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Poster 305

Differential diagnosis of Niemann-Pick A/B disease (ASMD) in cases of suspected Gaucher disease

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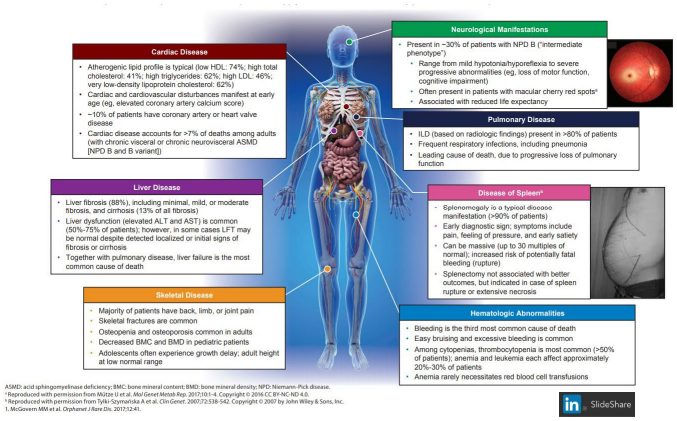
Introduction

Gaucher (GBA deficiency) and Niemann-Pick A/B disease (acid sphingomyelinase, ASM deficiency, ASMD) are autosomal recessive inherited disorders of metabolism that result from a deficiency of the enzymes glucocerebrosidase and acid-sphingomyelinase, respectively. Due to patients with Gaucher and Niemann-Pick A/B disease presenting with similar and overlapping clinical symptoms, a systematic laboratory workup evaluating both diseases in parallel is very important.

ASMD

The overall estimated incidence is 0.4 to 0.6 in 100,000 live births, and although ASMD is rare, this may be an underestimate of the true incidence due to under- or misdiagnosis. ASMD represents a wide clinical spectrum of disease with varying symptoms at presentation, age of onset, and degree and type of organ and systemic involvement. The disease manifestations can vary, but frequently involve hepatosplenomegaly with progressive organ dysfunction, interstitial lung disease, and bleeding. The cellular damage caused by sphingomyelin accumulation can be irreversible and can lead to life-threatening complications and reduced life expectancy. Quality of life is an important consideration for patients with ASMD and their families, as the disease has a substantial impact on functioning and day-to-day living.



ASMD: acid sphingomyelinase deficiency; BMC: bone mineral content; BMD: bone mineral density; NPD: Niemann- Pick disease.

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1. McGovern MM et al. *Orphanet J Rare Dis.* 2017;12:41.

How to diagnose ASMD?

A lack of disease awareness and non-specific presentation can result in delayed diagnosis. Accurate diagnosis is critical for appropriate management and monitoring, and to help patients and caregivers understand the prognosis and implications of the disease. Diagnostic delays arise from an overlap in symptomology with other diseases, leading to misdiagnoses, and a limited availability of diagnostic assays outside specialist laboratories. A number of diseases (including primary hepatic disease, Gaucher disease, NPC, and lysosomal acid lipase deficiency) present with symptoms similar to ASMD, and comparative assessments may be useful for a differential diagnosis. Although gene sequencing can be diagnostic if two pathogenic mutations are found, most genetic variants are not pathogenic. Identifying known disease-causing alleles of *SMPD1* facilitates individualized genetic counseling, carrier screening, and family planning.

Fully validated and accredited combined diagnostics available

All tests from one single DBS card

Enzyme activity: acid sphingomyelinase (ASM)

Biomarker: Lyso-SPM

(Isotopically labeled internal standard included; Intraday precision < 6%, inter-day precision <5%)

Genetics: confirmatory testing of *SMPD1*

• Our Lyso-SPM assay includes:

- 7-point calibrator for quantification
- 3-point quality control material
- Calibration range 0-1500 ng/mL
- Full documentation of manufacturing

• Our diagnostic testing includes:

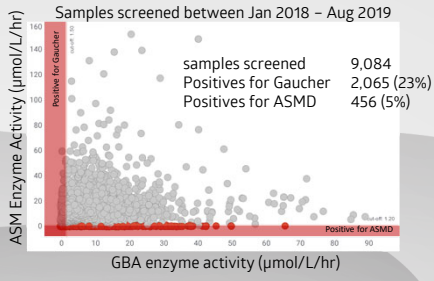
- Validated instruments and equipment
- Validated software for data analysis
- All requirements according to ISO 15189

Enzyme activity screening

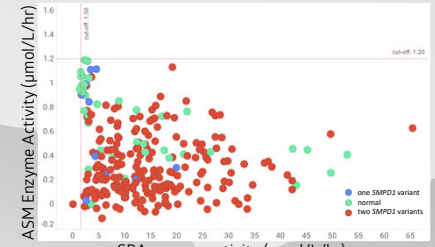
Biochemical testing of GBA and ASM enzyme activity have shown one case of ASM deficiency among each 5 patients suspected of Gaucher disease.

Samples in the study are based on high risk population screening.

ASMD positive cases are represented by the red dots.



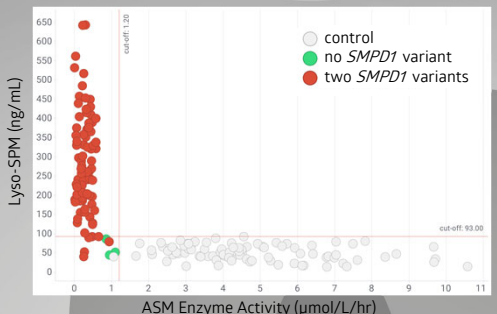
Genetic confirmatory testing



275 cases (with proper consent) have been submitted to genetic analysis.

Number of cases with *SMPD1* variant
Two 219 (80%)
One 14
No 42

Lyso-SPM Biomarker



Number of cases from genetic confirmatory testing with *SMPD1* variants:
Two 84
No 3

152 control samples

4 out of 5 lyso-SPM negative but genetic positive samples were in the age of 2-8 years. 1 out of 5 lyso-SPM negative but genetic positive sample was 28 years of age. Samples with normal enzyme activity do not have Lyso-SPM elevation.

Most frequent *SMPD1* varriants:

Nucleotide change	Amino acid change	# of cases
c.416T>C	p.Leu139Pro	20
c.740delG	p.Gly247AlafsTer10	6
c.1117C>T	p.Pro373Ser	4
c.1267C>T	p.His423Tyr	8
c.1327C>T	p.Arg443Ter	4
c.1493G>A	p.Arg498His	6
c.1556A>G	p.Tyr519Cys	11
c.1624C>T	p.Arg542Ter	6
c.1718G>C	p.Trp573Ser	4

87 different *SMPD1* variant have been identified.

Summary: Our results have shown that approximately 1 out of 5 (!) suspected Gaucher patients is suffering from ASM deficiency resulting in Niemann-Pick A/B disease underdiagnosis. For this reason, it is recommended to test suspected patients for both Gaucher and ASMD simultaneously.

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