Medicine at Mount Sinai
Department of Genetics and
Genomic Sciences,
1425 Madison Avenue
New York, NY 10029

T: (212) 659-6779
W: https://icahn.mssm.edu/research/niemann

Montefiore Medical Center
The Children's Hospital at Montefiore
3415 Bainbridge Avenue
Bronx, NY 10467-2403

T: (718) 741-2323
W: https://www.montefiore.org/

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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