Gaucher Disease and ASMD

Overview

Gaucher disease (GD) and Acid Sphingomyelinase Deficiency [(ASMD), historically known as Niemann-Pick disease (NPD) types A, A/B, and B], are rare lysosomal storage diseases with phenotypic overlap.

Gaucher disease is caused by pathogenic variants in *GBA1* which result in a deficiency of the enzyme glucocerebrosidase (GBA). Deficiency or absence of this enzyme leads to a build-up of glycosylceramide (GL-1) and glucosylsphingosine (lyso-GL-1).[1]

ASMD is caused by pathogenic variants in *SMPD1* which result in deficiency of the enzyme acid sphingomyelinase (ASM) and a subsequent accumulation of sphingomyelin and other lipids.[2]

Both diseases present with similar symptoms: anemia, thrombocytopenia, splenomegaly, and bone involvement due to displacement of normal marrow cells with disease-affected cells resulting in bone pain, osteopenia, and fractures.[1,2] Gaucher disease and ASMD each have a wide phenotypic spectra ranging from severe neuronopathic forms to chronic visceral forms.[1,2]

Some symptoms differ between the two diseases, for example: atherogenic dyslipidemia, liver disease, and pulmonary involvement are more commonly associated with ASMD.[2, 4, 5]

Incidence of GD

Incidence of GD:
1 in 50,000-100,000 in the general population worldwide,[3] and about 1 in 850 people of Ashkenazi Jewish heritage3 for GD type 1[3]

Incidence of ASMD

Incidence of ASMD is estimated at 0.5 per 100,000 births[2]

GD Inheritance

Autosomal recessive disease caused by pathogenic variants in both copies of the *GBA1* gene[1]

ASMD Inheritance

Autosomal recessive disease caused by pathogenic variants in both copies of the *SMPD1* gene[2]

Diagnosis

Definitive diagnosis of GD is established by:

- Acid β-glucosidase enzyme assay: demonstrating deficient activity[3]
- *GBA1* gene sequencing: demonstrating two pathogenic variants in *trans* (one from each parent). Though identification of pathogenic alleles is not required for diagnosis, it can provide secondary confirmation and important information related to phenotype.

Definitive diagnosis of ASMD is established by:

- Acid sphingomyelinase enzyme assay: demonstrating deficient activity[6]
  - Should be done in parallel with acid β-glucosidase enzyme assay or reflexed if acid β-glucosidase is normal.[4]
- *SMPD1* gene sequencing: demonstrating two pathogenic variants in trans (one from each parent).[2] Though identification of pathogenic alleles is not required for diagnosis, it can provide secondary confirmation and important information related to phenotype.

The following evaluations may support a diagnosis of GD or ASMD:

Laboratory Testing

Gaucher Disease	ASMD
• CBC: Thrombocytopenia, anemia[7]	• CBC: Thrombocytopenia, anemia[4]
• Lipids: normal LDL, normal triglycerides, low HDL[8]	• Lipids: low HDL, elevated LDL, elevated triglycerides[4]
• Hyperferritinemia[9], decreased clotting factors[7]	• LFTs: AST, ALT are typically elevated but can be normal[4]
• Bone marrow biopsy*: Gaucher cells (normal biopsy does not rule out Gaucher)[10]	• Bone marrow biopsy*: Lipid-laden foam cells (normal biopsy does not rule out ASMD)[4]
• Glucosylsphingosine (lyso-GL-1, glucopsychosine): markedly elevated[11,12]	• Lysosphingomyelin (LSM) may be measured alone or in panel of oxysterols: elevated in ASMD patients[4]

**Bone marrow aspirate/biopsy may have been performed if hematologic malignancy was suspected.*

Other

Gaucher Disease	ASMD
• Hepatosplenomegaly by volumetric MRI or CT scan[10]	• Imaging of liver: hepatomegaly, fibrosis, cirrhosis[4]
• Skeletal imaging: reduced bone density, pathologic fractures, delayed bone maturation[1]	• Imaging of spleen: splenomegaly, typically >5x normal[4]
• MRI of long bones: marrow infiltration, osteonecrosis, lytic lesions, Erlenmeyer flask deformity[6]	• Skeletal imaging: reduced bone density, pathologic fractures, delayed bone maturation[4]
• Neurological: polyneuropathy, radiculopathy, parkinsonism, subdural hematoma, intracerebral hemorrhage have been reported in type 1 patients[10]	• Opthalmologic: retinal changes (macular halo to cherry red maculae) can be seen in ASMD types A and B[14]
• Opthalmological (Neuronopathic forms): slowing of horizontal saccadic eye movement is virtually pathognomonic for Gaucher disease type 3 (GD3)[13]	• CT scan (pulmonary): ground glass appearance, interstitial lung disease, reticulonodular density[4]

References: 1. Baris HN, et al. *Pediatr Endocrinol Rev.* 2014;12:72-81. **2**. McGovern MM, et al. *Orphanet J Rare Dis.* 2017;12(1):41. **3.** Mistry PK, et al. *Am J Hematol.* 2011;86(1):110-5. **4.** McGovern MM, et al. *Genet Med.* 2017;19(9):967-974. **5.** Simpson WL, et al. *World J Radiol.* 2014;6:657-668. **6.** Pastores GM, et al. *NCBI Bookshelf*, a service of the National Library of Medicine, National Institutes of Health (NIH). Available at: https://www.ncbi.nlm.nih.gov/books/NBK1269/. Accessed July 5, 2022. **7.** Charrow J, et al. *Arch Intern Med.* 2000;160:2835-2843. **8.** Stein P, et al. J Inherit Metab Dis. 2011;34(2):429-37. **9.** Lorenz F, et al. *Blood Cells Mol Dis*. 2018;68:35-42. **10.** Grabowski GA, et al. The Online Metabolic and Molecular Bases of Inherited Disease Eds. Valle DL, et al. McGraw Hill, 2019. **11.** Murugesan V, et al. *Am J Hematol.* 2016;91:1082-1089. **12.** Schueler UH, et al. *Neurobiol Dis.* 2003;14:595-601 **13.** Eghbali A, et al. *Mol Genet Metab.* 2019 May;127(1):23-27. **14.** McGovern et al. McGovern MM, et al. *Ophthalmology* 2004 Jul;111(7):1424-7.

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Testing Options for Gaucher Disease and Acid Sphingomyelinase Deficiency

Some of the laboratories offering testing for both Gaucher disease enzyme assay (acid β-glucosidase), ASM enzyme assay (acid sphingomyelinase), and/or *GBA1* and *SPMD1* sequencing are listed below. There may be other testing appropriate for your patient, and this is not an endorsement of any specific laboratory. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. Consult each laboratory for a full range of options. Content is current at time of publication, and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics. Sanofi does not review or control the content of non-Sanofi websites. This listing does not constitute an endorsement by Sanofi of information provided by any other organizations.

Laboratory	Available Testing	GD	ASMD	Sample Requirements	Avg TAT
ArchimedLife	Enzyme	✓	✓	DBS card: 5 circles (min 3) *Note: this European lab does not yet have CLIA certification. Therefore, all results are reported on a research basis.*	10 d
	Sequencing	✓	✓		2 wks
	LSM		✓		10 d
	Lyso-GL-1	✓			10 d
ARUP Laboratories	Enzyme	✓		WB: 3ml ACD (yellow), EDTA (lavender), or sodium heparin (green) tube	3-10 d
	Sequencing	✓		WB: 3 ml ACD (yellow), EDTA (lavender) tube	2-3 wks
Centogene	Enzyme	✓	✓	WB: 5 ml EDTA (lavender) tube; DBS card: 10 circles	7 d
	Sequencing (+/- Del/Dup)	✓	✓	WB: 1 ml EDTA (lavender) tube; DBS card: 10 circles; Saliva; Buccal swab	15 d
	Lyso-GL-1	✓		WB: 1 ml EDTA (lavender) tube; DBS card: 10 circles	7 d
	LSM-509		✓	WB: 1 ml EDTA (lavender) tube; DBS card: 10 circles	7 d
Greenwood Genetic Center	Enzyme	✓	✓	WB: 5-10 ml (3-5 ml for ASMD) sodium heparin (green) tube; DBS card: 3 circles	2 wks
	Sequencing	✓	✓	WB: 5-6 mL EDTA (lavender) tube; DBS card: 10 circles; Saliva	3 wks
LabCorp	Enzyme	✓		WB: 2 x 10 mL EDT (lavender) tube (peds 1 x 10 ml);	3-13 d
	Sequencing	✓	✓	WB: 7 ml EDTA (lavender) or ACD (yellow) tube Note: For sequencing done via "Inheritest Gene-Specific Sequencing" (test code: 451910). Indicate *GBA* or *SMPD1* gene as needed	9-15 d
Mayo Clinic Laboratories	Enzyme	✓	✓	WB 6 ml ACD (yellow) tube	5-10 d
	Sequencing	✓		WB: 3 ml EDTA (lavender) or ACD (yellow) tube; DBS card: 2-5 circles	14-20 d
	Lyso-GL-1	✓		WB: 1 ml EDTA (lavender), ACD B (yellow), or sodium heparin (green) tubes; Plasma: 0.3 ml; DBS card: 2 circles (Note: Order codes GPSY, GPSYP, or GPSYW)	2-8 d
	Oxysterols		✓	WB: 1 ml EDTA (lavender), ACD B (yellow) or sodium heparin (sodium or lithium) (green) tubes; Frozen plasma: min 0.25 ml; DBS card: 2 circles	2-8 d
Revvity Omics (including The Lantern Project*)	Enzyme	✓	✓	WB: 2-10 ml sodium heparin (green) tube (volume varies with age); DBS card: 3 circles	3 d
	Sequencing	✓	✓	WB: 2-10 ml EDTA (lavender) tube (volume varies with age) DBS card: 3 circles; Saliva	3 wks
	Lyso-GL-1	✓		WB: 2-10 ml EDTA (lavender) tube (volume varies with age) DBS card: 3 circles	3 d

Laboratory	Kits	Mobile Phlebotomy	Billing	Contact
ArchimedLife	DBS	No	No charge*	E: eumedicalservices@sanofi.com W: http://webportal.archimedlife.com (account required)
ARUP Laboratories	No	No	Inst	P: 800-522-2787 E: clientservices@aruplab.com W: www.aruplab.com
Centogene	Blood, DBS, Saliva	No	Inst, Self-pay, Ins	P: 617-580-2102 W: www.centogene.com E: customer.support-US@centogene.com
Greenwood Genetic Center	Blood, DBS, Saliva	No	Inst, Self-pay, Ins (SC residents only)	P: 800-473-9411 E: labgc@ggc.org W: www.ggc.org
Labcorp	Blood, Buccal	Yes	Inst, Ins, Self-Pay	P: 800-345-4363 W: www.labcorp.com
Mayo Clinic Laboratories	DBS, Saliva	Yes	Inst (ins can be billed in some cases, Inst account required)	P: 800-533-1710 E: mcl@mayo.edu W: www.mayocliniclabs.com
The Lantern Project (Revvity Omics)	Blood, DBS, Saliva	Yes	Inst, Self-pay (Revvity), No charge*	P: 866-354-2910 E: genomics@revvity.com W: www.LanternProjectDx.com W: www.revvity.com

***Testing is performed at no charge; local charges may apply for sample collection, processing, or shipping.**

avg TAT = average turnaround time; d = days; DBS = dried blood spot; del = deletion; dup = duplication analysis; incl = including; Ins = insurance; Inst = institution; min = minimum; WB = whole blood; wks = weeks.

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