Enzyme Replacement Therapy for Lipid Storage Disorders

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Effects of Enzyme Therapy (ET) in Gaucher Disease Type 1

- Hepatosplenomegaly and peripheral blood cytopenias – Major corrections
  - Resolution of hepatosplenomegaly
  - Cortical and trabecular bone
    - Major issue of developing vs. mature skeleton
    - Differential remodeling in bony compartments
    - Bone density vs. irreversibly damaged bone

- Incomplete ET effect
  - Cortical/trabecular bone
  - Pulmonary hypertension and alveolar involvement
  - Lymph node infiltration
  - CNS involvement
LAL Deficiency (LALD)

Blocks egress of cholesterol and TG-derived FFA from lysosome
CEs and TGs accumulate in lysosomes
Cytoplasmic cholesterol deficiency
Metabolic cascade in *de novo* cholesterol synthesis turned on
Lysosomal Acid Lipase Deficiency
Lysosomal Acid Lipase (LAL) Deficiency

- LAL Deficiency is a rare, autosomal recessive disorder caused by a decrease or absence of the LAL enzyme.
- Leads to an accumulation of cholesteryl esters and triglycerides in various tissues, which results in hepatomegaly, splenomegaly, and liver fibrosis/cirrhosis.

Differential Diagnosis:
- Non-Alcoholic Fatty Liver Disease (NAFLD)
- Non-Alcoholic Steatohepatitis (NASH)
- Alcoholic Liver Disease
- Cryptogenic Cirrhosis
- Niemann-Pick Disease (NPD) Type C
- Chanarin Dorfman Syndrome
METABOLIC DEFECT IN FABRY DISEASE

\[ \text{Gal} \xrightarrow{?} \text{Gal} \rightarrow \text{Glu} \rightarrow \text{Ceramide} \]

\[ ?-\text{Galactosidase A} \]

\[ (?-\text{Gal A}) \]

\[ \text{Gal} + \text{Gal} \rightarrow \text{Glu} \rightarrow \text{Ceramide} \]
PHENOTYPIC SPECTRUM OF FABRY DISEASE

Affected Males

Later-Onset Phenotypes:

Classic Phenotype

<1% Increasing a-Gal A Activity

Cardiac Subtype

>1% Later-Onset Phenotype

Renal Subtype

Classic Phenotype

(Severe Disease)

Years

0 10 20 30 40 50 60 70 80 90 100
CLASSIC PHENOTYPE: FUNDAMENTAL PATHOLOGY

Microvascular Endothelial Glycolipid Deposition

Narrowing (Ischemia) \rightarrow Occlusion, Necrosis & Fibrosis
<table>
<thead>
<tr>
<th>Vascular Glycolipid Deposition</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Angiokeratoma</td>
</tr>
<tr>
<td>Peripheral Nerves</td>
<td>Acroparesthesias; Excruciating Pain</td>
</tr>
<tr>
<td>Sweat Glands</td>
<td>Hypohidrosis</td>
</tr>
<tr>
<td>Intestine</td>
<td>Abdominal Pain/Diarrhea</td>
</tr>
<tr>
<td>Heart</td>
<td>Myopathy, HCM, Arrhythmias</td>
</tr>
<tr>
<td>Brain</td>
<td>TIAs, Strokes</td>
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<tr>
<td><strong>Kidney</strong></td>
<td><strong>Renal Failure</strong></td>
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</tbody>
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**Average Age at Death** ~40 Years