Gaucher Disease

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Biochem 118Q: Genomics and Medicine
Gaucher Disease: Overview

- First described by Philippe Gaucher in 1832.
- Most common lysosomal storage disorder caused by a deficiency of the enzyme beta-glucocerebrosidase.
- Results in the accumulation of the lipid glucosylcerebroside.
- Symptomatically variable.
- There are three types of Gaucher disease:
  1) nonneuronopathic type I
  2) acute neuronopathic type II
  3) subacute neuronopathic type III
Biochemistry of the disease

Lysosome

Ceramide

Glucose
<table>
<thead>
<tr>
<th></th>
<th>TYPE I</th>
<th>TYPE II</th>
<th>TYPE III</th>
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<tbody>
<tr>
<td><strong>Gene</strong></td>
<td>GBA gene</td>
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<tr>
<td><strong>Neurological symptoms</strong></td>
<td>None</td>
<td>Severe and potentially lethal</td>
<td>Milder with slow progress of symptoms</td>
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<td><strong>Prevalence</strong></td>
<td>General Pop.- 1 in 60,000</td>
<td>1 in 100,000</td>
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<td>Ashkenazi Jews - 1 in 850</td>
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<td><strong>When Symptoms arise</strong></td>
<td>Any age</td>
<td>By 6 month after birth</td>
<td>By early childhood to teen years</td>
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<td><strong>Life expectancy</strong></td>
<td>Normal</td>
<td>Child dies before 2 years</td>
<td>Range from early childhood to adulthood</td>
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<td><strong>Organs affected</strong></td>
<td>spleen, liver, kidney, lungs, bone marrow</td>
<td>spleen, liver, and the brain</td>
<td>Spleen, liver, the brain, heart</td>
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Symptoms of Gaucher type I

- Enlargement of the spleen and liver
  - size of the spleen is 1500-3000 ml compared to 50-200 ml
- Acute abdominal pain
- Protruding abdomen
- Loss of appetite
- Low level of Platelets
- Anemia
- Easy bruising
- Bone weakness and degradation
- Bone crisis
- Osteonecrosis (low bone density)
- Delayed development
- Skin can be yellowish brown
- Fat visible on the cornea of the eye
Classical Diagnosis of Gaucher type I

- Physical clinical characteristics (spleen enlargement)
- Quantitative testing of glucocerebrosidase through urine analysis
- Measurement of the enzyme beta-glucosidase inside white blood cells.
- MRI
- Bone Marrow examination for presence of “Gaucher cells”
- Low white blood cell count
Molecular Genetics

- Autosomal recessive disease
- Mutation in the GBA gene
- Most common in Ashkenazi Jews
- Located on chromosome 1
- Different mutations on the same locus 1q21 causes the three types of Gaucher disease
- About 200 mutations identified
- Connections with Parkinson’s disease
Pros and Cons of Genetic Diagnosis

Molecular gene testing cannot be a replacement of biochemical testing for diagnosis.

Patients with Gaucher disease can have a spectrum of symptoms, ranging from mild to severe neurological effects. The classic categories of types 1, 2 and 3 have blurry edges along this continuum.
Classical Treatment

- Removal of the spleen
- Joint replacement
- Liver transplant
- Blood transfusion for anemia
- Pain medication
- Bisphosphonates and calcium supplements (prevent bone loss)
- Routine physical examination
- Bone marrow transplant
Novel Treatment

- **Enzyme Replacement Therapy**
  - intravenous infusions
  - Recombinant DNA with functional enzyme targeting macrophages
  - Cerezyme (1996)
  - Weekly treatment
  - Very effective for patients with Type I.

- **Substrate Reduction Therapy**
  - inhibitors of glucocerebroside formation
  - Zavesca

- **Future... GENE THERAPY**
Sources

- http://www.gaucherdisease.org/
- http://www.genome.gov/21519714
- http://path.upmc.edu/cases/case478/images/d-4.gif
- http://path.upmc.edu/cases/case478/dx.html