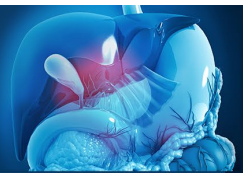
Improving Diagnosis and Clinical Monitoring of Acid Sphingomyelinase Deficiency



1. Overview

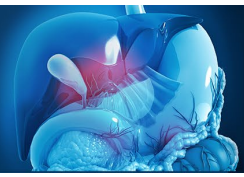
Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disorder that causes accumulation of sphingomyelin in macrophages and other cells within the alveolae, liver, and spleen, among other organs. ASMD is highly heterogeneous and can present with a range of symptoms and severities. Infantile neurovisceral ASMD (type A Niemann-Pick disease [NPD]) is the most severe form, presenting in childhood with severe neurodegeneration and, eventually, death. Chronic visceral ASMD (type B NPD) is the most common form of ASMD and the least severe, with a variable course that can present at any point in a patient's lifetime, from childhood to late adulthood. Chronic neurovisceral ASMD (type A/B NPD) falls in the middle of the spectrum and is moderate in severity.

	Type A or Infantile Neurovisceral ASMD[1-3]	**Type A/B or Chronic Neurovisceral ASMD[1,2,4]**	**Type B or Chronic Visceral ASMD[1,2,4,5] (most common)**
Severity	Most severe (life-threatening)	Moderate severity	Least severe
Rate of symptom progression	Rapid	Variable	Variable, slower
First appearance of symptoms	Early infancy	Infancy to childhood	Infancy to adulthood
Organ involvement	Multiorgan involvement, including neurodegeneration	Variable multiorgan involvement, typically including neurodegeneration	Variable multiorgan involvement, with limited or no neurodegeneration
Life expectancy	Childhood (mean, 2.3 years)	Childhood to mid-adulthood (mean, 10.3 years)	Childhood to late adulthood (mean, 32.9 years)

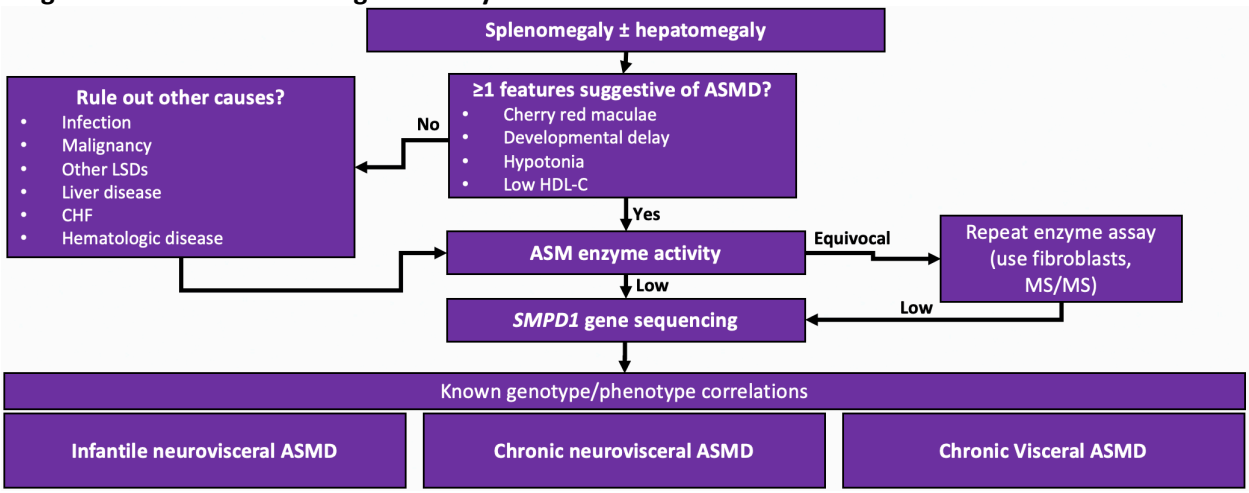
1. McGovern MM et al. *Orphanet J Rare Dis*. 2017;12(1):41. **2.** McGovern MM et al. *Genet Med.* 2017;19(9):967-974. **3.** McGovern MM et al. *Neurology*. 2006;66(2):228-232. **4.** Cassiman D et al. *Mol Genet Metab.* 2016;118(3):200-213. **5.** Cox GF et al. *JIMD Rep.* 2018;41:119-129.

2. Guidelines for the Diagnosis of ASMD

ASMD is highly heterogeneous and can present with a variety of manifestations across a range of organ systems. Splenomegaly and hepatomegaly are the most common presenting signs. Many patients with ASMD type A or A/B also present with developmental delay, low HDL cholesterol levels, hypotonia, and/or retinal changes. Adults with ASMD are more likely to present with interstitial lung disease and/or pathologic fractures. Confirmation of ASMD diagnosis requires testing of acid sphingomyelinase (ASM) enzyme activity. Gene sequencing of *SMPD1* may help identify genotype-phenotype associations.



Diagnosis of ASMD Presenting in Infancy or Childhood[2]



2. McGovern MM et al. *Genet Med*. 2017;19(9):967-974.

3. Clinical Management and Treatment Monitoring: Part 1

ASMD is a chronic condition, and treatment is typically based on symptoms. After diagnosis, patients with ASMD may be referred for initial evaluations and consultations to set baselines for neurologic function, liver function, growth and development, and physical function. Patients and families may also benefit from consultation with a medical geneticist or genetic counselor, occupational therapist, physical therapist, dietitian, and palliative care teams.

4. Clinical Management and Treatment Monitoring: Part 2

For patients with chronic ASMD, ongoing surveillance is a critically important component of management. In particular, liver function should be monitored, as liver disease is a major cause of morbidity and mortality in patients with type A and type A/B ASMD. Other considerations include lifestyle modifications and pharmacotherapy to mitigate cardiovascular risk and dyspnea.

5. Emerging Therapies: Efficacy and Safety Data From Phase 3 Trials

Olipudase alfa is an investigational enzyme replacement therapy developed for the treatment of patients with nonneurologic ASMD. Olipudase alfa is a recombinant form of ASM and has been shown to progressively clear sphingomyelin from liver and spleen cells. In several phase 2 and 3 trials, olipudase alfa has been shown to reduce liver and spleen volume, improve lipid parameters, lung function and various symptoms of ASMD. Olipudase alfa has also been shown to be a safe treatment option, with a good risk-benefit profile.

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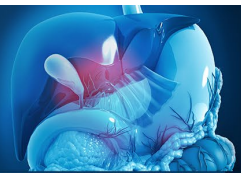
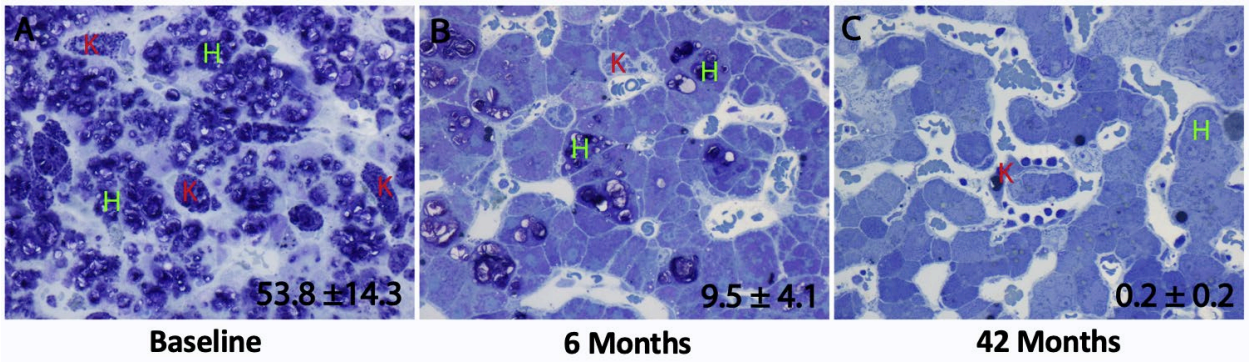


Progressive Sphingomyelin Clearance From Kupffer Cells (K) and Hepatocytes (H)[6]



6. Thurberg BL et al. *Mol Genet Metab*. 2020;131(1-2):245-252.