

# A guide to ASMD Niemann-Pick disease types A and B

Understanding acid sphingomyelinase deficient Niemann-Pick disease types A and B and their potential treatment

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disease types A and B and their potential treatment

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# Introduction

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Acid sphingomyelinase deficient Niemann-Pick disease (ASMD) 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, with particular emphasis on classical type B. Support for type A is around management of the severe symptoms and a separate care manual for NPA is available from the Niemann-Pick Disease Group (UK).

The scientific evidence associated with ASMD is presented first followed by information about what life is like for families with children and adults who have ASMD.

At first the scientific section may seem very technical for lay people to understand and also unfamiliar to many doctors. However, anyone who has an association with the disease will gradually learn more about the complexities of ASMD and understand the science related to it. The section for families provides first-hand accounts from parents and information about how to gain support. There is also information about the possible social and psychological impact of the disease.

This booklet is intended to help patients, their families, doctors and scientists gain a better understanding of the disease and how to manage it. As yet there is no cure for ASMD but clinical enzyme replacement therapy trials are in their early stages and offer hope for future advances.

## A scientist's perspective

Acid sphingomyelinase deficient disease (ASMD) has been known since the early 1960s as Niemann-Pick disease types A and B (NPA and NPB). However, it has become apparent over the last decade that there is a wide clinical spectrum of disease caused by the deficiency of the lysosomal enzyme acid sphingomyelinase (ASM).

Patients at the severe end of the spectrum (NPA) have a very rapidly progressive neurodegenerative disease usually resulting in death before the age of four. 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. A majority of NPB patients survive well into adulthood with little or no neurological involvement. Progressive pulmonary infiltration is the major disease-related complication for most patients, whilst the haematological effects of hypersplenism can also be severe, as can liver-related illness.

ASMD is inherited in an autosomal recessive manner with more than 100 published mutations having been identified. Currently there is no therapy for ASMD but clinical trials of enzyme replacement therapy are ongoing for those with the type B phenotype.

Because of the severity and complexity of ASMD it is important that patients are managed at specialist centres (see page 19) for inborn errors of metabolism 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. With continued efforts it is hoped that future research will lead to treatments and a cure. International research is in progress towards the development of therapies that could play a huge role in fighting this disease.



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# Acid sphingomyelinase deficient disease in summary

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Acid sphingomyelinase deficient disease (ASMD) is a rare autosomal recessive inborn error of metabolism that leads to the accumulation of sphingomyelin in cells and tissues and causes the clinical disorder known as Niemann-Pick disease (NPD) types A and B.<sup>1</sup>

Meikle (1999) estimates the incidence in newborns as being between 0.4 in 100,000 to 0.6 in 100,000<sup>2</sup>, although this is likely to vary widely among different populations. Historically, two distinct subtypes have been described on the basis of their phenotypes (types A and B).

**Type A** disease, which has an Ashkenazi Jewish predilection, 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**, which is pan ethnic, is characterised by hepatosplenomegaly, thrombocytopenia, interstitial lung disease and dyslipidaemia with most patients having little or no neurological involvement.<sup>3</sup>

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

The diagnosis of NPD type B is usually made in childhood after organomegaly is noted and it is common for individuals to survive well into adulthood. Treatment is, as yet, not available for ASMD although the first clinical trials of enzyme replacement therapy for type B have been completed, following promising results in an ASM knockout mouse model.<sup>5</sup> Gene therapy may also be a potential route for treatment.<sup>6</sup>

The following classifications are taken from Dr Margaret McGovern's presentation at the NPDG(UK) conference in 2007.

## NPD type A

### Consistent clinical findings and a stereotypical course

- massive organomegaly
- eye findings
- lung disease and infections
- cholesterol abnormalities
- rapid, progressive, neurologic disease
- failure to thrive
- death by the age of four

## NPD type B

### ASM deficient patients surviving early childhood: more variability

- eye findings in 34 per cent
- retinal findings were not a reliable predictor of the presence or severity of neurologic findings
- evidence of neurological involvement in 28 per cent
- progressive neurologic disease in less than 10 per cent
- most common findings are hypersplenism and dyslipidaemia
- progression lung disease occurs in most

### Variant patients

- disease symptoms ranged from severe to moderate
- initial development is normal
- neurological difficulties beginning between 18 months of age to seven years
  - language delay
  - unsteady gait
  - cognitive decline
- intellectual quotients ranged from 40 to 68

## The history of Niemann-Pick disease

### Types and nomenclature

In 1914 a German paediatrician Albert Niemann (1880–1921) described a young child with brain and nervous system impairment and hepatosplenomegaly.<sup>7</sup>

Ludwig Pick (1868–1944) studied tissues after the death of children who exhibited similar symptoms and provided evidence of a new disorder distinct from the lipid storage disorders which had been described previously.

In 1958, Crocker and Farber published a case series on patients with varied presentations of Niemann-Pick disease based on the presence of 'foam cells' (lipid laden macrophages) and increased tissue sphingomyelin.<sup>8</sup>

Because their patients included children with characteristic neurological symptoms as well as children showing little or no neurological symptoms, Crocker later characterised Niemann-Pick into four separate categories based on biochemical and clinical criteria.<sup>9</sup>

### Categories of Niemann-Pick disorders

**Group A** (ASMD-NPA) included patients with classic neurodegenerative disease leading to death in early infancy.

**Group B** (ASMD-NPB) included those showing organomegaly without nervous system involvement.

**Group C** (NPC) showed slowly progressive neurological illness.<sup>9</sup>

**Group D** (previously known as NPD) closely resembled group C except that



Group D is no longer regarded as a separate sub-type as it is biochemically and clinically indistinguishable from NPC. Importantly though, it was noted that non-neural tissues in NPC and NPD patients had relatively less sphingomyelin and more cholesterol storage compared with NPA and NPB. More recent research has shown that this was a highly relevant observation as it reflects the substantial differences in the underlying biochemical defect and pathophysiology of NPC compared with NPA and NPB.

In 1966 Kanfer et al. demonstrated that the primary biochemical defect in NPA and NPB (but not NPC) was severe generalised acid sphingomyelinase deficiency.<sup>10</sup>

This early finding, coupled with the observed accumulation of multiple complex glycosphingolipids in NPC (i.e. not only sphingomyelin) indicated that NPC should be considered as a separate entity from NPA and NPB. In 1982 an expert consensus decision was taken in Prague to formally separate NPC from types A and B.<sup>11</sup>

## The genetics of ASMD

### Regional mapping of the human ASM gene

In 1991 researchers identified the location of the ASM gene to the chromosomal region 11p15.1 to p15.4.<sup>12</sup>

Although a number of other sphingomyelinases and related phospholipases have been identified, these molecular studies identified only a single locus for human ASM – the SMPD1 gene – indicating the absence of homologous coding sequences and pseudo genes elsewhere in the genome. In addition, genomic Southern blotting experiments were consistent with a single ASM gene.

### The molecular genetics of ASM

Intron-exon junctions in the human SMPD1 gene					
Exon number	Exon size (NT)	Codons	5' donor splice site	Intron size (NT)	3' acceptor splice site
1	398	1-104	AG g <u>tgagc</u> (D1)	464	cag <u>A</u> (A1)
2	773	105-362	AG g <u>tactt</u> (D2)	1059	cag <u>A</u> (A2)
3	171	362-419	<b>AA</b> g <u>tgagg</u> (D3)	228	<u>t</u> ag G (A3)
4	77	420-446	AG g <u>tagga</u> (D4)	201	cag G (A4)
5	145	446-494	<u>T</u> G g <u>tgagt</u> (D5)	153	cag G (A5)
6	778	495-630			

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.<sup>1</sup> In an early study by Schuchman and Desnick there were eighteen published mutations.<sup>1</sup>

Of these, seven occurred in exon 2, three in exon 3, one in exons 4 and 5, five in exon 6, and one in an intronic splice site. There were 11 missense and two nonsense mutations. Of the three frameshift mutations, one was caused



by an in-frame 3-base deletion that led to the removal of a single amino acid, while the other two were caused by single base pair alterations.<sup>1</sup>

In 2010, the Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff listed 130 reported mutations.<sup>13</sup>

Mutation type	Number of mutations	Main references
<b>Missense/nonsense</b>	84	Pittis (2004) <sup>14</sup> Simonaro (2002) <sup>15</sup> Ricci (2004) <sup>16</sup> Dardis (2005) <sup>17</sup> Pavlu-Pereira (2005) <sup>18</sup> Takahashi (1992) <sup>19</sup> Sikora (2003) <sup>20</sup>
<b>Splicing</b>	1	Levrán (1993) <sup>22</sup>
<b>Small deletions</b>	16	Sikora (2003) <sup>20</sup> Pittis (2004) <sup>14</sup> Takahashi (1992) <sup>19</sup> Gluck (1997) <sup>21</sup> Ricci (2004) <sup>16</sup> Simonaro (2002) <sup>15</sup> Levrán (1993) <sup>21</sup> (1991) <sup>23</sup> Dardis (2005) <sup>17</sup> Pavlu-Pereira (2005) <sup>18</sup>
<b>Small insertions</b>	5	Ricci (2004) <sup>16</sup> Pittis (2004) <sup>14</sup> Simonaro (2002) <sup>15</sup> Ida (1996) <sup>24</sup>
<b>Public Total</b> (HGMD Professional 2008.4 total)	<b>106</b> (130)	

## Patterns of inheritance

ASMD 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. For most inherited metabolic diseases the phenotype of a particular inherited mutation (i.e. age of onset and profile/severity of symptoms) usually runs consistently within families.<sup>25</sup>

In each pregnancy of a carrier couple, there is a 25 per cent chance that they will both pass their non-functional mutant ASMD genes to a child, who would then be affected. There is a 50 per cent chance that only one of them would pass on a non-functional gene, making the child a heterozygote carrier like the parents. There is a 25 per cent 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 ASMD allele. Furthermore, each sibling of an affected individual's parents is at 50 per cent risk of being a carrier.

## Carrier detection and genetic counselling

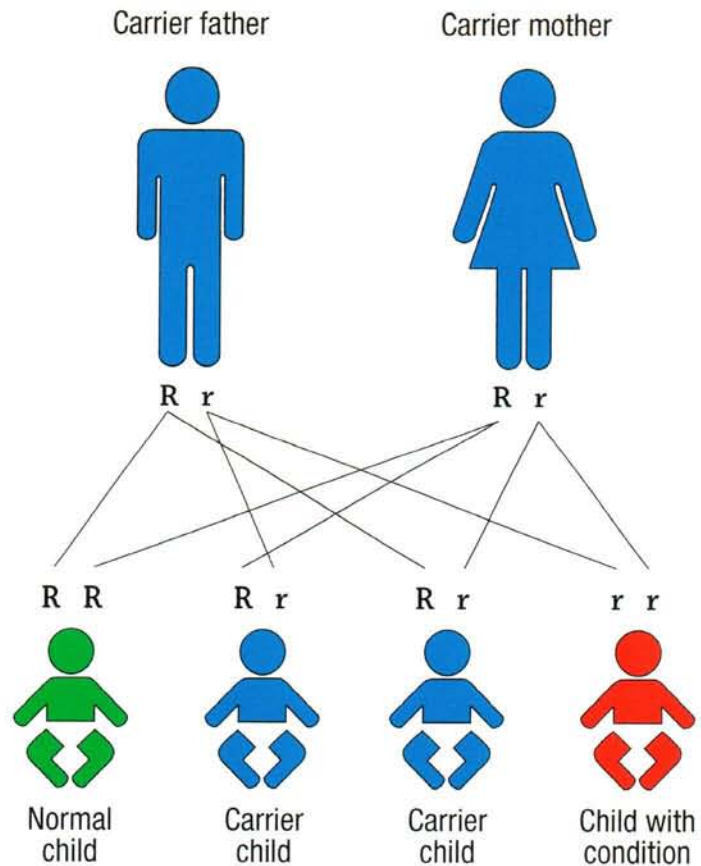
Biochemical testing cannot be relied upon to identify individuals who are heterozygous for ASMD mutations (carriers), because test results are similar to those seen in controls. Molecular analysis of the SMPD1 gene can be used to identify carriers if the mutations have been found in an identified, affected, family member.

Genetic counselling provides individuals and families affected by ASMD 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. The optimal time to determine genetic risk, clarify carrier status and discuss the availability of prenatal testing is before pregnancy.

## Genetic prenatal testing

Prenatal testing is provided to pregnant women where there is a 25 per cent risk of ASMD in the foetus. The most common way of doing prenatal testing is direct enzyme assay on uncultured CVB. In families where the mutations are known, molecular analysis of foetal cells can be diagnostic or confirmatory.

## Autosomal recessive inheritance



## Genotype/phenotype correlation

In 2002, a team at Mount Sinai Hospital in New York carried out a study of the demographics, distributions and mutations in NPB. Mutation analysis was carried out on 228 NPB patients. One mutation, A196P, was identified in patients with Scottish heritage in the United States, the United Kingdom and Canada. It was noted that where a patient carried only one copy, even alongside a null mutation, they had the adult form following an attenuated course. Three other mutations, (L137P, R474W, R600H) were also thought to be consistent with the milder end of the clinical spectrum of the disease. The most common type B mutation in North America and Western Europe is due to a small three base deletion in the SMPD1 gene, called  $\Delta R608$ .

In contrast H421Y, which occurred on more than 70 per cent of type B alleles in patients from Saudi Arabia, was associated with an early onset severe form of NPB.<sup>26</sup>



# Diagnosis

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## Clinical diagnosis

The relative rarity in frequency of different types of ASMD means that diagnosing the disease requires doctors and physicians to be aware of a number of symptoms and factors.

### Type A

Patients with type A present with hepatosplenomegaly, feeding problems and failure to thrive in early infancy, with the early organomegaly being apparent in the first few months of life.

By 3–6 months neurological involvement may be noted and developmental delay and/or loss of developmental milestones should alert physicians. About 50 per cent of babies with type A have macular cherry-red spots.

### Type B

In type B the first indicator is splenomegaly which is usually noted in childhood. However, because this may be very subtle in mild cases it may not be detected until adolescence or adulthood. In some patients respiratory disease with a gradual decline in respiratory function may be the most prominent symptom.

The presence of characteristic foam cells in bone marrow aspirates supports the diagnosis but as similar cells are seen in other lysosomal storage disorders (LSDs) including NPC all suspected cases should be confirmed by enzymatic studies.

## Enzymatic diagnosis

ASMD is readily diagnosed by the markedly deficient activity of acid sphingomyelinase in peripheral leucocytes or cultured skin fibroblasts.

In contrast, patients with type C often have mildly elevated ASM levels and those with Gaucher and other storage disorders presenting with hepatosplenomegaly and/or neurological problems would have normal or near normal levels.

In general, residual ASMD activity in type A and type B ranges from less than one per cent to about ten per cent of normal, with type B patients generally having higher levels, but this is not a reliable predictor of phenotypic severity.

There is also a significant overlap between normal and heterozygote enzyme activity levels and so enzymatic studies alone are not reliable for carrier detection.<sup>1</sup>

## Molecular diagnosis

The R496L, L302P and fsP330 mutations account for about 92 per cent of the mutant alleles in Ashkenazi Jewish type A patients which leads to rapid identification of molecular lesions in this population.

In non-Jewish type A and type B patients there is a tendency to unique mutations with the exception of  $\Delta R608$ .

In families in which the mutations have been identified family members can be accurately tested for carrier status by DNA analysis.



# Pathophysiology

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## 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 man-nose-6 phosphate residues on N-linked oligosaccharide side chains. Small amounts of enzyme are released from cells into the circulation but importantly, ASM needs zinc for full activity and inside the lysosome the enzyme is fully saturated with this cation. The secreted form is not fully saturated with zinc but 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 is a major constituent of membrane raft structures.<sup>27</sup>

## Splenomegaly

The spleen is an organ found in virtually all vertebrate animals with important roles in regard to red blood cells and the immune system. In humans, it is located in the left upper quadrant of the abdomen. It removes old red blood cells and holds a reserve of blood in case of haemorrhagic shock while also recycling iron. It synthesises antibodies and removes antibody-coated bacteria along with antibody-coated blood cells. In addition, the spleen has been found to host half of the body's circulating monocytes. These monocytes, upon moving to injured tissue, turn into more specialised cells and macrophages while promoting tissue healing. Finally it is one of the centres of activity of the reticuloendothelial system and can be considered analogous to a large lymph node, as its absence leads to a predisposition toward certain infections.

In a normal adult the spleen is about 11cm long and weighs about 150g. In patients who have ASMD storage there is a massive enlargement of the spleen. Recently, the spleen of a young adult was removed during surgery and weighed 2.5kg. This has an impact on digestion and breathing and can cause considerable discomfort.

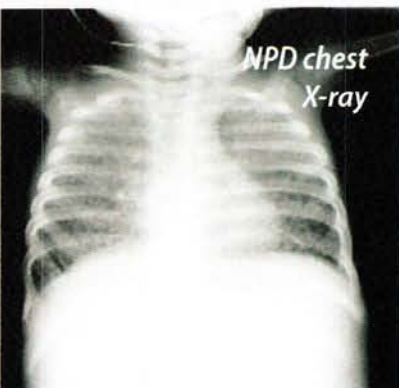
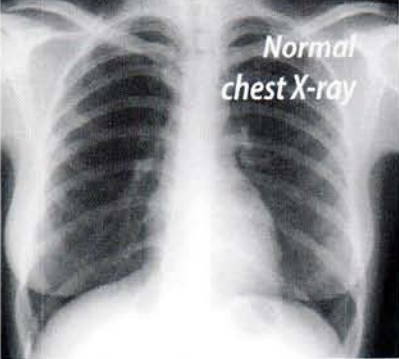
## Pulmonary disease in ASMD

These notes are taken from a presentation by Dr Margaret McGovern at the NPDG(UK) conference in 2007.

Pulmonary disease was a consistent finding in affected patients. Its severity varies widely. Most symptomatic patients are adults but severely affected children can also have clinically significant pulmonary disease. It is caused by storage of sphingomyelin in the lung.

In 2004 Buccoliero et al. noted that, in the ASM mouse model of NPA, levels of the primary storage material, sphingomyelin, were elevated as expected, and levels of other phospholipids were also significantly raised in the pulmonary surfactant and in lung tissue of 5–7 month old mice. These results suggested





that changes in the phospholipid levels and composition in lung surfactant may be a general feature of sphingolipids storage diseases. They may also in part be responsible for the susceptibility of these patients to respiratory infections.<sup>28</sup>

The slides of X-rays show examples of sphingomyelin storage causing interstitial lung disease (ILD).

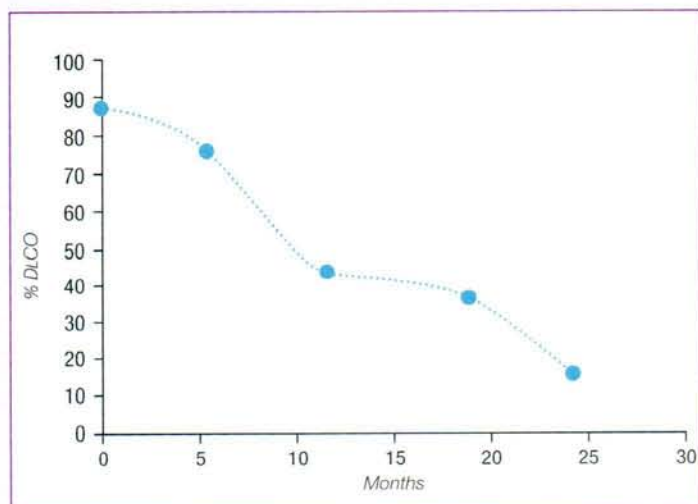
## Lung function and respiratory symptoms

In 2004 Wasserstein, McGovern et al. carried out a longitudinal study into the natural history of NPD type B.<sup>29</sup>

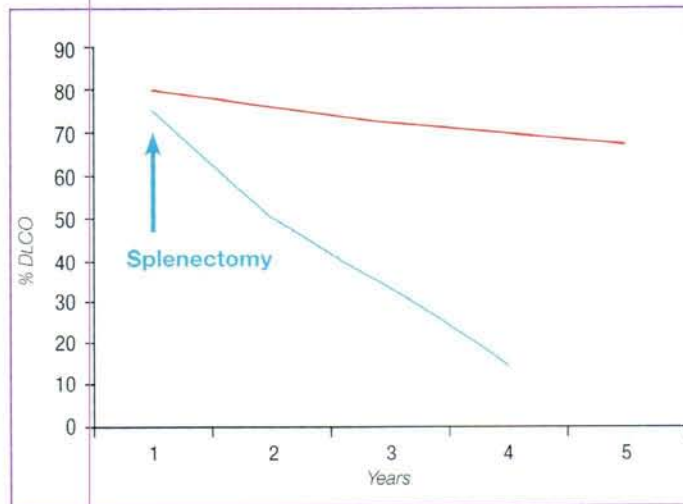
This study featured 53 patients aged between seven and 65. The patients all had chest X-rays, high-resolution chest CT scans (HRCT) and were then assigned a score for interstitial lung disease (ILD). Pulmonary function tests were also performed.

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.

These graphs represent findings related to the effect of splenectomy on lung function.<sup>30</sup>



**Left: Lung function in a splenectomised patient**



**Right: Lung function over time: splenectomised vs non-splenectomised patients**

## Treatment of interstitial lung disease (ILD)

- medication
  - steroids to help decrease inflammation. The response to treatment is related to the amount of inflammation present
- 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

## Other therapies: lung lavage cases

Two of many of the research studies which have been published illustrating conflicting opinions:

### Lung lavage in a child with NPD<sup>31</sup>

- 15-month-old child
- normal development
- respiratory symptoms
- left lung lavage
- no improvement
- succumbed

### Whole lung lavage in an adult<sup>32</sup>

- 48-year-old man with coronary artery disease
- treated with steroids with some improvement in pulmonary function tests
- whole lung lavage resulted in modest increases in oxygen in the blood
- alive for three years post-lavage but no long-term pulmonary follow-up reported
- discussed with author of paper and patient has moved abroad so no follow-up available

## Effects on lipid profile

In the cross-sectional study it was found that most patients had atherogenic lipid profiles and low high-density lipoprotein (HDL) was the most characteristic lipid abnormality. Of the patients studied, 74 per cent had this pattern and it was also found that 41 per cent had high total cholesterol levels, 62 per cent had high triglycerides, 46 per cent had high low-density lipoprotein level (LDL) and 62 per cent 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 had a splenectomy had a mean cholesterol/HDL ratio almost twice as high as those with intact spleens.



## Mean lipid values for male and female patients with types A and B NPD

		Male, mean (mg/dL)/(SD)	Female, mean (mg/dL)/(SD)	Desirable <sup>7</sup> (mg/dL)	Abnormal <sup>7</sup> (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)		

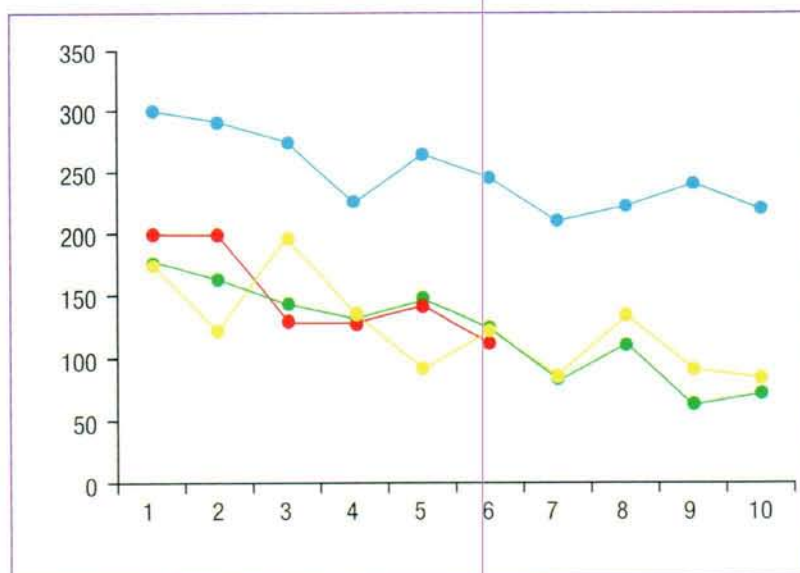
McGovern et al. concluded that lipid abnormalities are part of the phenotype in types A and B NPD and may be associated with early atherosclerotic heart disease.<sup>33</sup>

## Haematological problems

Bleeding is a frequent problem in patients with ASMD. In the study carried out by Dr McGovern and her team, 49 per cent of the patients had some bleeding problems.<sup>3</sup>

Most bleeding problems (29 per cent) were related to epistaxis or nose bleeds. In two patients these required repeated cauterisations and the case study on page 23 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 with their peers.



*Platelet counts over time in four patients (Normal range 150–450)*

## Bone problems

The association of bone problems with NPD was investigated and documented in a study by Dr Margaret McGovern and her team and presented at the NPDG(UK) conference in 2007.

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

### Normal bone metabolism

Bone is a living, growing tissue that turns over at a rate of about ten per cent a year. It is made up of collagen, a protein that gives the bone its strength and framework, and calcium phosphate that hardens the framework. Throughout life old bone is constantly being removed through resorption (the natural absorption of small amounts of bone by the body) and replaced by the formation of new bone. During early childhood and in the teenage years, new bone is added faster than old bone is removed and bones become larger, heavier, and denser. Bone formation happens faster than bone resorption until you reach your peak bone mass in your twenties. After that, bone resorption slowly begins to happen faster than bone formation.

### Problems with bone density

Osteoporosis, or porous bone, is a disease characterised by low bone mass. This means you may be more likely to get fractures particularly of the hip, spine, and wrist. Osteoporosis develops when bone resorption occurs too rapidly and bone formation fails to keep up.

### Bone resorption and formation

**Osteoclasts** are large cells that dissolve the bone. They are present in bone marrow and are related to white blood cells. It is possible to estimate osteoclast activity with certain blood tests that measure substances that result from collagen breakdown.

**Osteoblasts** are the cells that form new bone. They are also present in bone marrow. You can estimate osteoblast activity by measuring certain chemicals including bone-specific alkaline phosphatase and osteocalcin.

### How to measure bone density: DEXA scan

A DEXA scan is a special kind of X-ray of the bones. It provides a 'T score' which measures your bone density compared with what is normally expected in a healthy young adult of your gender.

For children a Z score is also used which shows how far the score falls above or below what is normally expected for someone of the same age, sex, weight and ethnic or racial origin. The Z score is also useful in young adults because it can help determine whether factors other than ageing might be causing bone loss.



## Preliminary results of the bone study

Results of studies show that osteoporosis is common among people with NPD. In one study, six adults were examined. Three had osteoporosis, two had osteopenia and one was rated as being normal for their age. Fifteen children were also studied, of whom eleven had osteoporosis and four had normal bone density for their age. All of the patients with abnormal DEXA scan results showed increased blood markers of osteoclast activity.

An unusual case was reported in 2002 in Belgium. A 55-year-old woman presented with a clinical picture of Parkinson's disease, severe back pain, splenomegaly and severe dyspnoea. X-rays indicated multiple vertebral fractures. She had markedly reduced sphingomyelin activity and was homozygous for deletion of codon 608 ( $\Delta R608$ ). Because of the patient's severe fractures she was screened for additional polymorphisms. It had previously been noted that polymorphisms were possibly associated with an increased risk of osteoporosis and several fractures were found.<sup>34</sup>

## Growth

Most children with ASMD have delayed growth. This is particularly noticeable in adolescence and can be the problem which causes 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  $\Delta R608$  mutation had normal height and weight, markedly less hepatosplenomegaly and bone age delay, and normal IGF-1 levels.<sup>35</sup>

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 who worry about whether they will grow to average height.

# Epidemiology

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## Incidence and prevalence

Although ASMD is pan ethnic, it is well documented that ASMD type A occurs more frequently among those of Ashkenazi Jewish origin. The carrier frequency in this population is estimated to be about 1:80 suggesting a disease frequency of 1 in 40,000. To put this into context the pan ethnic frequency is between 0.4 in 100,000 to 0.6 in 100,000 in newborns.<sup>2</sup> However, it must be noted that since no population-based screening programs have been undertaken for this disorder, the true frequency remains unknown.

There is documented evidence of lipid storage in NPD foetuses with type A having a higher frequency of spontaneous abortion. This means that the true incidence of type A may be higher than reported.

The incidence of type B in the Ashkenazi Jewish population is significantly less than that of type A. Among non-Jewish ASMD patients, the type B form is more prevalent but accurate estimates for frequency are unavailable. It is thought that because many type B patients have mild symptoms, the frequency of type B is likely to be higher than that quoted in literature.<sup>1</sup>

## Potential therapies

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Further information relating to therapies can be found in *The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease* (Schuchman, 2007).<sup>27</sup>

### 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 were similarly severe in others. 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, given the severe transplant related complications, this needs careful consideration.

### Splenectomy

Another approach has been a partial or full splenectomy. There is no documented rationale for this but it is possibly due to pain and/or the risk of splenic rupture. 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. Post-splenectomy there seems to be increased pulmonary storage and a faster progression and severity of pulmonary disease.



## Pulmonary lavage

This is discussed on page 13 but the general opinion is that these procedures only seem to have a temporary effect on pulmonary function. Over time inflammatory cells are likely to repopulate the airways and symptoms become as bad or even worse.

## Enzyme replacement therapy

Enzyme replacement therapy (ERT) is seen as the gold standard for achieving widespread delivery of enzyme to clinically affected organs. Recombinant human ASM (rASM) was produced in Chinese hamster ovary cells and extensively characterised. It was used to treat the knockout mouse model and overall, when administered intravenously into young mice, lipid storage could be prevented in RES organs. Progressive inflammatory disease was also prevented in these organs. Effects of the enzyme were dose dependant and most profound in the liver and spleen, followed by the lung. Despite showing marked improvement in RES organs there was no effect on the progression of neurological disease.

Phase 1 of the ERT clinical trials have now been completed at Mount Sinai to evaluate product safety.

## 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 which contained the full-length SMPD1 cDNA. These were used to transduce knockout bone marrow cells and were then transplanted into partially irradiated litter mates. 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 this over HSCT is that the patient's own bone marrow might be used and could potentially make toxic preconditioning unnecessary.

### Small molecule approaches

Substrate reduction therapy has been evaluated for other lysosomal storage disorders (LSDs) using inhibitors of glycolipid synthesis. The rationale is that glycolipids are primary or secondary storage products in many LSDs and prevention or slowing of synthesis may improve the lipid storage phenotype. Preliminary studies in the knockout mouse show little effect on progression of neurological disease.

Inhibitors of sphingomyelin (SPM) synthesis have also been considered to achieve substrate reduction. There are two potentially negative consequences in using sphingomyelin inhibitors. Slowing the synthesis of SPM might lead to increased intracellular ceramide levels and ceramide is a pro-apoptotic lipid that is generally toxic to cells. Also, SPM is an important structural component of cell membranes and reducing it may have profound effects on the structural integrity of cells.

## Molecular chaperones

Small molecule chaperones that are usually competitive inhibitors of the enzyme can be used to prevent degradation and enhance the residual activity of mutant enzymes. The chaperone is only effective in disorders where the mutation leads to misfolding of the enzyme protein and so this depends on the type of mutation. The principle of this approach has been proven in other lysosomal storage disorders but none have been licensed for use in clinical practice.

## Co-factor zinc supplementation

ASM requires zinc for full activity. It is thought that some mutations in ASMD patients might limit zinc binding to the mutant proteins. This approach was evaluated using cells from ASMD patients who were homozygous for several common mutations. Some enhancement of residual enzyme activity was seen but this might have been due to some general effect of zinc supplementation as opposed to any direct effect of zinc on the enzyme.

## Specialist centres

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### Mount Sinai School of Medicine, New York

The International Center for ASMD types A and B Niemann-Pick disease was established to provide information and support for patients diagnosed with these disorders, as well as interested scientists and physicians. It is a voluntary, not-for-profit organisation whose primary goals are to:

- promote medical research into the cause and treatment of types A and B NPD
- provide medical and educational information to assist in the correct diagnosis and referral of children with NPD
- provide support to families of children with NPD
- facilitate genetic counselling for parents who are known carriers of NPD
- encourage the sharing of research information among scientists

All NPD patients are encouraged to visit Mount Sinai's General Clinical Research Center (GCRC) to be evaluated by a team of NPD experts. Generally, this involves a two- to three-day stay in the GCRC, which is a special unit of the hospital designed for such clinical studies. Hospitalisation and other medical costs for these visits are free for US patients. (Courtesy of the NNPDP website)



## Contact details

Department of Genetics and Genomic Sciences  
Mount Sinai School of Medicine  
1425 Madison Avenue  
New York, NY 10029  
w [www.mssm.edu/departments-and-institutes/genetics-and-genomic-sciences](http://www.mssm.edu/departments-and-institutes/genetics-and-genomic-sciences)  
t 212 241 6500

## National Commissioning Group centres in the UK

Most patients with ASMD NPA and B are seen at one of the seven nationally funded specialist centres for lysosomal storage diseases. Most patients will be seen annually and assessed for lung function, cardiac function, haematological status and bone parameters. As treatment is not as yet available, symptomatic therapy will be used as appropriate.

## National centres for lysosomal diseases in the UK

Full address details are in the resources section on page 26

- o **Birmingham:** Birmingham Children's Hospital (children only)
- o **Cambridge:** Addenbrooke's Hospital (adults only)
- o **London:**
  - Great Ormond Street Hospital (children only)
  - National Hospital for Neurology and Neurosurgery (adults only)
  - Royal Free Hospital (adults only)
- o **Manchester:** Department of Genetic Medicine, St Mary's Hospital (children only)
- o **Salford:** Salford Royal Hospital Foundation Trust Hope Hospital (adults only)

## A call to action

### The Patient Association's view

When a child or individual is diagnosed with Niemann-Pick types A or B (ASMD), it can adversely affect the whole family. Due to the rarity of the condition, the path to this diagnosis can often be a difficult one. As health and social care services vary around the country, families can feel bewildered and isolated due to conflicting advice and a lack of clear information.

During this period of adjustment, families begin to contemplate their future, and how the disease might affect their loved one. To assist them in understanding the nature of the disease, they need a supply of accurate information which they can easily relate to.

At this point, families face a constant round of appointments with the long list of professionals that will now be involved in caring for their loved one. As the condition is so rare, they will invariably have to tell their story time and time again; this in itself can be extremely difficult.



As the disease progresses, families can struggle to cope with the emotional and financial implications of the condition and, as a result of this, the quality of family life can be severely affected.

In the UK, the Niemann-Pick Disease Group (NPDG(UK)) aims to make a difference to those affected by acid sphingomyelinase deficiency (ASMD) Niemann-Pick disease through the provision of care and support, accurate information and the promotion of relevant research. The group gives emotional, as well as practical support and has developed a strong family support network, helping to reduce feelings of isolation and despair.

Working in collaboration with patient groups across the world, NPDG (UK) hope to raise awareness of the disease, its presentation, signs and symptoms. Through the sharing of information and resources NP patient associations have created a valuable source of information for professionals. It is hoped that this information will be used to further develop services for those affected and to stimulate research that will improve understanding of the condition and help with therapy development.

Research is vitally needed to provide much needed data about this condition. The NPDG (UK) is active in promoting, and where possible funding, research that will improve understanding and lead to the development of future therapies. Clinical trials are currently taking place, both into the causes of the disease and potential treatments. The NPDG (UK) would like to ensure that, in the future, families affected by ASMD Niemann-Pick types A and B could be given the hope of a treatment – or even a cure – for this potentially life-limiting condition.

## Social and psychological impact

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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 this subject 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 disease groups. The following draws on the excellent work she has produced in covering this topic.<sup>36</sup>

### *Extract from Psychological aspects of patients with Niemann-Pick disease (Henderson, 2006)*

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. 17 patients over the age of 13 were interviewed.

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

- all participants identified limited physical activity, social isolation and peer rejection as significant stressors
- these stressors had a specific impact during the age span of 10–16 years
- parents and adult patients expressed significant frustration regarding the lack of information and treatment available



- patients described relying on close family relationships as a way of coping with the illness
- 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 the adolescent feels and how the parent thinks they feel, which is not unusual in this sort of survey.

Several parents did not realise how much their daughters had been hurt when they were teased about looking pregnant. Although most parents realise that their teenage child has concerns about their height this survey does show that it can have a massive impact on children. It is an age when most children are very sensitive about their appearance.

Many of the children also mentioned that when they were younger they did feel 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.

## The family perspective

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For parents and relatives of patients with Niemann-Pick the progress of the disease, 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 types A and B relate their experiences of the disease and the effects on their children.

### Case study 1: a girl, two and half-years-old

I am the grandparent of a child who passed away. She was 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. This was their first and only child. From the beginning 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. Her DNA was tested and still no type could be determined. So all we could go by was that she was meeting her milestones at that point.

But at about 13 months she stopped developing. At this point she didn't go backwards, just nothing new. She got to walking by holding on to things and she was able to hold a cup and feed herself. The only word she could say was 'Hi'. All through this time she would get colds and her constipation was horrible. She would take Miralax but that would cause her stomach pains and bad gas sometimes.





In March she got 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, including at night.

By October she was hospitalised with mono [glandular fever] and was in horrifying pain. She was in hospital for five weeks and in that time she also got 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. The hospice helped us get her home. After that she stopped being able to digest any food and after six days she passed away. There is so much more to her life that I would love to tell you about.

### Case study 2: 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 so good on an X-ray, but they appear to be functioning OK.

His bones are very weak and his muscle tone is poor. He struggles walking. About five minutes is the maximum time he will 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 3: 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 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.





# Support

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## The role of patient associations

ASMD can be a devastating condition that impacts upon the entire family. Medical therapy aside, support in terms of advice and education for both the patient and family throughout the course of ASMD is vital. If possible, counselling services should be made available to the whole family. Patient-centred umbrella organisations offer information at an international level, while national patient associations now offer information and counselling within many countries.

Patient associations provide information about specialist services to professionals, patients with ASMD and the public, and most provide at least basic educational material. Many patient associations also actively participate in fund-raising for the support of medical therapy and research in ASMD. A list of support organisations is provided in the Resources section.

## Referral to specialist care centres

Specialist care centres (see page 19) 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 have important roles in disease auditing and the maintenance of geographical coverage. Metabolic nurse specialists play vital roles in the day-to-day running of clinics, and deal with many of the familial aspects of work with patients and family members. Physical therapists, physiotherapists, occupational therapists and disease counsellors should also all be involved in supportive care for patients.

A prime concern amongst voluntary, patient-focused, organisations is the need for increased awareness among general health practitioners regarding the symptoms, diagnosis and management of ASMD. In some cases, initial health services can do 'more harm than good' if there is a lack of any specialist knowledge or expertise. It has been estimated that less than half of patients with an inherited metabolic disease are currently being looked after through specialist care centres, partially due to a general reluctance to refer, but also through a lack of local resources.<sup>37</sup>

# Conclusion

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Parents and relatives often regard non-neurological ASMD Niemann-Pick disease as the best type of NPD to have, if you have any, as it is usually the type associated with prolonged survival.

Although most patients do not have neurological problems, the respiratory disease, haematological problems, bone disease and psychological effects can be quite severe. It is very important to monitor the course of the disease and offer interventions to minimise complications from respiratory, cardiac, haematologic and bone disease.

The disorder can be very heterogeneous which means that it is not uniform and can affect people in different ways.

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

As with many chronic disorders the support group can be very valuable. As well as allowing access to other families in a similar position, it provides parents and patients with literature which is pertinent to their needs.



# Resources

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## Support organisations

### **Niemann-Pick Disease Group (UK)**

11 Greenwood Close  
Fatfield  
Washington  
NE38 8LR  
w [www.niemannpick.org.uk](http://www.niemannpick.org.uk)  
t 0191 415 0693  
e [niemann-pick@zetnet.co.uk](mailto:niemann-pick@zetnet.co.uk)

### **The National Niemann-Pick Disease Foundation (USA) (NNPDF)**

PO Box 49  
401 Madison Avenue, Suite B  
Fort Atkinson, WI 53538  
w [www.nnpdf.org](http://www.nnpdf.org)  
t 1-877-287-3672 (toll free)  
t 1-920-563-0930 (office)  
f 1-920-563-0931  
e [nnpdf@nnpdf.org](mailto:nnpdf@nnpdf.org)

### **Children Living with Inherited Metabolic Diseases (CLIMB)**

Climb UK  
Climb Building  
176 Nantwich Road  
Crewe  
CW2 6BG  
w [www.climb.org.uk](http://www.climb.org.uk)  
t 0800 652 3181  
e [info.svcs@climb.org.uk](mailto:info.svcs@climb.org.uk) (general)  
e [fam.svcs@climb.org.uk](mailto:fam.svcs@climb.org.uk) (family services)  
e [cya.svcs@climb.org.uk](mailto:cya.svcs@climb.org.uk) (children and young people's services)  
e [ir.svcs@climb.org.uk](mailto:ir.svcs@climb.org.uk) (information research)

## Other resources

[www.niemannpick.org.uk/care\\_and\\_support/useful\\_resources.html](http://www.niemannpick.org.uk/care_and_support/useful_resources.html)

## Specialist centres in the UK

### **Birmingham**

Birmingham Children's Hospital  
St Chads  
Queensway  
Birmingham  
B4 6NH  
t 0121 333 9999

## Cambridge

Addenbrooke's Hospital  
Cambridge University Hospitals NHS Foundation Trust  
Hills Road  
Cambridge  
CB2 0QQ  
t 01223 245151  
w [www.cuh.org.uk/addenbrookes/addenbrookes\\_index.html](http://www.cuh.org.uk/addenbrookes/addenbrookes_index.html)

## London

Great Ormond Street Hospital  
UCL Institute of Child Health  
30 Guilford Street  
London  
WC1N 1EH  
t 020 7242 9789  
w [www.ich.ucl.ac.uk](http://www.ich.ucl.ac.uk)

The Royal Free Hospital  
Pond Street  
London  
NW3 2QG  
t 020 7794 0500  
w [www.royalfree.nhs.uk](http://www.royalfree.nhs.uk)

National Hospital for Neurology and Neurosurgery  
Queen Square  
London  
WC1N 3BG  
t 0845 155 5000  
w [www.uclh.nhs.uk](http://www.uclh.nhs.uk)

## Manchester

Department of Genetic Medicine  
St Mary's Hospital  
Oxford Road  
Manchester  
M13 9WL  
t 0161 276 1234  
w [www.cmft.nhs.uk/childrens-hospitals/home.aspx](http://www.cmft.nhs.uk/childrens-hospitals/home.aspx)

## Salford

Salford Royal Hospital NHS Foundation Trust  
Stott Lane  
Salford  
M6 8HD  
t 0161 789 7373



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# Glossary of terms

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<b>Acid sphingomyelinase (ASM)</b>	Lysosomal enzyme that breaks down a substance called sphingomyelin. This enzyme is defective to a greater or lesser extent in ASMD
<b>ASMD</b>	Acid sphingomyelinase deficient disease (formerly known as Niemann-Pick disease types A and B)
<b>Allele</b>	A particular form of gene. Alleles occur in pairs, one on each chromosome inherited from each parent
<b>Autosomes</b>	Any chromosome other than the sex chromosomes
<b>Cation</b>	The ion in an electrolyte which carries a positive charge
<b>Chaperone</b>	A protein that aids in the folding of a second protein. The chaperone prevents proteins from taking conformations that would be inactive
<b>Dyslipidaemia</b>	Abnormal lipids
<b>ERT</b>	Enzyme replacement therapy
<b>Hepatosplenomegaly</b>	Enlarged liver and spleen
<b>Heterogeneous</b>	Consisting of diverse or dissimilar parts; having non-uniform structure or composition
<b>Heterozygous</b>	An individual is heterozygous at a locus if (s)he has two different alleles at that locus
<b>Homozygous</b>	An individual is homozygous at a locus if (s)he has two identical alleles at that locus
<b>ILD</b>	Interstitial (occurring between other structures) lung disease
<b>Ion</b>	Strictly, any atom or molecule which has a resultant electric charge
<b>Knockout mouse model</b>	Niemann-Pick mouse created by destroying the NP gene
<b>Lipids</b>	Oils, fats, waxes and related products found in living tissues
<b>Lysosome</b>	Sac-like intracellular organelle that contains various hydrolytic enzymes
<b>Macula</b>	Small yellow area seen on examination of the retina
<b>Mutation</b>	Change in the genetic material of an individual
<b>NPA</b>	Niemann-Pick type A



<b>NPB</b>	Niemann-Pick type B
<b>NPD</b>	Niemann-Pick disease
<b>Organomegaly</b>	Enlarged organs
<b>Phenotype</b>	The observable characteristics of an individual determined by interaction of genotype and environment
<b>Phospholipids</b>	Compound fat molecule in which there are two fatty acids and a phosphate group attached to glycerol
<b>Platelets</b>	Disc-like components in blood which play an important role in clotting
<b>Polymorphisms</b>	The occurrence in a population (or among populations) of several phenotypic forms associated with alleles of one gene or homologues of one chromosome
<b>Proband</b>	The person through whom a pedigree was discovered
<b>Reticuloendothelial system (RES)</b>	Mammalian defence system against foreign bodies, consisting of macrophage cells located in the lymph nodes, liver spleen and bone marrow
<b>Sphingomyelin</b>	Phospholipid composed of a long chain base, sphingosine, a long chain fatty acid and phosphocholine
<b>Splenectomy</b>	The removal of the spleen
<b>Splenomegaly</b>	Enlargement of the spleen
<b>Thrombocytopenia</b>	A low platelet count



**Niemann-Pick**  
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