Acid Sphingomyelinase Deficiency (ASMD)

What is acid sphingomyelinase deficiency (ASMD)?

ASMD is historically known as Niemann-Pick disease types A, A/B, and B[1,2]

ASMD is an **autosomal recessive disease** caused by pathogenic variants of the *SMPD1* gene[2-4], resulting in reduced acid sphingomyelinase activity, which can lead to:

- Accumulation of sphingomyelin
- Multiple organ damage
- Risk of early disease-associated mortality[1-7]

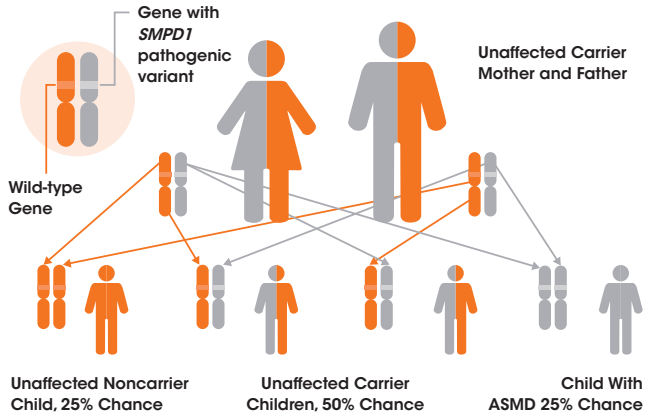
Global prevalence:

~0.5

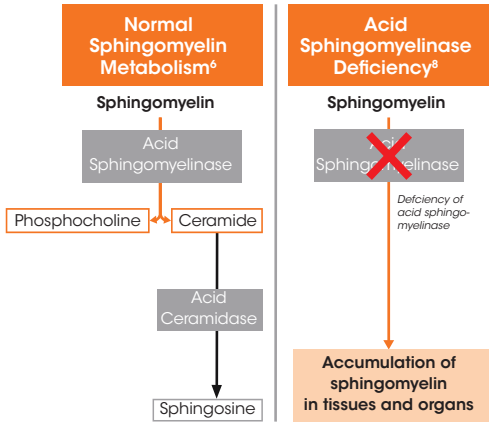
in **100,000** births [1,2]

ASMD is a rare, progressive, pan-ethnic lysosomal storage disease (LSD) with difficult differential diagnosis[2]

Inheritance is autosomal recessive[4]



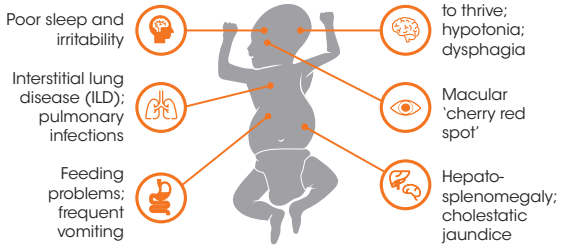
ASMD Pathophysiology



Manifestations of ASMD are varied and broadly categorized by ASMD type (A, A/B, or B)

ASMD TYPE A INFANTILE NEUROVISCERAL

Rapidly progressive neurodegeneration that develops within months of birth[2]

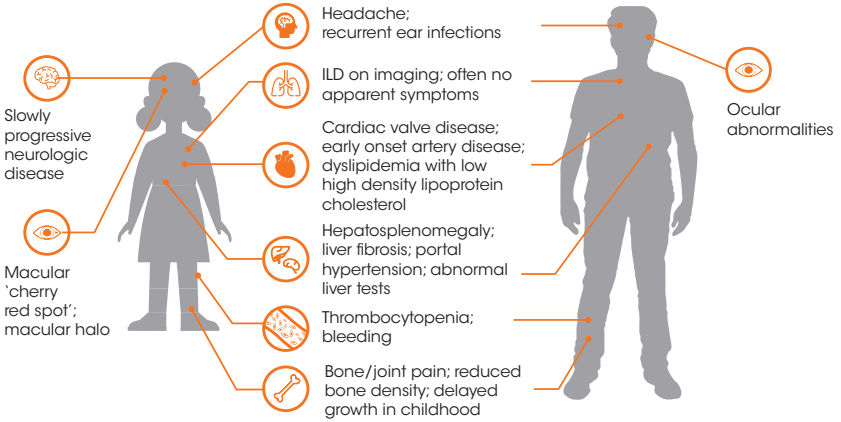


ASMD TYPE A/B CHRONIC NEUROVISCERAL

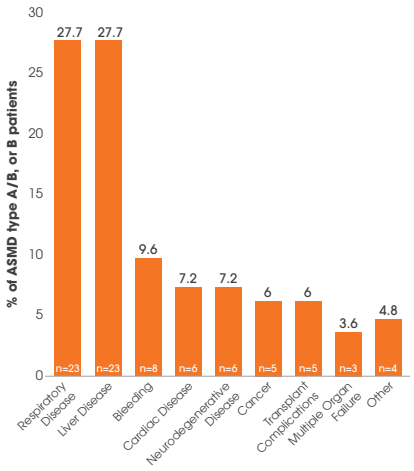
Similar to ASMD type B, plus slowly progressive neurodegeneration[2]

ASMD TYPE B CHRONIC VISCERAL

Slowly progressive systemic manifestations[2]



Primary cause of death in ASMD types A/B, and B[5]



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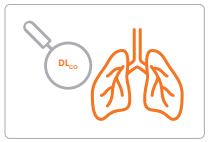
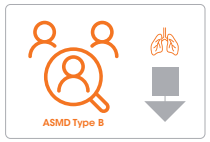
A closer look at ASMD manifestations

Pulmonary Manifestations

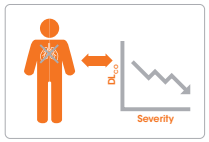
Progressively worsening pulmonary function tests (decreased DL_{CO})[9]



DL_{CO} is a measure of alveolar gas exchange*[10]



Diminished DL_{CO} is often observed in patients with ASMD type B†[1,8]

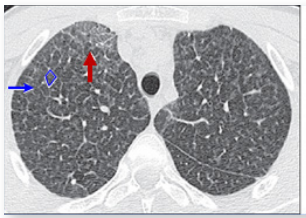


DL_{CO} is inversely related to the severity of interstitial lung disease[11]

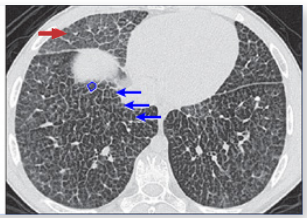
*Oxygen–carbon dioxide (CO_2) exchange occurs here; †ASMD type A/B would be expected to be similar, but data are not currently available.
ASMD, acid sphingomyelinase deficiency; **DL_{CO}**, diffusing capacity of the lung for carbon monoxide

- Interstitial Lung Disease as evidenced by:[12]
  - Interlobular septal thickening
  - Ground-glass density
  - Reticulonodular pattern
  - Subcentimeter (calcified) nodules

Severe Interlobular Septal Thickening on Chest Computed Tomography (CT) in a 19-year-old Man with ASMD type B[12]



Ground-glass density (red arrow)
Septal thickening (blue arrow)

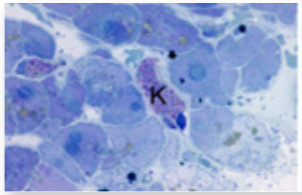


Diffusely scattered ground-glass density (red arrow)
Septal thickening (blue arrows)

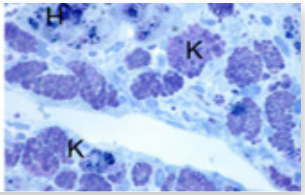
Hepatic Manifestations[13]

- Hepatosplenomegaly
- Fibrosis
- Increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Accumulation of Sphingomyelin (SM) in Liver Kupffer Cells[13]



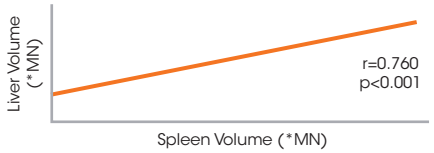
Presence of SM in a patient showing enlarged, foamy Kupffer cells (K)



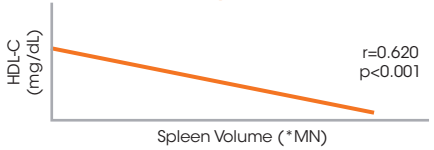
Presence of SM in a patient showing enlarged, foamy Kupffer cells (K) and foamy hepatocytes (H)

Image reproduced with permission from Thurberg BL, *et al.* Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick disease type B). *Am J Surg Pathol.* 2012;36(8):1234-1246.

Liver Volume vs Spleen Volume[1]



HDL-C vs Spleen Volume[1]



*MN: multiples of normal

Hematologic Manifestations[1]

- Thrombocytopenia
- Anemia

Dyslipidemia[1]

- low HDL cholesterol
- high total cholesterol
- high triglycerides
- high LDL cholesterol
- high VLDL cholesterol

HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein

Skeletal Manifestations[14]

- Osteopenia
- Osteoporosis
- Bone fractures
- Growth restriction in children

References

1. McGovern MM *et al. Pediatrics* 2008;122:e341–e349; **2**. McGovern MM *et al. Genet Med* 2017;19:967–974; **3**. Schuchman EH *et al. Best Pract Res Clin Endocrinol Metab* 2015;29:237; **4**. Wasserstein MP *et al.* In: *GeneReviews®* [Internet]. 2019; **5**. Cassiman D *et al. Mol Genet Metab* 2016;118:206-13; **6**. Schuchman EH, *et al. Mol Genet Metab.* 2017;120:27–33; **7**. Taksir TV *et al. J Histochem Cytochem* 2012;60:620; **8**. McGovern MM *et al. Orphanet J Rare Dis* 2017;12(1):41; **9**. Faverio P *et al. Int J Mol Sci* 2019;20(2):E327; **10**. Wasserstein MP *et al. Mol Genet Metab* 2015;116:88–97; **11**. McGovern MM, *et al. Orphanet J Rare Dis.* 16:212; **12**. Simpson WL Jr *et al. AJR Am J Roentgenol.* 2010;194(1):W12-W19; **13**. Thurberg BL, *et al. Am J Surg Pathol.* 2012;36(8):1234-1246; **14**. Wasserstein M, *et al. J Inherit Metab Dis.* 2013;36(1):123-7.

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