HEPATOSPLENOMEGALY IN THE YOUNG ADULT

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CASE PRESENTATION

A 22 year old woman who recently immigrated from Vietnam presented to hematology stating that she had thalassemia and hepatosplenomegaly and requested appropriate therapy.
A 22 year old woman who recently immigrated from Vietnam presented to hematology stating that she had thalassemia and hepatosplenomegaly and requested appropriate therapy.

• reported having a large liver and spleen since early childhood
• denied a history of blood transfusions
• denied other medical problems and review of systems pan-negative with exception of fatigue
• reports having had bone marrow biopsy at age 16 that was normal
• family history:
  • both parents healthy with no medical problems
  • oldest brother healthy with no medical problems
  • older brother has an enlarged liver and spleen and currently has cirrhosis
• physical exam notable for short stature (5’1’’”) with Tanner stage 3 development and palpable liver and spleen to level of the umbilicus
SPLENOMEGALY
DEFINITION OF SPLENOMEGALY

Normal Spleen:
100 - 250 grams
11 cm in craniocaudal dimension

Splenomegaly:
400+ grams
13+ cm craniocaudal dimension

Massive Splenomegaly:
500 - 1000 grams
# Causes of Splenomegaly

## Hypersplenism

<table>
<thead>
<tr>
<th>Clearance of Infectious Organisms and Antigens (immune hyperplasia)</th>
<th>Synthesis of Immune Molecules (IgG, properdin, tuftsin)</th>
<th>Removal of Damaged Erythrocyts</th>
<th>Extramedullary Hematopoiesis</th>
</tr>
</thead>
</table>

## Hypertrophy

<table>
<thead>
<tr>
<th>Congestive</th>
<th>Infiltrative</th>
<th>Neoplastic</th>
<th>Infectious</th>
<th>Traumatic</th>
</tr>
</thead>
</table>
## CAUSES OF SPLENOMEGALY

### HYPERSPLENISM

<table>
<thead>
<tr>
<th>Clearance of Infectious Organisms and Antigens (immune hyperplasia)</th>
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<th>Removal of Damaged Erythrocyts</th>
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</tr>
</thead>
<tbody>
<tr>
<td>viral infections (EBV, CMV, HIV, HCV, rubella)</td>
<td>systemic lupus erythematosus</td>
<td>thalassemia</td>
<td>thalassemia</td>
</tr>
<tr>
<td>bacterial infections (septicemia, endocarditis, typhus, syphilis, leptospirosis, Ehrlicosis, brucellosis, Q fever, psittacosis)</td>
<td>Felty syndrome (rheumatoid arthritis)</td>
<td>sickle cell anemia</td>
<td>myeloproliferative disorders</td>
</tr>
<tr>
<td>fungal infections (histoplasmosis, coccidioidomycosis)</td>
<td>serum sickness</td>
<td>pernicious anemia</td>
<td>acute myelogenous leukemia</td>
</tr>
<tr>
<td>protozoal infections (malaria, leishmaniasis, toxoplasmosis, trypanosomiasis)</td>
<td></td>
<td>hereditary spherocytosis hereditary elliptocytosis</td>
<td></td>
</tr>
<tr>
<td>helminth infections (fasciolosis)</td>
<td></td>
<td>G6PD deficiency pyruvate kinase deficiency</td>
<td></td>
</tr>
</tbody>
</table>
# Causes of Splenomegaly

## Hypertrophy

<table>
<thead>
<tr>
<th>Congestive</th>
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<th>Neoplastic</th>
<th>Infectious</th>
<th>Traumatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>portal hypertension</td>
<td>sarcoidosis</td>
<td>splenic cysts</td>
<td>large abscess</td>
<td>ischemia</td>
</tr>
<tr>
<td>right heart failure</td>
<td>amyloidosis</td>
<td>hamartomas</td>
<td>splenic tuberculosis</td>
<td>hematoma</td>
</tr>
<tr>
<td>hepatic sinusoidal obstructive syndrome</td>
<td>metabolic disease (lysosomal or glycogen storage disease)</td>
<td>hemangiomas lymphangiomias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>splenic vein thrombosis</td>
<td>myeloproliferative and lymphoproliferative disorders</td>
<td>splenic angiosarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metastatic solid tumor</td>
<td></td>
<td>primary splenic lymphomas</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HEPATOMEGALY
DEFINITION OF HEPATOMEGALY

Normal Liver:

- 1.4-1.5 kilograms in men
- 1.2-1.4 kilograms in women
- < 16 cm at midclavicular line
## Causes of Hepatomegaly

<table>
<thead>
<tr>
<th>Congestive</th>
<th>Infiltrative</th>
<th>Neoplastic</th>
<th>Infectious</th>
<th>Inflammatory</th>
<th>Biliary</th>
<th>Extramedullary Hematopoiesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budd Chiari syndrome</td>
<td>sarcoidosis</td>
<td>cysts</td>
<td>viral (HAV, HBV, CMV, EBV)</td>
<td>Wilson disease</td>
<td>biliary atresia</td>
<td>hemoglobinopathies</td>
</tr>
<tr>
<td>right heart failure</td>
<td>amyloidosis</td>
<td>adenoma</td>
<td>bacterial (rickettsia, leptospirosis, actinomycosis)</td>
<td>autoimmune hepatitis</td>
<td>primary biliary cirrhosis</td>
<td>acute myelogenous leukemia</td>
</tr>
<tr>
<td>hepatic sinusoidal obstructive syndrome</td>
<td>metabolic disease (lysosomal and glycogen storage, hemachromatosis, alpha-1-antitrypsin deficiency)</td>
<td>hepatocellular carcinoma, fibrolamellar carcinoma</td>
<td>protozoal (toxoplasmosis, schistosomiasis, amebiasis, malaria, leishmaniasis)</td>
<td>acute drug toxicity</td>
<td>primary sclerosing cholangitis</td>
<td>myeloproliferative disorders</td>
</tr>
<tr>
<td>peliosis hepatitis</td>
<td>fatty liver</td>
<td>cholangio carcinoma</td>
<td>fungal (coccidiodomycosis, histoplasmosis)</td>
<td>alcoholic hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>myeloproliferative and lymphoproliferative disorders</td>
<td>focal nodular hyperplasia</td>
<td>parasitic (ascariasis, toxocariasis, echinococcus)</td>
<td></td>
<td>acute liver ischemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metastatic solid tumor</td>
<td>hemangioma</td>
<td>abscess</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CAUSES OF CHRONIC HEPATOSPLENOMEGALY IN A YOUNG ADULT

Infection

Extramedullary Hematopoiesis

Congestion

Infiltration
A 22 year old woman who recently immigrated from Vietnam presented to hematology stating that she had thalassemia and hepatosplenomegalgy and requested appropriate therapy.

- CBC normal with exception of MCV of 78 and platelets of 138k
- peripheral blood smear normal with exception of mild thrombocytopenia
- reticulocytosis normal
- iron studies, hemoglobin electrophoresis, and thalassemia workup normal
- SPEP, UPEP, serum free light chain ratio normal
- BMP and TSH normal
- LFTs and coagulation studies normal with exception of mild transaminitis (AST 82, ALT 81)
- ferritin and alpha-1-antitrypsin levels normal
- anti-smooth muscle antibody and anti-LKM (liver kidney microsomal) antibody titers negative
- HIV, HAV, HBV, HCV, schistosomiasis screens negative
- US: 23 cm liver with normal parenchymal echogenicity and vascular flow; spleen 22 cm without thrombosis; no ascites
- immigration chest x-ray normal
CAUSES OF CHRONIC HEPATOSPLENOMEGALY IN A YOUNG ADULT

- Infection
- Extramedullary Hematopoiesis
- Congestion
- Infiltration
CAUSES OF CHRONIC HEPATOSPLENOMEGALY IN A YOUNG ADULT

Infection

Extramedullary Hematopoiesis

Congestion

Infiltration
CAUSES OF CHRONIC HEPATOSPLENOMEGALY IN A YOUNG ADULT

Infiltration

Lymphoproliferation
Myeloproliferation
Metastatic

Amyloid
Sarcoid
Metabolic
CAUSES OF CHRONIC HEPATOSPLENOMEGALY IN A YOUNG ADULT

Infiltration

Lymphoproliferation  Amyloid
Myeloproliferation  Sarcoid
Metastatic  Metabolic

Infection
Extramedullary Hematopoiesis
Congestion
CAUSES OF CHRONIC HEPATOSPLENOMEGALY IN A YOUNG ADULT

Metabolic Storage Disease

Lysosomal Storage Diseases
Glycogen Storage Diseases
LYSOSOMAL STORAGE DISEASES

- collectively rare, combined incidence 1/5,000-8,000 births
- more than 50 known mutational deficiencies
- autosomal recessive or X-linked recessive
- accumulation of non-metabolized products and dysfunctional cellular trafficking cause cellular dysfunction
- 66% cause progressive cognitive and motor dysfunction
# Lysosomal Storage Diseases

## Pie Chart

- **Gaucher** 14%
- **Hurler-Scheie** 9%
- **Metachromatic Leukodystrophy** 8%
- **Sanfilippo** 7%
- **Sandhoff** 2%
- **GM1 Gangliosidosis** 2%
- **Mucolipidosis type IV** 2%
- **Niemann-Pick A/B** 3%
- **Maroteaux-Lamy** 3%
- **Niemann-Pick C** 4%
- **Sanfilippo B** 4%
- **Tay-Sachs** 4%
- **Cystinosis** 4%
- **Morquio** 5%
- **Pompe** 5%
- **Krabbe** 5%
- **Hunter** 6%
- **Fabry** 7%

## Table

<table>
<thead>
<tr>
<th>LSD</th>
<th>Defective Enzyme</th>
<th>Neurological Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sphingolipidoses</strong></td>
<td>Lysosomal hydrolases (i.e. Hexosaminase A in GM2; Sphingomyelinase in NPC; Glucocerebrosidase in Gaucher disease)</td>
<td>Progressive neurological regression, seizures, spasticity,</td>
</tr>
<tr>
<td>• GM1 and GM2 gangliosidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Niemann-Pick disease (NPC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gaucher disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mucopolysaccharidoses</strong></td>
<td>Glycosaminoglycan cleaving enzymes</td>
<td>Mental retardation, behavioural disturbances and hyperactivity</td>
</tr>
<tr>
<td>• MPS-III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glycoproteinoses</strong></td>
<td>Glycoprotein cleaving enzymes (N-acetylglucosamine-1-phosphotransferase in Mucolipidosis-I)</td>
<td>Mental impairment, speech impairment, spasticity, neuroaxonal dystrophy</td>
</tr>
<tr>
<td>• Mucolipidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuronal Ceroid Lipofuscinosis</strong></td>
<td>Lysosomal proteins (e.g. proteases) (i.e. CLN3 in Batten)</td>
<td>Visual failure, epilepsy, decline in motor and cognitive skills</td>
</tr>
<tr>
<td>• Batten disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multiple Sulfatase Deficiency</strong></td>
<td>Sulfatase modifier</td>
<td>Rapid neurological deterioration</td>
</tr>
</tbody>
</table>
GAUCHER DISEASE

3 clinical subtypes

- Type 1: most common (90%)
  - highest residual enzyme activity; highest variability in clinical presentation
  - hepatosplenomegaly, cytopenias, osteopenia, osteolytic lesions
  - estimated that 60% of those harboring most common mutation never present to medical attention

- Type 2: most rare
  - lowest enzyme activity
  - hypertonia, seizures, mental retardation, death during infancy

- Type 3: intermediate in incidence, enzyme activity, clinical severity, age of onset
• most common lysosomal storage disease (1:75,000 births)
• Ashkenazi Jews (1:1,000 births)
• autosomal recessive
• more than 300 known mutations
• GBA gene (glucosidase, beta, acid) on chromosome 1
• acid beta-glucosidase hydrolyzes glucocerebroside
• enzymatic deficiency causes glucocerebroside accumulation in macrophages (Gaucher cells)
Dr. Roscoe Brady awarded National Medal of Science and Technology in 2008 for his demonstration of the enzymatic defect in Gaucher disease

**GAUCHER DISEASE**

**Diagnosis:**

- demonstration of Gaucher cells by bone marrow biopsy not uniformly helpful and no longer recommended

- enzymatic assay of glucocerebrosidase activity (0-30% of normal) (peripheral blood leukocytes, urine, skin fibroblasts)

- mutational analysis (9 most common genes account for 90-97% of cases in Ashkenazi population and 71-75% of cases in non-Ashkenazi population)
GAUCHER DISEASE

Substrate Reduction Therapy

Enzyme Replacement Therapy
GAUCHER DISEASE

Substrate Reduction Therapy

Enzyme Replacement Therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>Imiglucerase Corezym®</th>
<th>Velaglucerase VPRI®</th>
<th>Taliglucerase Uplys®</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Genzyme</td>
<td>Shire-HGT</td>
<td>Protalix-Pfizer</td>
</tr>
<tr>
<td></td>
<td>Mammalian</td>
<td>Human</td>
<td>Plant</td>
</tr>
<tr>
<td></td>
<td>Differs one aminoacid from human enzyme</td>
<td>Same as human enzyme structure</td>
<td>Differs one aminoacid from human enzyme</td>
</tr>
<tr>
<td></td>
<td>Chitobioso core glycan (fucosylation) (requires a second step)</td>
<td>High mannose type (nine mannose residues) (requires a second step)</td>
<td>Plant-type high mannose residues, more consistent glycosylation (no modification)</td>
</tr>
<tr>
<td></td>
<td>Antibodies 15% 6.6 reactions</td>
<td>1 in 54 naïve subjects developed antibodies</td>
<td>Antibodies 8% 6% reactions</td>
</tr>
</tbody>
</table>
**GAUCHER DISEASE**

**Substrate Reduction Therapy**

**Zavesca (Miglustat) 2003**  
oral D-glucose analog which inhibits production of glucosylceramide

**Cerdelga (Eliglustat) 2014**  
oral ceramide analog which inhibits production of glucosylceramide

$160,000 - $320,000 per year

**Enzyme Replacement Therapy**

$160,000 - $320,000 per year
CASE PRESENTATION

A 22 year old woman who recently immigrated from Vietnam presented to hematology stating that she had thalassemia and hepatosplenomegaly and requested appropriate therapy.

- beta-glucosidase enzymatic test normal
- reflexive mutational analysis not performed
CAUSES OF CHRONIC HEPATOSPLENOMEGALY IN A YOUNG ADULT

Metabolic Storage Disease

Lysosomal Storage Diseases

Glycogen Storage Diseases
GLYCOGEN STORAGE DISEASES

Liver and muscle involvement are central features. Most phenotypes are severe. Splenomegaly is not generally a feature unless secondary to cirrhosis. Diagnosis is often obtained with liver or muscle biopsy. Treatment may include dietary modification, enzyme replacement therapy, or liver transplant.
# Glycogen Storage Diseases

<table>
<thead>
<tr>
<th>GSD0</th>
<th>GSD1A Von Gierke</th>
<th>GSD1B Von Gierke</th>
<th>GSD2 Pompe</th>
<th>GSD3A Cori/Forbes</th>
<th>GSD3B Cori/Forbes</th>
<th>GSD4 Anderson</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycogen synthetase</td>
<td>glucose-6-phosphatase</td>
<td>glucose 6 phosphate translocase</td>
<td>alpha-1,4-glucosidase</td>
<td>alpha-1,6-glucosidase debranching</td>
<td>alpha-1,6-glucosidase debranching</td>
<td>alpha-1,4-glucosyl transferase</td>
</tr>
<tr>
<td>liver</td>
<td>liver</td>
<td>lysosomal</td>
<td>liver, muscle</td>
<td>liver</td>
<td>liver, muscle</td>
<td>liver, muscle</td>
</tr>
<tr>
<td>fasting hypoglycemia, hyperlipidemia, hyperuricemia, failure to thrive, renal failure, massive hepatomegaly</td>
<td>fasting hypoglycemia,</td>
<td>proximal myopathy and muscle weakness</td>
<td>hepatomegaly, cardiomegaly, hyperlipidemia, myopathy, micronodular cirrhosis</td>
<td>hepatomegaly, mild fasting hypoglycemia, hyperlipidemia, micronodular cirrhosis</td>
<td>hypotonia, cirrhosis, cardiac failure</td>
<td></td>
</tr>
<tr>
<td>asymptomatic to severe</td>
<td>severe</td>
<td>death by age 2 (respiratory failure)</td>
<td>moderate to severe</td>
<td>milder phenotype</td>
<td>death by age 5 (liver failure)</td>
<td></td>
</tr>
<tr>
<td>1:50,000-100,000 births</td>
<td>1:4,000-5,000 births</td>
<td>1:100,000 births</td>
<td>1:100,000 births</td>
<td>1:500,000 births</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## GLYCOGEN STORAGE DISEASES

<table>
<thead>
<tr>
<th>GSD5</th>
<th>GSD6</th>
<th>GSD7</th>
<th>GSD9</th>
<th>GSD11</th>
<th>GSD12</th>
<th>GSD13</th>
</tr>
</thead>
<tbody>
<tr>
<td>McArdle</td>
<td>Hers</td>
<td>Tauri</td>
<td></td>
<td>Fanconi-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>muscle glycogen phosphorylase</td>
<td>liver glycogen phosphorylase</td>
<td>muscle phosphofructokinase</td>
<td>phosphorylase kinase</td>
<td>glucose transporter 2</td>
<td>aldolase A</td>
<td>beta enolase</td>
</tr>
<tr>
<td>muscle</td>
<td>liver</td>
<td>muscle</td>
<td>liver</td>
<td>liver</td>
<td>muscle</td>
<td>muscle</td>
</tr>
<tr>
<td>muscle weakness with exercise, cramps, myalgias, myoglobinuria</td>
<td>hepatomegaly, mild fasting hypoglycemia, postprandial lactic acidosis, hyperlipidemia, cirrhosis</td>
<td>muscle weakness with exercise, cramps, myalgias, myoglobinuria</td>
<td>hepatomegaly, mild fasting hypoglycemia, hyperlipidemia, growth retardation</td>
<td>hepatomegaly, postprandial hyperglycemia, RTA, chronic diarrhea, ricketts, short stature</td>
<td>muscle weakness, muscle intolerance, muscle cramps</td>
<td>muscle weakness, muscle intolerance, muscle cramps</td>
</tr>
<tr>
<td>mild - moderate</td>
<td>benign - rare cirrhosis</td>
<td>mild - moderate</td>
<td>benign - severe (several forms)</td>
<td>severe</td>
<td>mild - moderate</td>
<td>mild - moderate</td>
</tr>
<tr>
<td>1:100,000-500,000 births</td>
<td>1:65,000-85,000 births</td>
<td>1:1,000,000 births</td>
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</tr>
</tbody>
</table>
GLYCOGEN STORAGE DISEASES

GSD 3b
- mild phenotype to cirrhosis
- hepatomegaly
- hyperlipidemia
- hypoglycemia
- short stature
- delayed puberty
- osteoporosis
- transaminitis
- fatigue
- risk of hepatocellular carcinoma

GSD 6
- often benign
- cirrhosis rare
- theoretical risk of hepatocellular carcinoma

Treatment
- frequent small meals to prevent hypoglycemia
- avoid simple sugar intake
- uncooked cornstarch (1 gm/kg) 1-3 times per day to avoid hypoglycemia
- high protein diet (3 gm/kg/day) to avoid gluconeogenesis
- growth hormone if growth delay
- liver transplant if severe hepatic dysfunction or hepatocellular carcinoma
A 22 year old woman who recently immigrated from Vietnam presented to hematology stating that she had thalassemia and hepatosplenomegaly and requested appropriate therapy.

- lipid panel: cholesterol 273, triglycerides 344, LDL 187, HDL 20
- creatinine kinase normal
CASE PRESENTATION

A 22 year old woman who recently immigrated from Vietnam presented to hematology stating that she had thalassemia and hepatosplenomegaly and requested appropriate therapy.

- Lipid panel: cholesterol 273, triglycerides 344, LDL 187, HDL 20
- Creatinine kinase normal
- Next generation sequencing panel for glycogen storage diseases (14 genes) normal
CHRONIC HEPATOSPLENOMEGALY IN THE YOUNG ADULT

- **Causes of Both Splenomegaly and Hepatomegaly to Consider:**
  - infection
  - hepatopathy that causes portal hypertension
  - extramedullary hematopoiesis
  - infiltrative lymphoid and myeloid proliferative disorders and malignancies
  - infiltrative metastatic solid tumor malignancy
  - granulomatous disease
  - amyloidosis
  - lysosomal storage disease (Gaucher disease most common and may have mild phenotype)
  - glycogen storage disease (type 3b and type 6 associated with milder phenotypes)

- **Gaucher Disease:**
  - often managed by hematologist (splenomegaly + cytopenias + osteolytic bone disease)
  - diagnosed by enzymatic test of blood (or urine); bone marrow biopsy not required
  - treatment includes enzyme replacement therapy or substrate reduction therapy (very expensive and recommended for symptomatic individuals)

- **Glycogen Storage Disease:**
  - type 3b and type 6 variants have milder phenotypes which may go undiagnosed until adulthood
  - hepatomegaly, dyslipidemia, hypoglycemia, growth/puberty delay, and osteoporosis common
  - treatment includes dietary changes and uncooked cornstarch
HEPATOSPLENOMEGALY IN THE YOUNG ADULT

Resource: NCBI Gene Reviews

Thank You!