Plasma lysosphingomyelin levels are positively associated with clinical severity in acid sphingomyelinase deficiency

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BACKGROUND

- Acid sphingomyelinase deficiency (ASMD) AKA Niemann-Pick Disease types A, A/B, and B, is a rare lysosomal storage disorder caused by deficiency of acid sphingomyelinase

- Estimated prevalence of 1 in 250,000 [Meikle et al. 1999]
- Diagnosis is made by:
  - detection of biallelic pathogenic variants in SMPD1 or less than 10% enzyme activity in peripheral blood or cultured skin fibroblasts
- Case definitions:

	Infantile ASMD	Chronic ASMD	
Subtype	Infantile Neurovisceral ASMD (NPD A)	Chronic Neurovisceral ASMD (NPD A/B)	Chronic Visceral ASMD (NPD B)
Onset + Prognosis	Onset in early infancy, death often by age 3	Onset in infancy to childhood. Death in childhood to mid-adulthood	Onset in infancy to adulthood, death from childhood to late adulthood
Clinical Features	Rapidly progressive severe visceral disease, neurodegeneration	Slowly progressive, variable visceral and neurologic features including developmental delay, intellectual disability, ataxia and peripheral neuropathy	Slowly progressive, variable visceral disease with little or no neurologic involvement
Severity	Severe	Moderate	Mild

- Lysosphingomeylin (LSM) = deacylated form of sphingomyelin and a candidate biomarker for this disease

Existing Knowledge	Knowledge Gap
LSM levels in dried blood spots from Chronic visceral ASMD are increased 5-fold compared to controls (Chuang et al. 2014) LSM levels are increased in all patients with ASMD – infantile and chronic patients and can be used to distinguish ASMD and Niemann-Pick Disease type C (Kuchar et al. 2017, Voorink-Moret et al. 2018)	The relationship between LSM levels and clinical sub-type or severity is not known

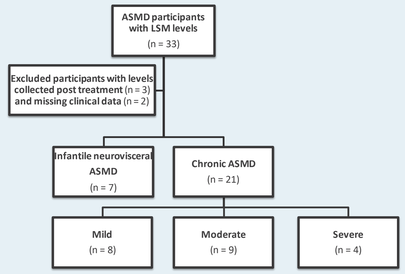
STUDY AIMS

- Primary aim: To assess the relationship between LSM levels and clinical subtype (Infantile ASMD versus Chronic ASMD)
  - Hypothesis: LSM levels will be higher in Infantile ASMD patients than in Chronic ASMD patients.
- Secondary aim: To assess the relationship between LSM levels and clinical severity among individuals with Chronic ASMD.
  - Hypothesis: LSM levels will be positively correlated to disease severity

METHODS

- Cross sectional analysis of ASMD patients at time of enrollment in the ASMD natural history study at the Children's Hospital at Montefiore (2016-7096), or first collection of LSM levels
- February 2015 – February 2019
- Inclusion Criteria:
  - ASMD
  - Enrolled in the ASMD natural history study
  - LSM measurement
- Exclusion Criteria:
  - Sample for LSM collected after disease-modifying clinical intervention or Missing clinical records

PARTICIPANTS

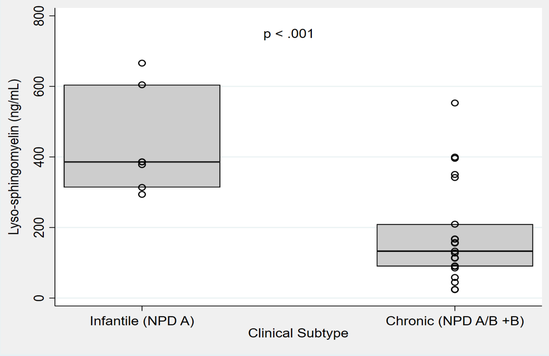


	Infantile ASMD (n=7)	Chronic ASMD (n= 21)
Sex		
Male	5 (71)	12 (57)
Female	2 (29)	9 (43)
Age in years - median (IQR)	1.3 (1.1, 1.5)	15.1 (5.5, 27.3)

RESULTS

PRIMARY AIM

- Comparison of LSM by ASMD clinical subtype.
- Medians compared with Wilcoxon rank sum test. p < .001.

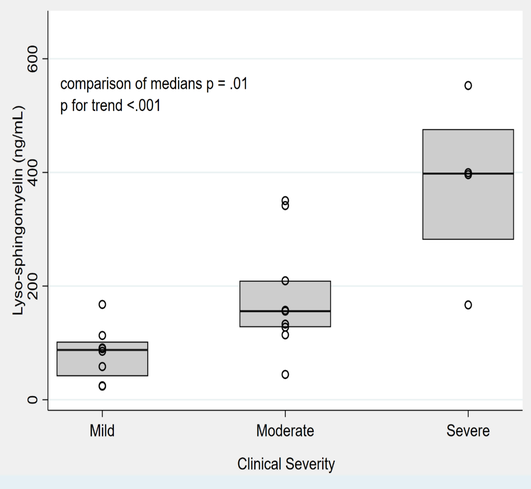


	Infantile ASMD (n=7)	Chronic ASMD (n=21)	p value
LSM (ng/mL) median (IQR) Reference range (0.04-3.8 (ng/mL))	386 (314, 605)	156 (133, 209)	<.001

SECONDARY AIM

- To study the relationship between LSM levels and clinical severity among patients with Chronic ASMD.
- Clinical severity defined (mild, mod, severe) based on expert opinion
- The presence and severity of the following clinical features were considered in severity sorting:

1. Interstitial lung disease
2. Transaminitis
3. Hepatosplenomegaly
4. HDL cholesterol concentration
5. Thrombocytopenia
6. Pediatric growth restriction
7. Development delays or intellectual disability



	Mild (n=8)	Moderate (n=9)	Severe (n=4)	Kruskal-wallis p	p for trend
LSM (ng/mL) median (IQR) Reference range (0.04-3.8 (ng/mL))	88 (42, 102)	156 (128, 209)	398 (282, 476)	.01	< .001

DISCUSSION

LIMITATIONS

- Main limitation: clinical severity determinations were made without a validated clinical severity score and the expert reviewer was incompletely blinded to LSM data
- Cross sectional analysis of data at a single center, no longitudinal data
- Patients were diagnosed and symptomatic

FUTURE DIRECTIONS

- Extension of this analysis to larger, multi-center cohorts that include patients with a wider phenotypic spectrum
- Addition of a second biomarker, lyso-sphingomyelin-509 to increase precision
- Pre-symptomatic biomarker levels, on pilot newborn screening programs, including ScreenPlus

CONCLUSIONS

- This study supports the prior finding that LSM levels are increased in patients with ASMD compared to reference ranges
- LSM levels were higher in patients with infantile ASMD (median LSM 386 ng/mL) compared to chronic forms of ASMD (median LSM 152 ng/mL)
- Among individuals with chronic ASMD, there was a positive relationship between LSM level and clinical severity (severe > moderate > mild)
- These results support further investigations into LSM as a biomarker for ASMD

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