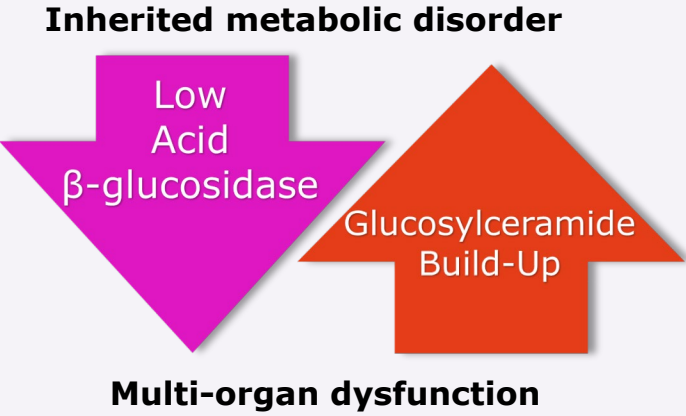


Gaucher Disease Type 3 (GD3): A Neuronopathic Form of Gaucher Disease

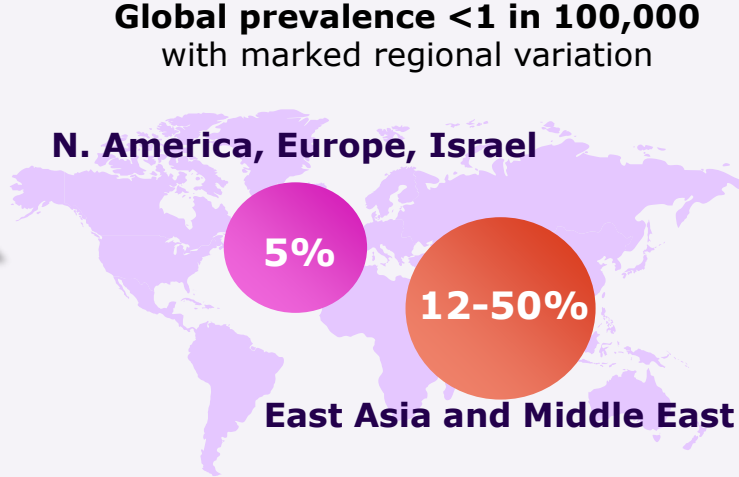
GD Pathology¹



Types of GD

- GD3** – chronic neuronopathic
- GD2** – acute neuronopathic
- GD1** – non-neuronopathic

Prevalence of GD3⁶⁻¹²



GD3: Chronic Neuronopathic Disease²⁻⁵

- CNS symptoms may manifest early in childhood
- Slow, variable progression
- Heterogeneity in neurologic and systemic manifestations
- Premature death

Neurologic Manifestations²

Hallmarks of GD3: 1

Eye Abnormalities
Gaze palsy with markedly slow or absent horizontal saccades

3 Cognitive Deficits
Variable, develop in childhood

2 Movement Disorders
Ataxia
Seizures
Myoclonic epilepsy
Tremor
Dystonia

3 Hyperreflexia
without a pyramidal syndrome

3 Bulbar Disorders
Stridor
Dysphagia
Dysarthria

Organ Enlargement
Splénomegaly
Hepatomegaly

3 Bone disease
Osteonecrosis
Osteoporosis
Pathologic fractures
Bone pain, bone crisis
Growth delay & deficits

Hematologic Abnormalities
Anemia
Thrombocytopenia

Systemic Manifestations¹

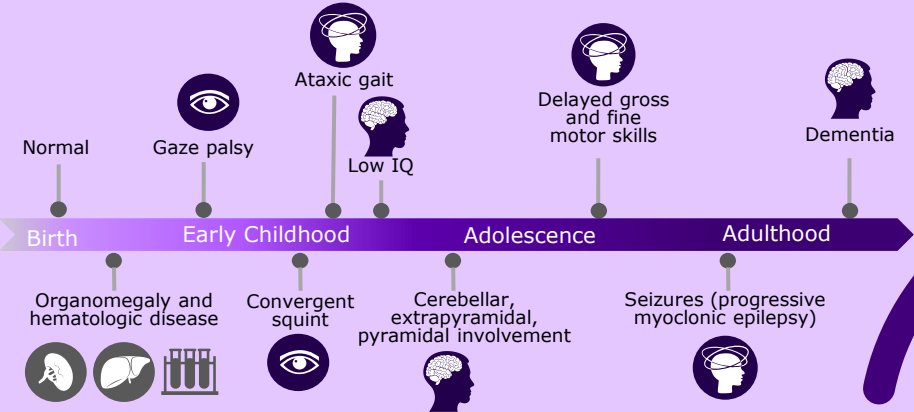
CNS, central nervous system; ERT, enzyme replacement therapy; SRT, substrate reduction therapy.
 1. Grabowski GA. *Lancet*. 2008; 372: 1263-71; 2. Schiffmann R, et al. *J Inherit Metab Dis*. 2020;1-4. <https://doi.org/10.1002/jimd.12235>; 3. Vellodi A, et al. *J Inherit Metab Dis*. 2009 Oct;32(5):660-4; 4. Tytki-Szymańska A, et al. *J Inherit Metab Dis*. 2010;33:339-346; 5. Grabowski GA, et al. *Am J Hematol*. 2015. 90:S12-S18.; 6. Poupetova H, et al. *J Inherit Metab Dis*. 2010;33(4):387-396; 7. Charrow J, et al. *Arch Intern Med*. 2000; 160(18):2835-2843; 8. Tajima A, et al. *Mol Genet Metab*. (2009); 94(4):272-7; 9. Jeong SY et al. *Blood Cells Mol Dis*. 2011; 46(1):11-14; 10. El-Morsy Z, et al. *World J Pediatr*. 2011;7(4):326-330; 11. Choy FY, et al. *Blood Cells Mol Dis*. 2007;38(3):287-293; 12. Bdelwahab M, et al. *Neurol Genet*. 2016;2 (2):e55; 13. El-Beshlawy A, et al. *Mol. Genet. Metab*. 2017;120:47-56; 14. Stirmemann J, et al. *Int J Mol Sci*. 2017, 18, 441; doi:10.3390/ijms18020441; 15. Hamed A, et al. A conceptual framework of patient-reported outcomes for Gaucher disease type 3. 13th Annual WORLD Symposium, Feb. 13-17, 2017; 16. Peterschmitt MJ, et al. *Clin Pharm Drug Dev*. 2021;10(1):86-98; 17. Parenti G. *EMBO Mol Med*. 2009;1:268-279; 18. Blum A. National Gaucher Foundation. March 20, 2020: <https://www.gaucherdisease.org/blog/gene-therapy-for-gaucher-disease-aav-lentivirus-more/>.



Disease Course, Diagnosis, and Management of GD3

Neurologic Disease Course^{1,2}

Significant heterogeneity of neurologic manifestations, with eye movement disorder as a hallmark



No approved treatment for neurologic GD manifestations

Impact on Quality of Life¹⁵

- Difficulty shifting gaze or tracking objects
- Lack of self confidence, Distress over work/school performance, Depression/anxiety
- Slow information processing, Difficulty solving problems/making decisions, Diminished intelligence, Memory problems
- Declining independence, Less ability to work or attend school, Limited social engagement, Limited travel ability
- Fatigue/low energy

Diagnosis^{1,2}



Laboratory Testing

- Reduced acid β -glucosidase activity and *GBA1* gene mutations
- Genotype: p.Leu483Pro (formerly L444P) variant is common and correlated with neurologic involvement in homozygous individuals
 - 81% have at least one allele¹³
 - 60% are homozygous¹³



Clinical Assessment

- Primary: gaze palsy, predominantly horizontal with slow or absent saccades
- Other variable neurologic deficits (see previous page)

Emerging Treatment Concepts

- Systemic manifestations in GD3 patients historically have been treated with ERT^{2,14}
- Therapies that cross the blood-brain barrier are needed to treat neurological manifestations

Emerging Therapies in Development



Substrate Reduction Therapy¹⁶
small-molecule, oral administered glucosylceramide synthase inhibitor



Gene Therapy¹⁸
viral vector-based delivery of a functional *GBA1* gene



Pharmacologic Chaperones¹⁷
chaperone molecules that correct folding of mutated enzymes to improve lysosomal trafficking

