**Abstract Title:** HSCT in Lysosomal Storage Disorders

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**Abstract:** Lysosomal storage disorders result from inherited gene mutations that disturb lysosomal homeostasis. Deficiency of lysosomal enzymes and also some non-enzymatic lysosomal proteins lead to abnormal storage of macromolecular substrates in the lysosomes and other membrane bound organelles within the cell.

Majority have an autosomal recessive pattern of inheritance except three of which have an X linked inheritance pattern (MPS II, Fabry disease and Danon disease). LSD have an incidence of 1 in 5000 live births. Gaucher's disease was the first LSD described and has become a prototype for the clinical description and phenotypic variability of more than 50 LSDs.

Pathogenesis: LSDs occur from primary substrate accumulation (due to the respective enzyme deficiency) followed by secondary substrate accumulation (due to inhibition of catabolic enzymes by the accumulated primary substrate). This initiates a cascade of events with aberrant inflammatory response and activation of apoptotic signalling pathways that impacts other organelles (mitochondria, endoplasmic reticulum, golgi apparatus, peroxisomes) leading to cellular dysfunction and death and ultimately organ damage.

Clinical phenotypes of LSDs: The main classes of LSDs include-Sphingolipidosis, Mucopolysaccharidosis (MPS), Glycoproteinosis, Glycogen storage disorders and Neuronal ceroid lipofuscinosis- based on type of storage material Age of onset of symptoms and clinical spectrum differ depending on the degree of protein function affected by specific mutations, toxicity of stored material and cell type where storage occurs. Most babies are normal at birth (apart from those LSDs with substrate storage in bone and cartilage). Central nervous system involvement is common with classical presentation being Neurodegenerative disorder of infancy /childhood; (adult onset variants also occur uncommonly) , other features being coarse facial features, organomegaly, skeletal dysostosis and defective immune system.

Role of HSCT :

Donor derived myeloid cells produce enzymes, which are then taken up by enzyme deficient host cells. Superiority of HSCT over ERT lies in its exploitation of donor derived cells to mitigate across the blood brain barrier and differentiate into tissue macrophages(microglia) which secrete the deficient enzyme to the CNS, improving neurocognitive outcomes. HSCT however has been beneficial only in selected group of LSDs

**Area of expertise:** Stem Cell Transplant