Lysosomal Storage Diseases
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Lysosomes are intracellular organelles. Lysosomes contain a number of enzymes used to catabolize proteins, nucleic acids, lipids and complex carbohydrates. Each lysosomal enzyme reduces a particular macromolecule to a smaller component. These smaller pieces can then be eliminated from the body. Defects in various enzymes in these pathways result in the accumulation of proteins, carbohydrates, lipids or complex carbohydrates. These defects are large to be eliminated from the cell/body.

Group of over 40 known disorders.
Inborn error of metabolism.
Incidence 1:7700 for all lysosomal disorders
- Cystic Fibrosis
  1:3000 (Caucasians)
- Down Syndrome
  1:700-1000, 1:100 for moms > 40
Graph of all Lysosomal Diseases

- Gaucher
- MPS I – Hurler
- WCD
- MPS II – Sanfilippo
- MPS II – Hunter
- Niemann-Pick
- Krabbe
- Pompe
- MPS IV – Morquio
- Tay-Sachs
- Fabry

Lysosomal Storage Disorders

Metachromatic leukodystrophy

Sulfatides

GMαmannosidase

Tay-Sachs

GMαgalactosidase

Gaucher

Ceramide trihexosidase

Sphingomyelin

Niemann-Pick

When to suspect a Lysosome Storage Disorder

- Organomegaly
- Unexplained joint stiffness
- Coarse facial features, especially if they are worsening.
- Unexplained pain in children, burning neuropathic pain or bone pain.
- Loss of developmental milestones and progressive dementia can be a sign of a muscular or neurologic problem.
Case 1

This is a 9 month old boy who comes for a well child check.

- Mom concerned that he has gross motor and speech delays – he sits unassisted, but is not pulling to stand, not crawling. He babbles, no mama, dada. He reaches for objects with open hand, rake grasp.
- He was born at 32 weeks premature, corrected 7 months now.

Physical Exam

- Weight 10kg (95% corrected), Length 28cm (75% corrected), Head Circumference 50cm (>95%)
- HEENT: macrocephalic, external canals small, PE tubes bilaterally, nasal congestion.
- Abdomen: soft, nontender, liver 1cm below costal margin.
- Firm mass on his thoracic back, mid-line.
- Extremities: short fingers, decreased joint mobility

More subtle physical exam features

- Coarse facial features
- Depressed nasal bridge
- Upturned nose
- Large tongue
- Hirsutism – eyebrows bushy, low hair line
- Broad hands and feet, stubby fingers
- Umbilical hernia
- Protuberant abdomen
Gibbus

- Structural kyphosis
- Sharply angled spinal curve
- More prominent when sitting or leaning forward
- Forms because anterior vertebral body collapses forming a "wedge deformity"
- Differential?
  - Infections especially TB (Pott's disease)
  - Mucopolysaccharidosi (MPS)
  - Mucolipidosis
  - Achondroplasia
  - Meningomyelocoele

A study which can be used to determine if the individual has a mucopolysaccharide disorder is

- A. Serum amino acids
- B. Urine organic acids
- C. Urine for glycosaminoglycans
- D. Lactic acid
- E. Serum Carnitine

Mucopolysaccharidosis

MPSI

Hurler
Hurler-Scheie
Scheie
Glycosaminoglycans (GAGs) are used in many tissues for structural support.
Lysosomal enzymes are responsible for the degradation of glycosaminoglycans (GAGs).
Deficiency in alpha-L-iduronidase in MPS I
Other enzyme deficiencies result in other lysosomal storage disorders.

Autosomal recessive
Carriers are asymptomatic
Affects all ethnic groups equally
1/100,000

Coarse facial features
- Short nose with wide upturned nostrils
- Flat face
- Prominent forehead
- Large head
- Thick lips, large tongue
- Contractures of fingers
- Usually normal at birth and typical features become more prominent as the child ages.
Progression Of the disease process

Clinical Complications

- **Ocular:**
  - corneal clouding (ground glass)
  - glaucoma
  - retinal disease
- **ENT:**
  - chronic rhinitis
  - otitis media
- **Cardiovascular:**
  - valvular disease
  - cardiomyopathy
  - MOST COMMON cause of death
- **CNS:**
  - hydrocephalus
  - progressive developmental delay

Skeletal Manifestations

- Gibbus deformity
- Abnormal clavicles (short and thick)
- Hip dysplasia
- Claw hand deformity
- Joint stiffness
- Growth retardation
Diagnosis of MPS1

- Urinary Glycosaminoglycans (Gags) is an inexpensive screening test when a mucopolysaccaride diagnosis is considered.
- Dermatin and Heparin Sulfate are both elevated in patients with MPS1 and MPS2.
- Enzyme assay is needed to confirm a specific diagnosis.
- Most affected patients have < 1% enzyme activity for the alpha-l-iduronidase enzyme.
- DNA analysis for the IDUA gene identifies 2 gene mutations in 100% of affected patients.

Disease Course

- Severity depends on the amount of alpha-l-iduronidase enzyme.
- Patients with little to no enzyme die from cardiac issues and respiratory infection usually before age 10.

Enzyme Replacement

- Aldurazyme® (laronidase) has been approved for clinical trial therapy. It is infused on a weekly basis.
- In early studies patients show improvement in organomegaly and skeletal features.
- Enzyme cannot cross blood brain barrier.
- In Scheie and Hurler Scheie, there is enough enzyme that patient do not have cognitive delays.
A study which can be used to determine if the individual has a mucopolysaccharide disorder is
A. Serum amino acids
B. Urine organic acids
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Hunter Syndrome MPSII
- X-linked Recessive Inheritance
- Occurs in 1/100,000 live born males
- Clinical Features similar to Hurlers
- Presents between ages 2 and 4.
- Disease only seen in males
- Female carriers are usually asymptomatic

Clinical Features of Hunter Syndrome
- Progressive developmental delay
- Hearing impairment
- Progressive thickening of the heart wall.
- Growth deficiency
- Aggressive behavior
- No corneal clouding
- May have progressive visual loss due to pressure on the optic nerve.
- Nodular skin lesion on the skin
Diagnosis of Hunter Syndrome

- Elevation of Dermatin and Heparin Sulfate on urine glycosaminoglycan screen (GAG’s)
- Enzyme Deficiency: Iduronate Synthetase.
- Enzyme therapy is available.

Sanfilippo Syndrome

MPS III

- Three types, A,B,C
- They are caused by different enzyme deficiencies.
- All are inherited autosomal recessive
- Enzyme therapy is currently being studied.

Clinical Features of Sanfilippo A

- Hepatosplenomegaly
- Progressive coarsening of facial features
- Progressive mental retardation
- Athetoid movements
- Normal skeletal features, no joint involvement
- Urine glycosaminoglycans shows elevation of only Heparin Sulfate
- No treatment available
Morquio Syndrome MPS VII

- Severe skeletal anomalies
- Cloudy cornea
- Aortic regurgitation
- Coarse facies
- Pectus carinatum
- Intelligence normal
- Deficiency of the enzyme galactosamine-6-sulfatase deficiency
- Autosomal recessive
- Urine glycosaminoglycans shows elevation of Keratin sulfate
- Enzyme treatment is available clinically.

Case 2

- A 12-year-old male has a 1 year history of pain and tingling in his hands and feet.
- He has difficulty sweating. He comes in the house in the summer with a red face and can’t tolerate outdoor sports.
- Recently he began having developing a nonblanching rash on his abdomen.

Family History

- The mother had an MI at age 46
- She has one sister who had a stroke at age 44, now 53
- Another sister had a stroke at 42 and died of an MI at age 45.
- The maternal grandmother died of an MI at age 56.
- Her brother died of renal failure at age 39.
Fabry’s Disease

- Occurs in 1/40,000 individuals
- Males often first start showing signs of this disorder in early adolescence.
- Early symptoms include inability to sweat, whorl keratopathy, acroparesthesias (pains in the hands and feet), angiookeratomas (rash)

Inheritance Pattern

- X-linked inheritance pattern
- Heterozygous females can have symptoms ranging from mild to severe.

Fabry Disease

- Caused by deficiency of the enzyme alpha galactosidase A.
- This results in deposition of globotriaosylceramide in vascular endothelium
- The glycolipid deposits in endothelial cells of smooth muscle in the blood vessels.
- This results in narrowing of the vessels and ischemia.
- Smallest capillaries, kidney heart brain.
In Fabry disease the most common cause of death in males and females is

- A. Stroke
- B. Renal Failure
- C. Myocardial Infarction
- D. Leukemia
- E. Hyperthermia

Clinical Features of Fabry

- Clinical Features include
  - Angiokeratomas (non blanching lesions)
  - Inability to sweat
  - Intolerance of heat and cold
  - Acroparesthesia
  - Cardiac abnormalities
    - Left ventricular hypertrophy
    - Mitral valve prolapse and/or regurgitation
  - Premature stroke

Ocular Finding

- Whorl karotopathy
- Can also be seen in females
- This can be used to diagnosed carrier females.
Many of the women with one abnormal gene for the enzyme Alpha Galactosidase A have symptoms as severe as a male with no functional gene. Renal failure often occurs later than their male counterparts however heart disease especially arrhythmias and early stroke are more common in females.

The main problem seen with these patients is the accumulation of lysosomal byproducts in the cells. This occludes the microvasculature in the kidneys, heart and brain. This occlusion results in the death of tissues or ischemia. Cardiovascular disease is the most common cause of death in both males and females.
Enzyme Replacement

- Biweekly treatments with enzyme replacement has been shown to slow the progression of renal disease and improve neurologic symptoms.
- There is a new therapy known as a "chaperone". This is a substance that helps "fold" to protein so it can enter the golgi and be brought to the lysosomes.

Molecular Chaperone Therapy

- A chaperone is a substance which stabilizes and restores the 3-D structure of the nonfunctioning enzyme. This restores the activity of the enzyme.
- These are oral medications

In Fabry disease the most common cause of death in males and females?
- A. Stroke
- B. Renal Failure
- C. Myocardial Infarction
- D. Leukemia
- E. Hyperthermia
Case 3

- Mr. W is a 48 year old man who presents to his primary care physician complaining of pain in the left upper quadrant.
- A CBC indicates mild thrombocytopenia with a platelet count of 82.
- CT scan of the abdomen indicates moderate splenomegaly and hepatomegaly.

Past Medical History

- Mr. W has suffered from right shoulder pain for the past 10 years.
- He was diagnosed with a low platelet count 7 years ago.
- He had a history of anemia for the past 3 years.

Physical Exam

- The spleen is palpable 4cm below the costal margin.
- The liver is palpable 6.5cm below the right costal margin.
Family History

- His mother was diagnosed with idiopathic thrombocytopenia. She had a splenectomy.
- She is of Jewish and Italian descent.
- The father is of Jewish descent.
- The patient has two children ages 17 and 15. Both are healthy.

Medical Complications

- Hepatosplenomegaly
- Thrombocytopenia
- Anemia
- Family history of thrombocytopenia

Differential Diagnosis?

- What disorders result in anemia, thrombocytopenia and hepatosplenomegaly?
- How does the pain fit in?
- What laboratory studies would be helpful?
Laboratory studies
- CBC
- Liver function tests
- Iron
- Ferritin
- Bone marrow biopsy
- Peripheral smear
- Hb 9.5, Plt 82 WBC 2.1
- Alb 6.0, SGT 200
- 50 (nl 60–170)
- 10 (nl 12–300)
- Kupfer cells noted
- Inclusion bodies

Smear

Bone marrow
Beta-glucosidase enzyme activity is absent.

A 48 year old Caucasian male of Ashkenazi Jewish descent is noted to have hepatosplenomegaly and thrombocytopenia. The most likely diagnosis is

- A. Familial idiopathic thrombocytopenia
- B. Fabry’s Disease
- C. Gaucher’s disease
- D. Hemochromatosis
- E. Nieman Pick type C

Gauchers Disease
Genetics of Gaucher’s

- Autosomal Recessive inheritance
- GBA gene, N370S common mutation
- Most common Lysosomal storage disorder
- Type I seen more frequently in the Ashkenazi Jewish population (1/500).
- Incidence of 1/50,000 in the general population.

GAUCHER DISEASE ENZYME PATHWAY

Clinical Features of Gauchers disease

- Fatigue
- Thrombocytopenia
- Hepatomegaly
- Growth retardation
- Pathologic bone crisis
- Neurologic degeneration
- Anemia
- Splenomegaly
- Avascular necrosis
- Osteopenia
Clinical Manifestations Reflect Cellular Sites of Substrate Storage

Nonneuronopathic (Type 1)
Most Common Symptoms
- Splenomegaly
- Hepatomegaly
- Bone disease
- Thrombocytopenia
- Anemia
- Growth retardation
- Bruising/bleeding
- Fatigue
- Bone pain/crisis
- Abdominal pain

Goucher Disease Symptomatic Treatment
- Hematologic
  - Iron and vitamin supplementation
  - Blood transfusions
  - Splenectomy
- Skeletal
  - Pain management
  - Joint Prosthesis
  - Fracture management
  - Calcium supplementation
  - Core decompression
Gaucher Disease Treatment

- Synthetic enzyme replacement is available for Gaucher disease.
- It is administered IV every 2 weeks.
- There are also oral medications.
- Patients on this therapy show improvement of symptoms in the first few months.

Therapeutic effects of Enzyme Replacement

- Hematologic:
  - 2.5 g/d Hb increase in 9 months of therapy
  - 50% increase in Platelets in patients with spleen after 9 months of therapy
- Visceral: Hepatomegaly, Splenomegaly
  - 20% decrease in Liver volume after 9 months of therapy
  - 45% in spleen size after 9 months of therapy

Substrate Reducer

- Substrate reducers inhibit the synthesis of the product, in the Gaucher’s disease, glucocerebroside.
- The residual enzyme activity is hoped to be sufficient to prevent progressive accumulation of glucocerebroside.
- These are oral medications.
- There are currently 2 medications in clinical use.
- Patients need pharmacogenetic testing to be certain they do not metabolize this medication too quickly.
- In Gaucher Disease oral substrate reducers can now be a first line therapy in adults.
- Results show are similar results when compared to IV enzyme for decrease in hepatosplenomegaly and bone disease.
GBA gene Carriers

- It has recently been noted that carriers for one nonfunctional copy of the GBA gene are at increased risk to develop a tremor in their 50's-60's.
- This disorder looks like Parkinson's disease

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- B. Fabry's Disease
- C. Gaucher's disease
- D. Hemochromatosis
- E. Nieman Pick type C

A 6 month old male has lost developmental milestones including smiling. He has "startling" spells. The family history indicates his parents are both of Ashkenazi Jewish descent, consanguinity is denied. There is concern he may have Tay Sachs. When enzyme analysis is recommended?

- A. Iduronate Sulfatase
- B. Hexosaminidase B
- C. Alpha galactosidase
- D. Hexosaminidase A
- E. Alpha glucosidase
A 3 month old female presents with failure to thrive.
It takes over 60 minutes to consume 3oz of formula.
On exam she has head lag with poor central and peripheral muscle tone as well as hepatosplenomegaly
An echocardiogram indicated cardiomyopathy

She is the 3rd child of non consanguineous parents
She has a 3 year old brother and 6 year old sister.
No one in the extended family has muscle weakness or failure to thrive.

Pompe Disease: Glycogen Storage Type 2
Progressive muscle weakness characterized by hypotonia, head lag and delayed milestones.
- Respiratory complications including frequent infections, sleep apnea
- Significant cardiomyopathy resulting in early death.

Cardiomegally is present in 92% of infants by 4 months of age.

EKG Changes
- **Shortened** PR interval
- Tall QRS complex
- WPW
Features of Pompe's in Infancy
- Failure to thrive
- Feeding problems, including difficulty sucking and swallowing
- Poor weight gain
- Moderate hepatomegaly and macroglossia
- Cardiomegaly
- Markedly elevated plasma creatine kinase (CPK)
- Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT)

Confirming the Diagnosis of Pompe Disease
- Enzyme analysis of acid alpha-glucosidase (GAA).
- GAA enzyme activity on dried blood spot.

Pompe Disease
- Healthy myofibrils are replaced by glycogen.
- There is intralysosomal accumulation of glycogen
- This results in loss of muscle function/hypotonia.
Symptomatic treatment of cardiomyopathy and muscle weakness.

**Myozyme**: Enzyme replacement is available

Myozyme received FDA approval faster than any other medication

**BMT**: A few have been performed. Results are not encouraging.

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**Natural History of Infantile-Onset Pompe Disease**

Survival curve, patients with infantile Pompe disease (2003 study data)

- **Survived (%)**
- **Age at Death (months)**


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**Alglucosidase alfa: Study 1 Survival Data**

Ventilator-free survival in ERT-treated infants versus survival in an untreated historical cohort

<table>
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<tr>
<th>Age (months)</th>
<th>Survived (%)</th>
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<tbody>
<tr>
<td>12</td>
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<tr>
<td>18</td>
<td>70</td>
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<td>30</td>
<td>30</td>
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<td>36</td>
<td>10</td>
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*Note: 142 infants in ERT-treated group
Two patients younger than 10 months of age after 12 weeks of treatment were censored in the analysis.
Two patients were censored as their survival status was unknown. They were censored at the age at which they were last known to be alive.

Data from He F et al. Neurology.
Adult Onset Pompe Disease

- Progressive muscle weakness, proximal>distal
- Elevation of Creatine kinase (CPK)
- Can look like Limb-Girdle Muscular dystrophy
- Cardiomyopathy
- Restrictive pulmonary disease
- Enzyme therapy is also useful in this group

Tay Sachs

- Caused by a mutation in the enzyme Hexosaminidase A
- Primarily results in lipid accumulation in the neurons, gangliocytosis
- Halo results from abnormal lipid accumulation in the ganglion cells (cherry red spot)
- No contractures or hepatosplenomegaly
- Autosomal Recessive
- Individuals of Ashkenazi descent carrier frequency 1/30
- General Population carrier frequency 1/300

Nieman Pick

- There are 3 types, A, B and C
- They are all autosomal recessive
- They are all caused by inability to break down lipids (lipid storage disease)
More common in Ashkenazi Jewish population (carrier freq 1/90)

Enzyme deficiency of the enzyme sphingomyelinase

Type A: severe neurologic disease, death in the first few years of life
Type B: no neurologic symptoms, enlarged spleen and liver.

Unable to metabolism cholesterol and lipids resulting in accumulation of lipids in the liver and spleen.

Progressive ataxia and cognitive delays and early dementia
Can present in infancy, early childhood or adulthood
Gene testing for the NPC1 gene is available. Mutations are identified in 90% of affected patients.
There is a treatment in clinical trials for a medication which helps to clear cholesterol and lipids from the cells.

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A. Iduronate Sulfatase  
B. Hexosaminidase B  
C. Alpha galactosidase  
D. Hexosaminidase A  
E. Alpha glucosidase
Conclusion

- Enzyme therapy cannot cross the blood brain barrier therefore neurologic symptoms cannot be reversed.
- Early diagnosis can result in better prognosis/outcome for the LSD where enzyme replacement is available.
- As new treatments are becoming available, early diagnosis is critical to improve prognosis.
- Newborn screening for LSD’s is offered as part of the newborn screen in Illinois.
- It will allow both early diagnosis as well as long term treatment.
- Correct diagnosis will also allow for genetic counseling of the family.

USMLE Like Questions

- A 50-year-old female has recently been diagnosed with a movement disorder, Parkinson disease. The family history is positive for her father who was diagnosed with Parkinson symptoms at age 60. She has a 55-year-old brother with Gaucher disease. He has no symptoms of a movement disorder. What gene is likely related to her symptoms of Parkinson disease?
  - A. GLA
  - B. GBA
  - C. IDUA
  - E. HEXA

USMLE LIKE QUESTION

A 2 year old boy is diagnosed with a biochemical defect involving hexosaminidase. A. The patients condition would be most appropriately categorized as belonging to which of the following general classes of defects?
  - A. Aminoacidopathy
  - C. Gangliosidosis
  - D. Carbohydrate metabolism
  - D. Mucopolysaccharidosis
  - E. Porphyrria