U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Wasserstein MP, Schuchman EH. Acid Sphingomyelinase Deficiency. 2006 Dec 7 [Updated 2015 Jun 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Acid Sphingomyelinase Deficiency

Melissa P Wasserstein, MD[1] and Edward H Schuchman, PhD[2]

Created: December 7, 2006; Updated: June 18, 2015.

Summary

Clinical characteristics

Acid sphingomyelinase (ASM) deficiency has been categorized in the past as either neuronopathic (Niemann-Pick disease type A [NPD-A]), with death in early childhood, or non-neuronopathic (Niemann-Pick disease type B [NPD-B]). While forms intermediate to these two extremes occur, all ASM deficiency that is not NPD-A is designated in this review as NPD-B, despite its wide range of manifestations and severity. The first symptom in NPD-A is hepatosplenomegaly, usually noted by age three months; over time the liver and spleen become massive. Psychomotor development progresses no further than the 12-month level, after which neurologic deterioration is relentless. A classic cherry-red spot of the macula of the retina, which may not be present in the first few months, is eventually present in all affected children. Interstitial lung disease caused by storage of sphingomyelin in pulmonary macrophages results in frequent respiratory infections and often respiratory failure. Most children succumb before the third year. NPD type B, later in onset and milder in manifestations than NPD type A, is characterized by hepatosplenomegaly with progressive hypersplenism and stable liver dysfunction, gradual deterioration in pulmonary function, osteopenia, and atherogenic lipid profile. Progressive and/or clinically significant neurologic manifestations occur infrequently. Survival to adulthood can occur.

Diagnosis/testing

The diagnosis of ASM deficiency is established by detection of either biallelic pathogenic variants in *SMPD1* or residual ASM enzyme activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts).

Management

Treatment of manifestations:

Author Affiliations: 1 Associate Professor & Director of Program for Inherited Metabolic Diseases Icahn School of Medicine at Mount Sinai, New York, New York; Email: melissa.wasserstein@mssm.edu. 2 Genetic Disease Foundation, Francis Crick Professor & Vice Chairman for Research of Genetics & Genomic Sciences Icahn School of Medicine at Mount Sinai, New York, New York; Email: edward.schuchman@mssm.edu.

- NPD-A. Physical and occupational therapy; feeding tube for nutrition and sedatives for irritability and sleep disturbance as indicated.
- NPD-B. Transfusion of blood products for life-threatening bleeding; supplemental oxygen for symptomatic pulmonary disease; treatment of hyperlipidemia in adults; adequate calorie intake.

Surveillance:

- NPD-A. Periodic assessments of nutritional status and gross and fine motor skills.
- NPD-B. Annual (or more frequent) assessments: growth in children and weight in all ages; changes in activity level; bleeding; shortness of breath; abdominal pain; neurologic function; liver enzymes, platelet count, and fasting lipid profile; pulmonary function and chest radiograph; dual-energy x-ray absorptiometry (DEXA) as indicated in those with osteoporosis.

Circumstances to avoid: NPD-B: Contact sports in those who have splenomegaly.

Genetic counseling

ASM deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if both *SMPD1* pathogenic variants in the family are known. Prenatal diagnosis for pregnancies at 25% risk is also possible by testing of ASM enzyme activity.

GeneReview Scope

Acid Sphingomyelinase Deficiency: Included Phenotypes
• Niemann-Pick disease type A (NPD-A) • Niemann-Pick disease type B (NPD-B) [1]

1. In this review, all forms of acid sphingomyelinase deficiency that are not NPD-A are designated NPD-B, recognizing that NPD-B encompasses a broad range of somatic and neurologic features of varying severity.

Diagnosis

Acid sphingomyelinase (ASM) deficiency has traditionally been categorized as either neuropathic or non-neuronopathic:

- **Neuronopathic.** Niemann-Pick disease type A (NPD-A), characterized by a brief period of normal development followed by a severe neurodegenerative course and death in early childhood
- **Non-neuronopathic.** Niemann-Pick disease type B (NPD-B)

However, forms intermediate to these two extremes occur as a continuum of neurologic findings in those who survive early childhood. In this review, all forms of ASM deficiency that are not NPD-A are designated NPD-B, recognizing that NPD-B encompasses a broad range of somatic and neurologic features of varying severity.

Suggestive Findings

NPD-A should be suspected in infants with the following clinical findings or results on newborn screening:

Clinical findings

- Hepatosplenomegaly
- Developmental delay
- Evidence of interstitial lung disease on chest radiograph

- Cherry-red maculae

NPD-B, as defined in this review, should be suspected in individuals with the following:

- Hepatosplenomegaly
- Interstitial lung disease
- Hyperlipidemia
- Thrombocytopenia

Results on newborn screening. At present, New York state is conducting a pilot newborn screening program for four lysosomal storage disorders, including NPD-A and NPD-B. Acid sphingomyelinase activity is measured in newborn dried blood spots using a high throughput multiplex tandem MS assay. Other states are considering implementation of newborn screening for NPD-A and B.

Acid sphingomyelinase deficiency cannot be diagnosed solely on clinical grounds.

Establishing the Diagnosis

The diagnosis of ASM deficiency is established by detection of either biallelic pathogenic variants in *SMPD1* on molecular genetic testing (Table 1) or residual ASM enzyme activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts).

Molecular testing approaches include **single-gene testing** and use of a **multigene panel**.

Single-gene testing. For individuals from populations in which common *SMPD1* pathogenic variants occur (e.g., individuals of Ashkenazi Jewish background with a severe neurodegenerative form of the disease suggestive of NPD-A, individuals of North African descent with NPD-B, or individuals from Chile, Saudi Arabia, and Turkey):

1. Perform targeted analysis for pathogenic variants.
2. If targeted analysis does not identify both pathogenic variants in individuals from these populations, sequence analysis of *SMPD1* is appropriate.

For individuals who are not in the populations discussed above:

1. Perform sequence analysis.
2. If no or only one pathogenic variant is identified, consider gene-targeted deletion/duplication analysis.

A multigene panel that includes *SMPD1* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Acid Sphingomyelinase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
SMPD1	Targeted analysis for pathogenic variants [3]	90% [4, 5]
	Sequence analysis [6]	>95% [7]
	Gene-targeted deletion/duplication analysis [8]	Unknown [9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Pathogenic variants included in a panel may vary by laboratory.
4. In NPD type A, three variants (p.Arg498Leu, p.Leu304Pro, p.Phe333SerfsTer52) account for approximately 90% of pathogenic alleles in the Ashkenazi Jewish population.
5. In NPD type B, the variant p.Arg610del may account for: almost 90% of pathogenic alleles in individuals from the Maghreb region of North Africa (i.e., Tunisia, Algeria, and Morocco); 100% pathogenic alleles in Grand Canaria Island [Fernández-Burriel et al 2003]; and about 20%-30% of pathogenic variants in the US.
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
7. Sequence analysis of the coding region may detect pathogenic variants in 95% of individuals with enzymatically confirmed ASM deficiency.
8. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
9. No deletions or duplications involving *SMPD1* have been reported to cause acid sphingomyelinase deficiency. While new deletion/duplication testing methods may identify such pathogenic variants in individuals who did not have a pathogenic variant identified by sequence analysis, the detection rate is unknown and may be very low.

Measurement of acid sphingomyelinase (ASM) enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts. Compared to controls, affected individuals typically have less than 10% residual enzyme activity [van Diggelen et al 2005].

Note: (1) Individuals with the *SMPD1* pathogenic variant p.Gln294Lys may have apparently normal enzymatic activity when artificial substrate is used [Harzer et al 2003]. (2) The level of residual enzyme activity is not a reliable predictor of phenotype. (3) As the diagnosis of acid sphingomyelinase deficiency can be confirmed through assay of enzyme activity performed on peripheral blood leukocytes, bone marrow examination or liver biopsy is not necessary to establish the diagnosis.

Bone marrow examination. Because of the bone marrow involvement in ASM deficiency, in many cases other specialists have performed bone marrow examination (and identified lipid-laden macrophages) prior to the suspicion of Niemann-Pick disease. Note that bone marrow examination is **not** necessary for diagnosis and should not be performed unless specific clinical indications are present.

Clinical Characteristics

Clinical Description

Although the phenotype of acid sphingomyelinase (ASM) deficiency occurs along a continuum, individuals with a severe early-onset form, which has historically been called Niemann-Pick disease type A (NPD-A), can be distinguished from individuals with later-onset and milder forms of the disease, referred to as Niemann-Pick disease type B (NPD-B) in this review.

Severe Early-Onset Form (NPD-A)

Hepatosplenomegaly. The first symptom in most children with NPD-A is hepatosplenomegaly, which typically is noted by age three months [McGovern et al 2006]. Non-neurologic findings include feeding problems, failure to thrive, gastrointestinal complaints (e.g., constipation, diarrhea, and vomiting), recurrent respiratory infections, persistently elevated transaminases, and irritability. Frequent vomiting can contribute to insufficient caloric intake.

The hepatosplenomegaly worsens with time; eventually, the liver and spleen become massive.

Pulmonary disease. Affected infants have evidence of interstitial lung disease on chest radiograph caused by storage of sphingomyelin in the pulmonary macrophages. Low pO_2 on arterial blood gas determination is usually found later in the disease course. Frequent respiratory infections are common and respiratory failure can be a cause of death.

Ophthalmologic findings. Fundus examination reveals retinal changes at the time of diagnosis in most children. The accumulation of lipid in the retinal ganglion cells results in a white ring of lipid-laden neurons encircling the red, ganglion cell-free fovea and appears as either a macular halo or a cherry-red macula, depending on the degree of opacity and diameter of the white annulus surrounding the fovea. Although a classic cherry-red spot may not be present early in the disease course, all children with NPD-A develop one with time.

Neurologic findings. The neurologic examination at the time of presentation can be normal except for slight hypotonia. Hypotonia is progressive and deep tendon reflexes are lost with time. Cranial nerve function remains intact.

Psychomotor development does not progress beyond the 12-month level for any domain and skills are lost with disease progression [McGovern et al 2006]. Developmental age usually does not progress beyond age ten months for adaptive behavior, 12 months for expressive language, nine months for gross motor skills, and ten months for fine motor skills.

Neurologic deterioration is relentless, and most children succumb before the third year.

Growth. Linear growth is within the normal range, whereas weight attainment declines in the first year of life.

NPD-B

In this review, all forms of ASM deficiency that are not NPD-A are designated NPD-B, recognizing that NPD-B encompasses a broad range of somatic and neurologic features of varying severity.

NPD-B, later in onset and milder in manifestations than NPD-A, is characterized by hepatosplenomegaly with progressive hypersplenism, worsening atherogenic lipid profile, gradual deterioration in pulmonary function, and stable liver dysfunction [Wasserstein et al 2004, McGovern et al 2008]. Individuals with acid sphingomyelinase deficiency who survive early childhood can have progressive and/or clinically significant neurologic manifestations.

Survival to adulthood can occur.

Hepatosplenomegaly. The degree of hepatosplenomegaly ranges from mild to massive. Those with significant organomegaly have hypersplenism with secondary thrombocytopenia. Infarction of the spleen can cause acute abdominal pain.

Liver enlargement is common. Many individual with NPD-B have elevated transaminases and some have histologic abnormalities ranging from hepatic fibrosis to frank cirrhosis [Thurberg et al 2012]. In rare instances, liver failure has required liver transplantation [McGovern et al 2013].

Pulmonary involvement. Pulmonary involvement is common in affected individuals of all ages [Minai et al 2000, Mendelson et al 2006]. Clinical impairment ranges from none to oxygen dependence and severe limitations of activity. Most affected individuals have evidence of interstitial lung disease on chest radiographs and thin-section CT. Although most individuals have progressive gas exchange abnormalities, the extent of the radiographic findings may not correlate with impairment of pulmonary function.

Calcified pulmonary nodules can also be seen.

Ophthalmologic manifestations. Up to one third of individuals with NPD-B have a macular halo or a cherry-red macula. Most have no evidence of progressive neurologic disease; the presence of a macular halo or a cherry-red macula is not an absolute predictor of neurodegeneration [McGovern et al 2004b].

Neurologic signs. The neurologic findings can include cerebellar signs and nystagmus [Obenberger et al 1999], extrapyramidal involvement, intellectual disability, and psychiatric disorders. In a review of 64 persons with NPD-B, Wasserstein et al [2006] determined that 19 (30%) had neurologic abnormalities. Of the 19, 14 (22%) had minor and non-progressive findings and five (8%) had global and progressive findings (peripheral neuropathy, retinal abnormalities) with onset between age two and seven years. The five with progressive findings had the p.Gln294Lys pathogenic variant.

Growth. Abnormal linear growth and delayed skeletal maturation are common in children and adolescents and can result in significant short stature in adulthood. In one study, the mean Z scores for height and weight were -1.24 (29th centile) and -0.75 (34th centile) respectively, and skeletal age in children under age 18 years was delayed by an average of 2.5 years [Wasserstein et al 2003]. Short stature and low weight are correlated with large organ volumes, delayed bone age, and low serum IGF-1 concentrations.

Hyperlipidemia. Low serum concentration of high-density lipoprotein-cholesterol (HDL-C) is common in NPD-B [McGovern et al 2004a]. In most individuals the low serum concentration of HDL-C is accompanied by hyperlipidemia characterized by hypertriglyceridemia and elevated serum concentration of low-density lipoprotein-cholesterol (LDL-C). Lipid abnormalities are evident from the earliest age studied.

Early coronary artery disease, identified in some adults with NPD-B, is presumably related to the dyslipidemia.

Osteopenia. Skeletal involvement is common in NPD-B. In one study, lumbar spine Z scores for children ranged from 0.061 to -4.879. Most adults with NPD-B had osteopenia or osteoporosis at one or more sites according the WHO classification of bone marrow density [Wasserstein et al 2013]. Pathologic fractures have been reported.

Other. Calcifications in organs other than the lungs have been described.

Pregnancy and childbirth. Pregnancy in a mildly affected woman has been reported and 17 pregnancies monitored in women with a wide spectrum of somatic manifestations have been successful [McGovern, personal communication]. Most affected women, even those with significant pulmonary disease, can have normal pregnancies and childbirth. Hepatosplenomegaly does not usually pose a threat to fetal growth.

Genotype-Phenotype Correlations

The most consistent genotype-phenotype correlation in ASM deficiency is a milder clinical course than average in individuals homozygous for the p.Arg610del pathogenic variant [Wasserstein et al 2004]. In contrast to individuals with other pathogenic variants, individuals homozygous for the p.Arg610del pathogenic variant usually have normal height and weight, markedly less hepatosplenomegaly and bone age delay, and normal serum concentration of IGF-1.

Lipid abnormalities occur with all genotypes, including homozygosity for the p.Arg610del pathogenic variant.

Some evidence suggests that the p.Leu139Pro, p.Ala198Pro, and p.Arg476Trp pathogenic variants result in a less severe form of NPD-B.

The p.His423Tyr and p.Lys578Asn pathogenic variants, found most commonly in Saudi Arabia, lead to an early-onset severe form of the disease [Simonaro et al 2002].

The p.Gln294Lys pathogenic variant, associated with intermediate phenotypes with later-onset neuronopathic disease, appears to be relatively common in individuals of Czech and Slovak heritage [Pavlů-Pereira et al 2005].

Homozygosity or compound heterozygosity for some combination of the common *SMPD1* pathogenic variants observed in individuals with NPD-A predicts the type A phenotype.

Prevalence

The estimated prevalence of acid sphingomyelinase deficiency is 1:250,000 [Meikle et al 1999]. However, population-wide screening has not been performed, and this and other estimates are based on the number of clinically diagnosed cases referred for biochemical confirmation. More recently in Chile, screening of 1,691 healthy individuals for a common *SMPD1* pathogenic variant, p.Ala359Asp, found a heterozygote frequency of 1:105.7, predicting a disease incidence of 1:44,960 [Acuña et al 2016].

Pathogenic variants causing the severe neurodegenerative form of the disease (NPD-A) are more prevalent in the Ashkenazi Jewish population in which the combined carrier frequency for the three common *SMPD1* pathogenic variants (p.Arg498Leu, p.Leu304Pro, and p.Phe333SerfsTer52) is between 1:80 and 1:100. Carrier screening programs and the availability of prenatal diagnosis have resulted in a low birth incidence in this population.

The later-onset and mild forms of acid sphingomyelinase deficiency (i.e., NPD-B) are pan ethnic. Genotype information on individuals with NPD-B from 29 different countries has been reported [Simonaro et al 2002].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *SMPD1*.

Differential Diagnosis

Lysosomal storage diseases (LSD). The clinical features of acid sphingomyelinase deficiency may overlap with other lysosomal storage diseases such as Gaucher disease; however, biochemical testing permits correlation with the molecular findings in such a serious disorder. In addition, the pulmonary infiltration and the low serum concentration of HDL cholesterol are distinctive features that are present very early in the NPD disease course.

Hepatosplenomegaly also occurs in Gaucher disease, hexosaminidase A deficiency, Sandhoff disease, Niemann-Pick disease type C (NPD type C), Wolman disease, the mucopolysaccharidoses, and the oligosaccharidoses (see *GNPTAB*-Related Disorders, Mucolipidosis IV). However, these disorders should be distinguishable from acid sphingomyelinase deficiency based on other associated features such as coarse facial features and dysostosis multiplex in the mucopolysaccharide disorders, specific neurologic findings in NPD type C, and enzymatic studies in Gaucher disease and Sandhoff disease.

Hepatosplenomegaly can also accompany some infectious diseases and other genetic disorders, including familial hemophagocytic lymphohistiocytosis and glycogen storage diseases (see Glycogen Storage Disease Type I). The diagnosis in infants with NPD-A is sometimes delayed during evaluation for an infectious etiology.

Interstitial lung disease can result from many causes including environmental exposures, connective tissue diseases, and infections. However, the presence of hepatosplenomegaly in acid sphingomyelinase deficiency helps distinguish it from these other causes of interstitial lung disease.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with acid sphingomyelinase (ASM) deficiency, the following evaluations are recommended:

Infants with NPD-A

- Ophthalmologic examination, if not yet performed
- Comprehensive neurologic evaluation
- Compete blood count
- Serum chemistries including liver function tests
- Dietary consultation
- Occupational and physical therapy evaluations
- Consultation with a clinical geneticist and/or genetic counselor

NPD-B

- Chest radiograph to assess the extent of interstitial lung disease
- Pulmonary function testing, including assessment of diffusing capacity, in individuals old enough to cooperate
- Bone age in children under age 18 years
- Ophthalmologic examination
- Neurologic examination
- Baseline laboratory studies including complete blood count, fasting lipid profile, serum chemistries, liver function tests
- Liver biopsy in individuals with evidence of deteriorating liver function
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Severe neurodegenerative form (NPD-A)

- **Progressive neurologic disease.** Physical and occupational therapy to maximize function and to prevent contractures is appropriate. Aggressive therapy is not warranted and the plan for such treatment should be made in consultation with the neurologist, therapist(s), and family to establish realistic goals.
- **Nutrition.** Feeding difficulties can make provision of adequate calories a major challenge. Regular consultation with a dietician should be provided. The use of nasogastric tube feeding or surgical placement of a feeding tube should be discussed with the family.
- **Sleep disorder.** Irritability and sleep disturbance are quality-of-life issues for the entire family that sometimes require the use of sedatives.

NPD-B

- **Bleeding.** Most affected individuals have thrombocytopenia. When bleeding is life threatening, transfusion of blood products is indicated. While partial splenectomy may be considered for individuals with severe hypersplenism, total splenectomy should be avoided because removal of the spleen exacerbates the pulmonary disease.

- **Pulmonary disease.** Individuals with symptomatic pulmonary disease may require supplemental oxygen. Other measures to treat interstitial lung disease, such as steroids, have not been well studied. Several individuals have undergone bronchopulmonary lavage with variable results [Nicholson et al 2002].
- **Hyperlipidemia.** Adults with hyperlipidemia should be treated to bring the serum concentration of total cholesterol into the normal range.
- **Growth retardation.** Dietary assessment is indicated in all cases to assure that calorie intake is adequate for growth.

Note: Orthotopic liver transplantation in an infant with NPD-A and amniotic cell transplantation in several individuals with NPD-B have been attempted with little or no success [Kayler et al 2002].

Prevention of Primary Manifestations

Hematopoietic stem cell transplantation (HSCT). Variable results have been reported with HSCT. Shah et al [2005] reported successful HSCT for NPD-A. Successful engraftment can correct the metabolic defect, improve blood counts, and reduce increased liver and spleen volumes. However, stabilization of the neurologic component following HSCT has not been reported; therefore, any attempts to perform HSCT in individuals with clinically evident neurologic disease should be considered experimental. The morbidity and mortality associated with HSCT limit its use.

Enzyme replacement therapy. See Therapies Under Investigation.

Prevention of Secondary Complications

Liver function needs to be monitored in individuals receiving medications with known hepatotoxicity (e.g., statins for treatment of hypercholesterolemia).

Surveillance

Individuals with **NPD-A** should receive routine care from a pediatrician and a neurologist including evaluation of the following:

- Nutrition status
- Occupational and physical therapy needs

Individuals with **NPD-B** should be evaluated at least yearly for the following:

- History (at least every 6-12 months): growth and weight gain in children; fatigue; any change in social, domestic, or school- or work-related activities; bleeding, shortness of breath; abdominal pain; headaches; extremity pain
- Physical examination including assessment of neurologic function
- Blood tests including liver enzymes, platelet count, and fasting lipid profile
- Pulmonary function testing and chest radiograph
- Skeletal assessment by dual-energy x-ray absorptiometry (DEXA)
- Nutrition assessment

Agents/Circumstances to Avoid

Individuals who have splenomegaly should avoid contact sports.

Evaluation of Relatives at Risk

If the *SMPD1* pathogenic variants in the family are known it is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from early identification and treatment.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

For pregnant women with NPD-B, prenatal care by a high-risk obstetrician is indicated to ensure appropriate monitoring of pulmonary function and hematologic status.

Therapies Under Investigation

Enzyme replacement therapy. A Phase I study of recombinant human acid sphingomyelinase in five adults with NPD-B using an intra-patient dose-escalation scheme was recently completed. This regimen was generally well tolerated with study subjects showing a reduced liver and spleen volumes and improved lung-diffusing capacity [Wasserstein et al 2015]. A Phase II study is currently under way in children with NPD-B, and a Phase II/III study is planned in adults with NPD-B.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Acid sphingomyelinase (ASM) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *SMPD1* pathogenic variant).
- Some heterozygotes have been found to have the lipid abnormalities associated with acid sphingomyelinase deficiency.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a heterozygote, and a 25% chance of being unaffected and not a carrier.
- Some heterozygotes have been found to have the lipid abnormalities associated with acid sphingomyelinase deficiency.

Offspring of a proband

- Individuals with Niemann-Pick disease type A (NPD-A) do not reproduce.

- The offspring of an individual with Niemann-Pick disease type B (NPD-B) are obligate heterozygotes (carriers) for a pathogenic variant in *SMPD1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SMPD1* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *SMPD1* pathogenic variants in the family.

Carrier identification by determination of ASM enzymatic activity is not reliable.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *SMPD1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Biochemical genetic testing. Prenatal diagnosis for pregnancies at 25% risk is also possible using biochemical testing of acid sphingomyelinase (ASM) enzyme activity in cultured amniocytes obtained by amniocentesis (usually performed at ~15-18 weeks' gestation) or chorionic villus sampling (usually performed at ~10-12 weeks' gestation).

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Niemann-Pick disease
- **National Niemann-Pick Disease Foundation (NNPDF)**
  401 Madison Avenue
  Suite B
  PO Box 49

Fort Atkinson WI 53538
Phone: 877-287-3672 (toll-free); 920-563-0930
Fax: 920-563-0931
Email: nnpdf@nnpdf.org
www.nnpdf.org

- **Center for Jewish Genetics**
  Ben Gurion Way
  30 South Wells Street
  Chicago IL 60606
  Phone: 312-357-4718
  Email: jewishgeneticsctr@juf.org
  www.jewishgenetics.org
- **Metabolic Support UK**
  5 Hilliards Court, Sandpiper Way
  Chester Business Park
  Chester CH4 9QP
  United Kingdom
  Phone: 0845 241 2173
  Email: contact@metabolicsupportuk.org
  www.metabolicsupportuk.org
- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**
  2001 Beacon Street
  Suite 204
  Boston MA 02135
  Phone: 800-906-8723 (toll-free)
  Fax: 617-277-0134
  Email: info@ntsad.org
  www.ntsad.org
- **International Niemann–Pick Disease Alliance**
  Email: info@inpda.org
  www.inpda.org
- **International Niemann-Pick Disease Registry (INPDR)**
  www.npuk.org/research/international-niemann-pick-disease-registry-inpdr

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Acid Sphingomyelinase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SMPD1	11p15.4	Sphingomyelin phosphodiesterase	SMPD1 database	SMPD1	SMPD1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Acid Sphingomyelinase Deficiency (View All in OMIM)

257200	NIEMANN-PICK DISEASE, TYPE A
607608	SPHINGOMYELIN PHOSPHODIESTERASE 1, ACID LYSOSOMAL; SMPD1
607616	NIEMANN-PICK DISEASE, TYPE B

Molecular Pathogenesis

Acid sphingomyelinase (ASM) deficiency is an inborn error of metabolism that results from a deficiency of acid sphingomyelinase (ASM) (sphingomyelin phosphodiesterase; EC 3.1.4.12) and the subsequent accumulation of sphingomyelin in cells and tissues.

Gene structure. *SMPD1* is ~5 kb in length and the coding sequence is divided among six exons. Exon 2 is unusually large, encoding 258 amino acids, or approximately 44% the mature ASM polypeptide. The regulatory region upstream of the *SMPD1* coding sequence is GC rich and contains putative promoter elements, including SP1, TATA, CAAT, NF1, and AP1 binding sites. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Two common benign variants lead to amino acid substitutions at codons 322 and 506. The common alleles are Thr322 and Gly506 with frequencies of 0.6 and 0.8, respectively, while the less common alleles are Ile322 and Arg506. In addition to these benign variants, the number of alanine/leucine repeats within the ASM signal peptide region is polymorphic.

Pathogenic variants. More than 100 pathogenic variants causing acid sphingomyelinase deficiency have been published [Simonaro et al 2002, Schuchman 2007] including missense, nonsense, and frameshift variants and one in-frame three-nucleotide deletion that results in the removal of a single amino acid from the ASM polypeptide. One splice site alteration has also been described.

Three common pathogenic variants account for more than 90% of the mutated alleles in individuals of Ashkenazi Jewish ancestry with NPD-A (Table 2). Two are missense variants, p.Arg498Leu and p.Leu304Pro, and the third, p.Phe333SerfsTer52, is a single-nucleotide deletion resulting in a frameshift and the introduction of a premature stop at codon 385 within the ASM open reading frame. In contrast to the Ashkenazi Jewish population, each individual affected with NPD-A studied in other populations has a unique *SMPD1* pathogenic variant.

In individuals with NPD-B, one of the most common pathogenic variants is p.Arg610del, which is frequently found in individuals with NPD-B originating from the Maghreb region of North Africa (i.e., Tunisia, Algeria, and Morocco), in whom it may account for almost 90% of mutated alleles. In the United States, p.Arg610del accounts for approximately 20%-30% of the mutated alleles found in individuals with NPD-B.

Table 2. Selected *SMPD1* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.971C>T	p.Thr324Ile (Thr322Ile)	NM_000543.3 NP_000534.3
c.1522G>C	p.Gly508Arg (Gly506Arg)	
c.416T>C	p.Leu139Pro (Leu137Pro)	
c.592G>C	p.Ala198Pro (Ala196Pro)	

Table 2. continued from previous page.

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.874C>A	p.Gln294Lys (Gln292Lys)	
c.911T>C	p.Leu304Pro (Leu302Pro)	
c.996delC (990delC)	p.Phe333SerfsTer52 (Pro330SerfsTer382, or fsP330)	
c.1076C>A	p.Ala359Asp	
c.1267C>T	p.His423Tyr (His421Tyr)	
c.1426C>T	p.Arg476Trp (Arg474Trp)	
c.1493G>T	p.Arg498Leu (Arg496Leu)	
c.1734G>C	p.Lys578Asn (Lys576Asn)	
c.1828_1830del	p.Arg610del (Arg608del or DeltaR608)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Normal gene product. Acid sphingomyelinase (sphingomyelin phosphodiesterase) is a lysosomal enzyme responsible for hydrolyzing sphingomyelin to ceramide and phosphorylcholine.

Abnormal gene product. *SMPD1* pathogenic variants result in an enzyme with altered activity that leads to decreased hydrolysis of the substrate and its subsequent accumulation in cells, particularly in the monocyte macrophage system.

Note: Paternal imprinting of *SMPD1* has been described [Simonaro et al 2006]. The influence of imprinting on the NPD phenotype has not been studied in detail.

References

Published Guidelines / Consensus Statements

ACOG Committee on Genetics. ACOG committee opinion. Number 298, August 2004. Prenatal and preconceptional carrier screening for genetic diseases in individuals of Eastern European Jewish descent. Obstet Gynecol. 2004;104:425–8. PubMed PMID: 15292027.

Literature Cited

Acuña M, Martínez P, Moraga C, He X, Moraga M, Hunter B, Nuernberg P, Gutiérrez RA, González M, Schuchman EH, Luis Santos J, Miquel JF, Mabe P, Zanlungo S. Epidemiological, clinical and biochemical characterization of the p.(Ala359Asp) SMPD1 variant causing Niemann-Pick disease type B. Eur J Hum Genet. 2016;24:208–13. PubMed PMID: 25920558.

Fernández-Burriel M, Peña L, Ramos JC, Cabrera JC, Marti M, Rodríguez-Quiñones F, Chabás A. The R608del mutation in the acid sphingomyelinase gene (SMPD1) is the most prevalent among patients from Gran Canaria Island with Niemann-Pick disease type B. Clin Genet. 2003;63:235–6. PubMed PMID: 12694237.

Harzer K, Rolfs A, Bauer P, Zschiesche M, Mengel E, Backes J, Kustermann-Kuhn B, Bruchelt G, van Diggelen OP, Mayrhofer H, Krageloh-Mann I. Niemann-Pick disease type A and B are clinically but also enzymatically heterogeneous: pitfall in the laboratory diagnosis of sphingomyelinase deficiency associated with the mutation Q292 K. Neuropediatrics. 2003;34:301–6. PubMed PMID: 14681755.

Kayler LK, Merion RM, Lee S, Sung RS, Punch JD, Rudich SM, Turcotte JG, Campbell DA Jr, Holmes R, Magee JC. Long-term survival after liver transplantation in children with metabolic disorders. Pediatr Transplant. 2002;6:295–300. PubMed PMID: 12234269.

McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann Pick disease. Genet Med. 2013;15:618–23. PubMed PMID: 23412609.

McGovern MM, Wasserstein MP, Giugliani R, Bembi B, Vanier MT, Mengel E, Brodie SE, Mendelson D, Skloot G, Desnic RJ, Kuriyama N, Cox GF. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. Pediatrics. 2008;122:e341–9. PubMed PMID: 18625664.

McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of Type A Niemann-Pick disease: possible endpoints for therapeutic trials. Neurology. 2006;66:228–32. PubMed PMID: 16434659.

McGovern MM, Pohl-Worgall T, Deckelbaum RJ, Simpson W, Mendelson D, Desnick RJ, Schuchman EH, Wasserstein MP. Lipid abnormalities in children with types A and B Niemann Pick disease. J Pediatr. 2004a;145:77–81. PubMed PMID: 15238911.

McGovern MM, Wasserstein MP, Aron A, Desnick RJ, Schuchman EH, Brodie SE. Ocular manifestations of Niemann-Pick disease type B. Ophthalmology. 2004b;111:1424–7. PubMed PMID: 15234149.

Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999;281:249–54. PubMed PMID: 9918480.

Mendelson DS, Wasserstein MP, Desnick RJ, Glass R, Simpson W, Skloot G, Vanier M, Bembi B, Giugliani R, Mengel E, Cox GF, McGovern MM. Type B Niemann-Pick disease: findings at chest radiography, thin-section CT, and pulmonary function testing. Radiology. 2006;238:339–45. PubMed PMID: 16304086.

Minai OA, Sullivan EJ, Stoller JK. Pulmonary involvement in Niemann-Pick disease: case report and literature review. Respir Med. 2000;94:1241–51. PubMed PMID: 11192962.

Nicholson AG, Wells AU, Hooper J, Hansell DM, Kelleher A, Morgan C. Successful treatment of endogenous lipoid pneumonia due to Niemann-Pick Type B disease with whole-lung lavage. Am J Respir Crit Care Med. 2002;165:128–31. PubMed PMID: 11779742.

Obenberger J, Seidl Z, Pavlu H, Elleder M. MRI in an unusually protracted neuronopathic variant of acid sphingomyelinase deficiency. Neuroradiology. 1999;41:182–4. PubMed PMID: 10206162.

Pavlů-Pereira H, Asfaw B, Poupctová H, Ledvinová J, Sikora J, Vanier MT, Sandhoff K, Zeman J, Novotná Z, Chudoba D, Elleder M. 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;28:203–27. PubMed PMID: 15877209.

Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase deficient Niemann-Pick disease. J Inherit Metab Dis. 2007;30:654–63. PubMed PMID: 17632693.

Shah AJ, Kapoor N, Crooks GM, Parkman R, Weinberg KI, Wilson K, Kohn DB. Successful hematopoietic stem cell transplantation for Niemann-Pick disease type B. Pediatrics. 2005;116:1022–5. PubMed PMID: 16199719.

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;71:1413–9. PubMed PMID: 12369017.

Simonaro CM, Park JH, Eliyahu E, Shtraizent N, McGovern MM, Schuchman EH. Imprinting at the SMPD1 locus: implications for acid sphingomyelinase-deficient Niemann-Pick disease. Am J Hum Genet. 2006;78:865–70. PubMed PMID: 16642440.

Thurberg BL, Wasserstein MP, Schiano T, O'Brien F, Richards S, Cox GF, McGovern MM. Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick Disease Type B). Am J Surg Pathol. 2012;36:1234–46. PubMed PMID: 22613999.

van Diggelen OP, Voznyi YV, Keulemans JL, Schoonderwoerd K, Ledvinova J, Mengel E, Zschiesche M, Santer R, Harzer K. A new fluorimetric enzyme assay for the diagnosis of Niemann-Pick A/B, with specificity of natural sphingomyelinase substrate. J Inherit Metab Dis. 2005;28:733–41. PubMed PMID: 16151905.

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;149:554–9. PubMed PMID: 17011332.

Wasserstein MP, Desnick RJ, Schuchman EH, Hossain S, Wallenstein S, Lamm C, McGovern MM. The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. Pediatrics. 2004;114:e672–7. PubMed PMID: 15545621.

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;142:424–8. PubMed PMID: 12712061.

Wasserstein MP, Jones SA, Soran H, Diaz GA, Lippa N, Thurberg BL, Culm-Merdek K, Shamiyeh E, Inguilizian H, Cox GF. Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. Mol Genet Metab. 2015;116:88–97. PubMed PMID: 26049896.

Wasserstein M, Godbold J, McGovern MM. Skeletal manifestations in pediatric and adult patients with Niemann Pick disease type B. J Inherit Metab Dis. 2013;36:123–7. PubMed PMID: 22718274.

Chapter Notes

Author History

Margaret M McGovern, MD, PhD; Stony Brook University School of Medicine (2006-2015)
Edward H Schuchman, PhD (2006-present)
Melissa P Wasserstein, MD (2015-present)

Revision History

- 18 June 2015 (me) Comprehensive update posted live
- 25 June 2009 (me) Comprehensive update posted live
- 7 December 2006 (me) Review posted live
- 8 May 2006 (mm) Original submission

License