AN INTERACTIVE GUIDE TO THE UNDERDIAGNOSED AND UNDERESTIMATED BUT TREATABLE METABOLIC DISORDERS

Lysosomal Storage Disorders (LSDs) are more common than you might think but recognizing them can be difficult

Epidemiology

Individually

1: 50,000 – 1,000,000

Together

1: 7,000

Newborn screening programs find **5–80x** more cases than estimated

- Late-onset or attenuated variants may not be recognized or diagnosed
- Misdiagnosis is common
- Missed diagnoses are also common
- Variable presentation–in same family or even same genotype–makes diagnosis difficult

Barriers to recognition

- Misdiagnosis is common and leads to diagnostic delays

Mean time to correct diagnosis after first symptoms in patients with Fabry Disease

13.7 Years **16.3 Years**

- Affected infants may appear healthy at first
- Symptoms overlap with other disorders
- LSD presentations are highly variable, even within the same family
- Mild early symptoms may be present but not spotted
- Family history may be misleading because of missing information, missed diagnoses or misdiagnoses, or the inheritance pattern

Identifying an LSD requires clinical recognition of red flags that implicate multi-system involvement

Look for clinical signs and symptoms of multi-organ symptom complexes

Apply consensus diagnostic algorithms in patients who have signs and symptoms that put an LSD in the differential diagnosis

Interpret newborn screening results (where available)

Treatments are available but must be started early

Enzyme Replacement Therapy (ERT)

Replaces the missing enzyme with a recombinant enzyme

1% to 5%
Amount of enzyme activity needed to correct deficiency

1. Enzyme is modified for cellular uptake and transport to lysosome
2. Recombinant enzyme is produced in cell culture and isolated
3. Patients receive weekly or monthly intravenous or intrathecal injections
4. Enzyme enters lysosome...
5. ...and breaks down the accumulated substrate

In some LSDs, HSCT can be used to replace the missing enzyme activity or may be the preferred approach

ERT does not reach all tissues equally, and does not cross the blood-brain barrier

Risk of anti-enzyme antibody response can reduce treatment effectiveness

Oral Chaperone Therapy (OCT)

Corrects the defect caused by some mutations

1. Some mutations affect the enzyme structure or trafficking, as well as its function
2. These proteins can be labeled for degradation or rescued by a chaperone
3. A chaperone stabilizes the enzyme structure, allowing proper trafficking and improved function
3. Misfolded or defective enzymes are sent to the proteasome for degradation

Small molecule chaperones may cross the blood brain barrier

Only works for specific missense mutations (aka, "amenable mutations"), and never for deletions

Substrate Reduction Therapy (SRT)

Affects the upstream biochemical pathway to reduce production of the substrate before it can accumulate

Normal Metabolism

1. Metabolic processes produce substrate
2. Metabolite sent to lysosome for degradation
3. Enzyme catalyzes the conversion of the metabolite to the product
4. Normal pathway leads to metabolism of the product

Substrate → Enzyme → Product

Disrupted Metabolism in LSDs

1. Metabolic processes continue to produce substrate
2. Metabolite accumulates in lysosome
3. Absent or defective enzyme cannot complete metabolic pathway

Substrate → Enzyme

SRT disrupts the upstream metabolic processes to avoid substrate accumulation in the lysosome