INBORN ERRORS OF METABOLISM - II

CLINICAL PRESENTATION AND ENZYME REPLACEMENT THERAPY IN LYSOSOMAL STORAGE DISORDERS - LESSONS FROM INDIA AND GLOBAL CENTRES

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Abstract: *Lysosomal storage disorders are a group of genetic metabolic disorders which usually present with a chronic course and have varied manifestations with multisystemic involvement including hepatosplenomegaly, cytopenias, global developmental delay and/or psychomotor regression, seizures and growth failure. This group consists of around 70 clinically and genetically heterogeneous conditions. The past few decades have witnessed the development of enzyme replacement therapies and other disease-specific treatment strategies for lysosomal storage disorders. This article reviews the clinical presentations, available enzyme replacement therapies and other therapeutic modalities with special reference to some of the relatively common lysosomal storage disorders i.e., Gaucher disease, Pompe disease, mucopolysaccharidoses and Fabry disease.*

Keywords: *Lysosomal storage disorders, Clinical manifestations, Enzyme replacement therapy.*

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Points to Remember

- ***Enzyme replacement therapy (ERT) improves systemic manifestations but cannot cross the blood-brain barrier, so neurological disease generally continues to progress.***
- ***Early initiation of ERT-especially in infantile Pompe disease, severe MPS I and Fabry disease-produces significantly better clinical outcomes.***
- ***ERT requires lifelong weekly or biweekly infusions and remains expensive, making sustained access a major challenge in India.***
- ***Although ERT benefits visceral, cardiac, and skeletal systems, it has limited effect on poorly vascularized tissues such as the cornea and bones.***
- ***Emerging treatments like substrate reduction therapy, chaperone therapy and gene therapy are increasingly important additions where ERT alone is insufficient.***

References

1. Fuller M, Meikle PJ, Hopwood JJ. Epidemiology of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 2. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11603/
2. Penati R, Fumagalli F, Calbi V, Bernardo ME, Aiuti A. Gene therapy for lysosomal storage disorders: recent advances for metachromatic leukodystrophy and mucopolysaccharidosis I. J Inherit Metab Dis. 2017; 40(4):543-554.
3. Sheth J, Nair A, Jee B. Lysosomal storage disorders: from biology to the clinic with reference to India. Lancet Reg Health Southeast Asia. 2022;9:100108.
4. Hughes DA, Pastores GM. Gaucher Disease. 2000 Jul 27 [Updated 2023 Dec 7]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1269/

Cite as: Prajnya Ranganath, Sankar VH, Clinical presentation and enzyme replacement therapy in lysosomal storage disorders - Lessons from india and global centres, Indian J Pract Pediatr. 2025; 27(4):315-322.

5. Sperry E, Leslie N, Berry L, et al. Pompe Disease. 2007 Aug 31 [Updated 2025 Aug 21]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1261/
6. Zhou J, Lin J, Leung WT, Wang L. A basic understanding of mucopolysaccharidosis: Incidence, clinical features, diagnosis, and management. Intractable Rare Dis Res. 2020;9(1):1-9.
7. Clarke LA. Mucopolysaccharidosis Type I. 2002 Oct 31 [Updated 2024 Apr 11]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1162/
8. Scarpa M, Lampe C. Mucopolysaccharidosis Type II. 2007 Nov 6 [Updated 2025 Jan 16]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1274/
9. Mehta A, Hughes DA. Fabry Disease. 2002 Aug 5 [Updated 2024 Apr 11]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1292/
10. Rosenfeld MG, Kreibich G, Popov D, Kato K, Sabatini DD. Biosynthesis of lysosomal hydrolases: their synthesis in bound polysomes and the role of co- and post-translational processing in determining their subcellular distribution. J Cell Biol. 1982; 93(1):135-43.
11. Muro S. New biotechnological and nanomedicine strategies for treatment of lysosomal storage disorders. Wiley Interdiscip Rev NanomedNanobiotechnol. 2010; 2(2):189-204.
12. Fernández-Pereira C, San Millán-Tejado B, Gallardo-Gómez M, Pérez-Márquez T, Alves-Villar M, Melcón-Crespo C,et al. Therapeutic Approaches in Lysosomal Storage Diseases. Biomolecules. 2021;11(12):1775.
13. Elder ME, Nayak S, Collins SW, Lawson LA, Kelley JS, Herzog RW, et al. B-Cell depletion and immunomodulation before initiation of enzyme replacement therapy blocks the immune response to acid alpha-glucosidase in infantile-onset Pompe disease. J Pediatr. 2013; 163(3):847-54.e1.
14. Schiffmann R, Goker-Alpan O, Holida M, Giraldo P, Barisoni L, Colvin RB, et al. Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: A 1-year Phase 1/2 clinical trial. J Inherit Metab Dis. 2019; 42(3):534-544.
15. Malatack JJ, Consolini DM, Bayever E. The status of hematopoietic stem cell transplantation in lysosomal storage disease. Pediatr Neurol. 2003; 29(5):391-403.
16. Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebícek M, et al. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet. 2000; 355(9214): 1481-1485.
17. Parenti G, Pignata C, Vajro P, Salerno M. New strategies for the treatment of lysosomal storage diseases (review). Int J Mol Med. 2013; 31(1):11-20.
18. Stirnemann J, Belmatoug N, Camou F, Serratrice C, Froissart R, Caillaud C, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. Int J Mol Sci. 2017; 18(2):441.
19. Desnick RJ, Schuchman EH. Enzyme replacement and enhancement therapies: lessons from lysosomal disorders. Nat Rev Genet 2002; 3: 954–966.
20. Donald A, Horgan C, De Castro Lopez MJ, Jones SA, Wynn RF. Gene therapy in neuronopathic lysosomal storage disorders. Eur J Pediatr Neurol. 2025; 57:41-49.
21. Muranjan M, Karande S. Enzyme replacement therapy in India: Lessons and insights. J Postgrad Med. 2018; 64(4):195-199.
22. National Policy for Rare Diseases, 2021. Available at: https://rarediseases.mohfw.gov.in/uploads/Content/1624967837_Final-NPRD-2021.pdf.