The ratio of Niemann-Pick A/B disease to cases of Gaucher disease varies by country

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Introduction

Gaucher (GBA deficiency) and Niemann-Pick A/B disease (acid sphingomyelinase (ASM) deficiency) 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.

The overall estimated incidence is 0.4 to 0.6 in 100,000 live births, and although ASMD is rare, it 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. Symptoms frequently involve hepato-splenomegaly with progressive organ dysfunction, interstitial lung disease, and bleeding. The cellular damage caused by ASMD can be irreversible and can lead to life-threatening complications and reduced life expectancy.

A lack of disease awareness and non-specific presentation can result in delayed diagnosis. A number of diseases (such as Gaucher disease, NPD C, and lysosomal acid lipase deficiency) present with symptoms similar to ASMD, and comparative assessments may be useful for a differential diagnosis.

Results

In this multicenter, prospective study, we investigated a cohort of **31,838 individuals** from **61 countries** between 2017 and 2022 suspected to have Gaucher disease based on clinical presentation.

For all samples, both Acid-β-glucocerebrosidase and acid sphingomyelinase enzyme activities were measured in dried blood spot specimens by tandem mass spectrometry followed by genetic confirmatory testing in potential positive cases.

In total, **5,933 symptomatic cases** showed decreased enzyme activities and were submitted for genetic confirmatory testing. (63% children <2 Years)

- **1,411** (24%) cases were identified with Gaucher disease
- **550** (9%) cases were identified with ASMD

→ **one in four** cases suspected for Gaucher disease is diagnosed with ASMD

Figure 2. Confirmed GD and ASMD cases per country. Countries without confirmed ASMD cases are not included.

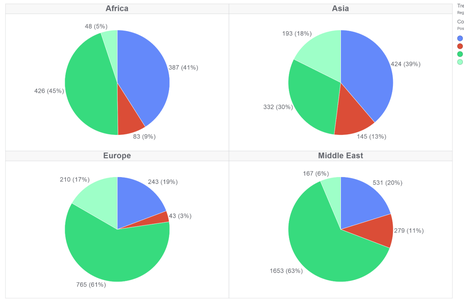

Figure 1. Cases submitted to genetic confirmatory testing. In total, 5,933 cases were submitted to genetic confirmatory testing. 1,171 cases for SMPD1 gene sequencing and 4,762 for GBA gene sequencing. 1,411 GD patients (blue color) with at least two GBA genetic variants and 550 ASMD patients (red color) with at least two SMPD1 genetic variants were confirmed. Cases with no genetic variants are shown in green colors. Two samples with no variants (one from Australia and one from unknown region) are not shown. The distribution of samples per region. The highest percentage of ASMD patients is in Asia countries following by Middle East countries. The highest distribution of GD patients is in Asia countries.

The highest ratio was found in Middle East countries (1 to 2 ratio) and Asia (1 to 3 ratio), follow by Africa (1 to 4 ratio). On the other hand, in Europe only 1 out of 5 suspected GD patient is suffering from ASMD. The highest percentage of confirmed ASMD patients have been identified in Pakistan, Iraq, and Turkey (Figure 2). In Europe, most of ASMD patients have been identified in Romania, Poland, and Italy with highest ratio of ASMD to GD in Romania (1 to 2).

Conclusion

Our results have shown that depending on the region 1 out of 2 to 1 out of 5 suspected Gaucher patients is suffering from ASM deficiency resulting in Niemann-Pick A/B disease diagnosis. For this reason, it is recommended to test suspected patients for both Gaucher and Niemann-Pick diseases simultaneously.
In addition, Lyso-SPM shows promise as a useful biomarker for ASMD patients for both diagnostics and monitoring. Further prospective studies are needed to provide more evidence.

The ratio of ASMD to GD varies by region (Figure 1; Table 1)

Table 1. Summary of genetic tests and region

	GBA		*SMPD1*		ASMD
	tests	confirmed	tests	confirmed	to GD
Africa	813	315	131	83	1 in 4
Asia	756	398	338	145	1 in 3
Europe	1007	207	253	43	1 in 5
Middle East	2184	490	446	279	1 in 2

One *GBA* tests from UK, one from unspecified country and three *SMPD1* test from Australia are not listed.

Table 2. Summary of confirmed cases by age

Patients	N of **ASMD** cases (%)	N of **GD** cases (%)
Newborns (until 28 days of life)	283 (51%)	288 (20%)
Children (below 10 years)	65 (12%)	497 (35%)
Children/adolescents (10 - 18 years)	141 (26%)	195 (14%)
Adults (>18 years)	61 (11%)	431 (31%)

227 distinct *SMPD1* sequence variants were identified. Most of the variants are only present once/private; except 10 more frequent variants (p.Leu139Pro; p.Arg542Term; p.His423Tyr; p.Arg498His; p.Gly247AlafsTer10; p.Tyr519Cys; p.Pro373Ser, p.Trp573Ser, p.Leu551Pro; p.Arg443Term; p.Cys228Gly). Classification by phenotypes is on-going.

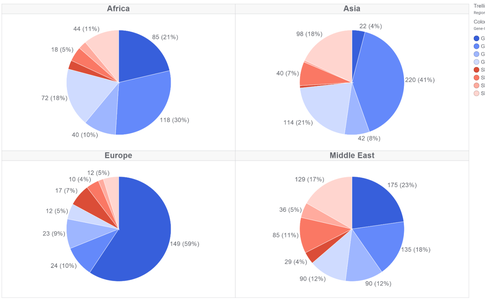

Figure 3. Confirmed cases by age and region. 1,411 GD patients (blue color) and 550 ASMD patients (red color) are shown per age group per region. Most of the cases from Middle East and Asia are newborns, while cases in Europe are mostly adults.

Over 51% of confirmed ASMD cases were newborns (age below 28 days of life) and 12% below 2 years of age. Remining 37% were older children (Figure 3; Table 2).

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Reference:
[1] Deodato F, Boenzi S, Taurisano R, et al. The impact of biomarkers analysis in the diagnosis of Niemann-Pick C disease and acid sphingomyelinase deficiency. Clin Chim Acta. 2018;486:387–394. doi:10.1016/j.cca.2018.08.039
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