Gaucher Disease and ASMD

Overview

Gaucher disease (GD) and acid sphingomyelinase deficiency (ASMD, historically known as Niemann-Pick disease (NPD) A, A/B, and B) are rare lysosomal enzyme deficiency disorders with phenotypic overlap.

Gaucher disease is caused by a deficiency in glucocerebrosidase (GBA) enzyme activity, encoded by the *GBA* gene. Deficiency or absence of this enzyme leads to a buildup of glycosylceramide (GL-1) and glucosylsphingosine (lyso-GL-1).[1]

ASMD is caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene that results 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 have a wide phenotypic spectrum ranging from severe neuronopathic forms to chronic visceral forms, with a chronic neurovisceral form between these two ends of the spectrum.[1,2]

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

Incidence of GD

Prevalence of non-neuronopathic Gaucher:
1 in 50,000-100,000 in the general population worldwide[3] and about 1 in 850 people of Ashkenazi Jewish heritage[3]

Incidence of ASMD

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

Diagnosis

Definitive diagnosis of GD is established by:

- Glucocerebrosidase enzyme assay: demonstrating deficiency[3]
- *GBA* 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
    - Six pathogenic variants (N370S, R496H, V394L, 84insG, A→1G+IVS2, and L444P) account for the majority (97%) of all pathogenic alleles in patients of Ashkenazi heritage[6]

Definitive diagnosis of ASMD is established by:

- Acid sphingomyelinase enzyme assay: demonstrating deficiency[7]
    - Should be done in parallel with glucocerebrosidase or reflexed if glucocerebrosidase is normal[4]
- *SMPD1* gene sequencing: demonstrating two pathogenic variants in *trans* (one from each parent)[2]
    - Three pathogenic variants (R496L, L302P, and fsP330) account for more than 90% of *SMPD1* mutant alleles in neuronopathic ASMD patients with Ashkenazi Jewish heritage. A single pathogenic variant, ΔR610, appears to be neuroprotective and is a common pathogenic variant in the chronic visceral form in multiple ethnic groups[4]

Gaucher Disease and ASMD

Inheritance GD

Autosomal recessive disorder caused by mutations in both copies of the *GBA* gene[1]

Inheritance ASMD

Autosomal recessive disorder caused by mutations in both copies of the *SMPD1* gene[2]

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

Clinical Findings

Gaucher Disease

- Hepatosplenomegaly, easy bruising and bleeding, bone and joint pain, pathologic fractures, fatigue, delayed growth in childhood, delayed puberty[7]
- Neuronopathic forms have eye movement abnormalities and a range of neurologic issues[3]

ASMD

- Hepatosplenomegaly, easy bruising and bleeding, bone and joint pain, fatigue, delayed growth in childhood, pulmonary dysfunction, frequent respiratory infections[2,4]
- Neuronopathic forms: Neurologic issues ranging from mild to severe developmental delay +/- regression, to ataxia and peripheral neuropathy[2]

Laboratory Testing

Gaucher Disease

- CBC: Thrombocytopenia, anemia[8]
- Hyperferritinemia[9]
- Clotting factors: decreased[8]
- Bone marrow aspirate/biopsy.* Gaucher cells, pseudogaucher cells. (normal biopsy does not rule out Gaucher)
- Glucosylsphingosine (lyso-GL-1, glucopsychosine): markedly elevated[10,11]

ASMD

- CBC: Thrombocytopenia, anemia[4]
- Lipids: low HDL, elevated LDL, elevated triglycerides[4]
- LFTs: AST, ALT are typically elevated but can be normal[4]
- Bone marrow biopsy*: Lipid-laden foam cells; (normal biopsy does not rule out ASMD)[4]
- 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

- MRI of long bones: marrow infiltration, osteonecrosis, lytic lesions, Erlenmeyer flask deformity[7]
- Skeletal imaging: reduced bone density, pathologic fractures, delayed bone maturation[1]
- Liver and spleen volumes may be measured by volumetric MRI or CT scan: splenomegaly <5 x to >15x normal[12]
- Opthalmological (Neuronopathic forms): slowing of horizontal saccadic eye movement is virtualy pathognomonic for GD3[13]

ASMD

- CT scan (pulmonary): ground glass appearance, interstitial lung disease, reticulonodular density[4]
- Imaging of liver: hepatomegaly, fibrosis, cirrhosis[4]
- Imaging of spleen: splenomegaly <5x to 30x normal[4]
- Skeletal imaging: reduced bone density, pathologic fractures, delayed bone maturation[4]
- Opthalmologic: retinal changes (macular halo to cherry red maculae) can be seen in type A and B[14]

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MAT-US-2013809v1.0 July 2020

Testing Options for Gaucher Disease and Acid Sphingomyelinase Deficiency

Sanofi Genzyme does not review or control the content of non-Sanofi Genzyme websites. These listings do not constitute an endorsement by Sanofi Genzyme of information provided by any other organizations. The following is a selection of laboratories offering both Gaucher disease enzyme assay (β-glucosidase or glucocerbrosidase), ASM enzyme assay (acid sphingomyelinase) and/or *GBA* and *SMPD1* sequencing, respectively. This is not an exhaustive list of labs that offer one or the other, or an endorsement of any one lab. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. Content is current at time of printing and tests may not be available in all states; please contact the laboratory to confirm test availability, sample shipping information, and all other logistics.

Lab	Available Testing	GD	ASMD	Sample Requirements	Kits	Avg TAT	Mobile Blood Draw	Billing	Contact
ARUP Laboratories	Enzyme	√		WB: 3 ml ACD (yellow), EDTA (lavender) or sodium heparin (green) tube	No	3-10 d	No	Inst	**P:** 800-522-2787 **E:** clientservices@aruplab.com **W:** www.aruplab.com
	Sequencing	√		WB: 3 ml ACD (yellow), EDTA (lavender) tube		2-3 wks			
Centogene	Enzyme	√	√	WB: 5ml EDTA (lavender) tube; DBS card: 10 circles	Blood, DBS, Saliva	7 d	Yes	Inst, Self-pay, Ins	**P:** 617-580-2102 **E:** customer.support-US@centogene.com **W:** www.centogene.com
	Sequencing (+/- Del/Dup)	√	√	WB: 1ml EDTA (lavender) tube; DBS card: 10 circles; Saliva; Buccal swab		15 d			
	Lyso-GL-1	√		WB: 1ml EDTA (lavender) tube; DBS card: 10 circles		7 d			
	LSM-509		√	WB: 1ml EDTA (lavender) tube; DBS card: 10 circles		7 d			
EGL Genetics/ Eurofins	Enzyme	√		WB: 3-5 ml sodium heparin (green) tube	Blood, DBS, Saliva	7-10 d	No	Inst, Self-pay, Ins	**P:** 855-831-7447 **E:** eglcs@egl-eurofins.com **W:** www.egl-eurofins.com
	Sequencing	√	√	WB: 2-10 ml EDTA (lavender) tube (volume varies with age);Saliva (per Oragene kit)		6 wks			
	Del/Dup		√			2 wks			
Greenwood Genetic Center	Enzyme	√	√	WB: 5-10 ml (3-5 ml for ASMD) sodium heparin (green) tube; DBS card: 3 circles	Blood, DBS, Saliva	2 wks	No	Inst, Self-pay, Ins (SC residents)	**P:** 800-473-9411 **E:** labgc@ggc.org **W:** www.ggc.org
	Sequencing	√	√	WB: 5-6 ml EDTA (lavender) tube; DBS card: 3 circles; Saliva		3 wks			
LabCorp/ Integrated Genetics	Enzyme	√		WB: 2x 10ml EDTA (lavender) tube (peds 1 x 10ml) Note: LabCorp Test Code: 451780; Integrated Test Code: 370	Blood, Buccal	7-13 d	Yes	Inst Self-Pay, Ins	**LabCorp Customers:** **P:** 800-345-4363 **W:** www.labcorp.com **Integrated Customers:** **P:** 800-848-4436 **E:** asklGclientservices@integratedgenetics.com **W:** www.integratedgenetics.com
	Sequencing	√	√	WB: 8.5 ml EDTA (lavender) or ACD (yellow) tube Note: For sequencing done via "Inheritest Gene-Specific Sequencing". Indicate *GBA* or *SMPD1* gene as needed		9-15 d			
The Lantern Project (PerkinElmer Genomics)	Enzyme	√	√	WB: 2-10 ml sodium heparin (green) tube (volume varies with age); DBS card: 3 circles	Blood, DBS, Saliva	3 d	Yes	No charge*	**P:** 866-354-2910 **E:** genomics@perkinelmer.com **W:** www.LanternProjectDx.com
	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			
Mayo Clinic Laboratories	Enzyme	√		WB: 6 ml ACD (yellow) tube	DBS, Saliva	5-10 d	Yes	Inst, Ins (can be billed in some cases but account required)	**P:** 800-533-1710 **E:** mcl@mayo.edu **W:** www.mayocliniclabs.com
	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); Plasma: 0.3 ml; DBS card: 2 circles *(Note: Order codes GPSY, GPSYP, or GPSYW)*		2-8 d			
	Oxysterols		√	WB: 1ml 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			
National Gaucher Foundation	Enzyme	√	√	Contact the National Gaucher Foundation at www.gaucherdisease.org/intakeform			Yes	No charge*	**W:** www.gaucherdisease.org/intakeform
	Sequencing	√	√						
Seattle Children's Hospital	Enzyme	√		WB: 10 ml ACD (yellow) or sodium heparin (green) tube	DBS, Saliva	7-10 d	No	Inst, Self-Pay, Ins	**P:** 206-987-2617 **E:** labGC@seattlechildrens.org **W:** https://seattlechildrenslab.testcatalog.org
	Sequencing	√	√	WB: 1- 3 ml EDTA (lavender) or ACD (yellow) tube		2-3 wks			
Sema4	Enzyme	√	√	WB: 5-10 ml sodium heparin (green) tube	Blood, Saliva	7 d	Yes	Inst, Self-Pay, Ins	**P:** 800-298-6470 **E:** clientservices@sema4.com **W:** www.sema4.com
	Sequencing	√	√	WB: 5-10 ml ACD (yellow) AND 2 x 5-10 ml EDTA (lavender); Saliva		14 d			
	Lyso-GL-1	√		WB: 1-2 ml EDTA (lavender) or heparin (green) tube; Frozen plasma: 0.5-1 ml		5 d			

***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; GPSY = glucopsychosine; Ins = insurance; Inst = institution; min = minimum; peds = pediatric patients; WB = whole blood; wks = weeks.

MAT-US-2013809v1.0 July 2020