Gaucher Disease

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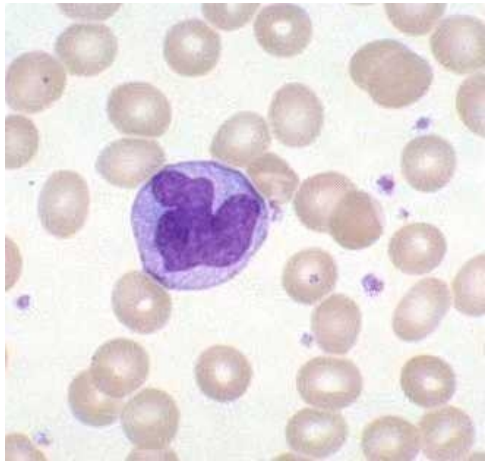
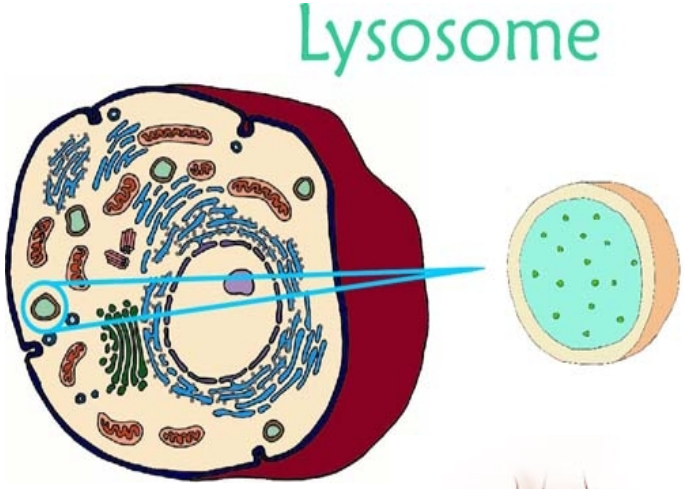
Biochem 118Q: Genomics and Medecine

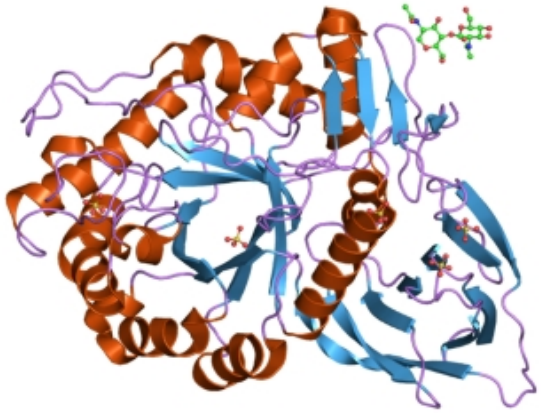
Gaucher Disease: Overview

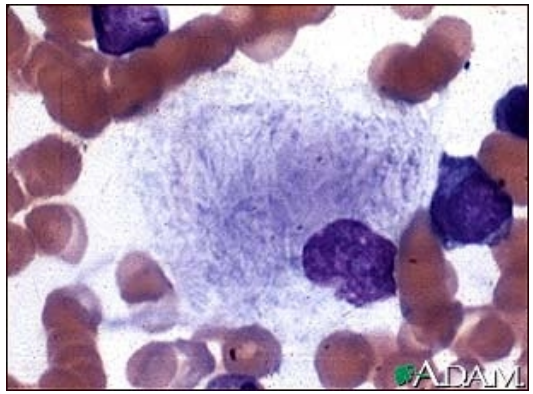
- First described by Philippe Gaucher in 1832.
- Most common lysosomal storage disorder caused by a deficiency of the enzyme beta-glucocerebrosidase.
- Results in the accumulation of the lipid glucosylcerebroside
- Symptomatically variable
- There are three types of Gaucher disease:
    1) nonneuronopathic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

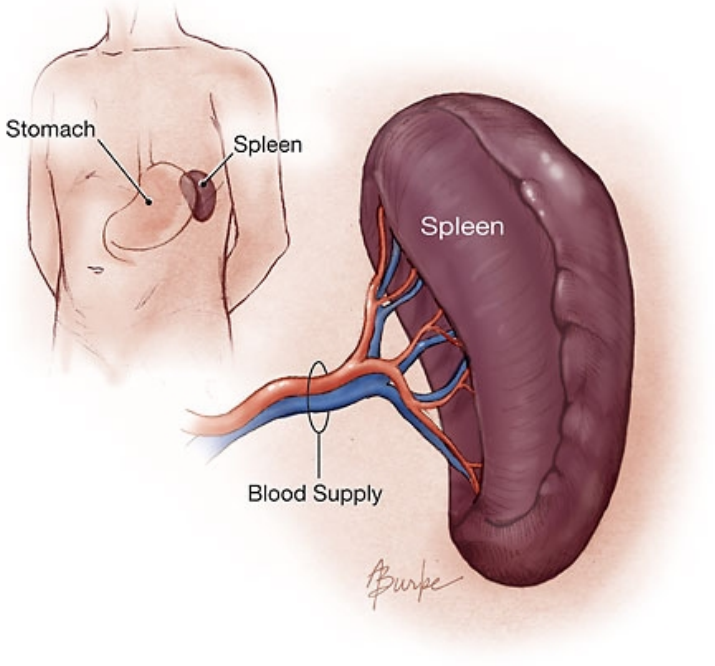
Biochemistry of the disease

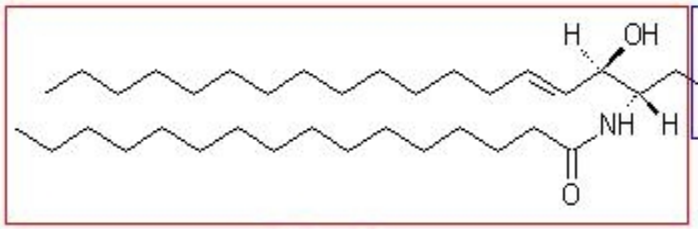


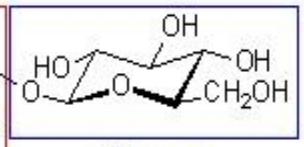








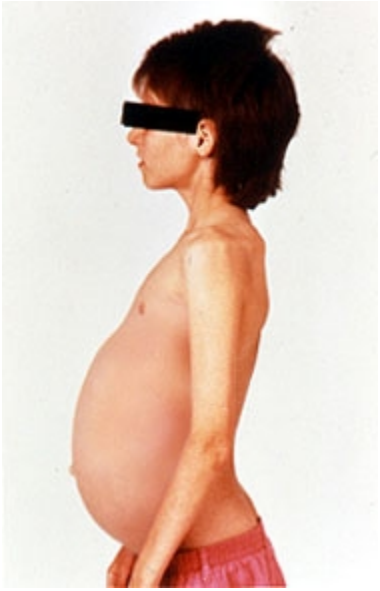




	TYPE I	TYPE II	TYPE III
Gene	GBA gene	GBA gene	GBA gene
Neurological symptoms	None	Severe and potentially lethal	Milder with slow progress of symptoms
Prevalence	General Pop.- 1 in 60,000 Ashkenazi Jews - 1 in 850	1 in 100,000	1 in 100,000
When Symptoms arise	Any age	By 6 month after birth	By early childhood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

Symptoms of Gaucher type I

- Enlargement of the spleen and liver
  - size of the spleen is1500-3000 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

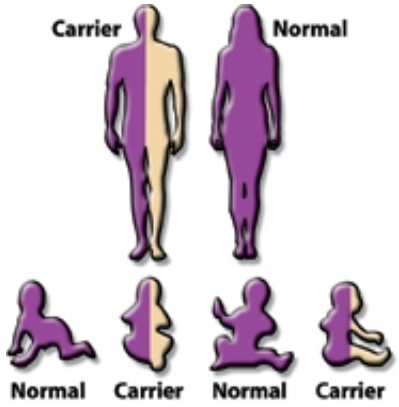


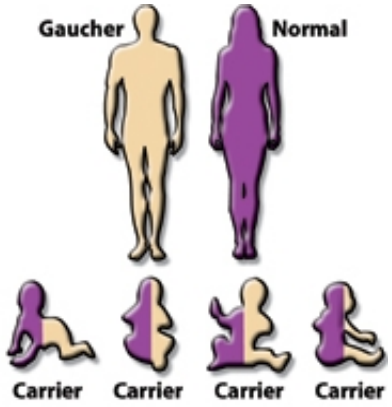
Classical Diagnosis of Gaucher type I

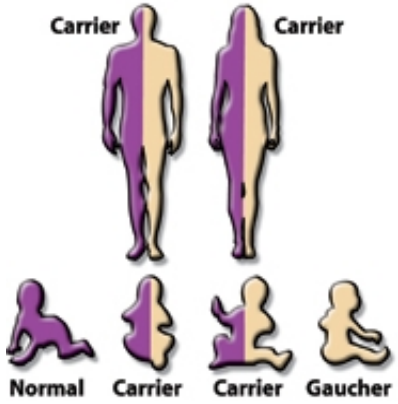
- Physical clinical characteristics (spleen enlargement)
- Quantitative testing of glucocerebroside through urine analysis
- Measurement of the enzyme beta-glucosidase inside white blood cells.
- MRI
- Bone Marrow examination for presence of “Gaucher cells”
- Low white blood cell count

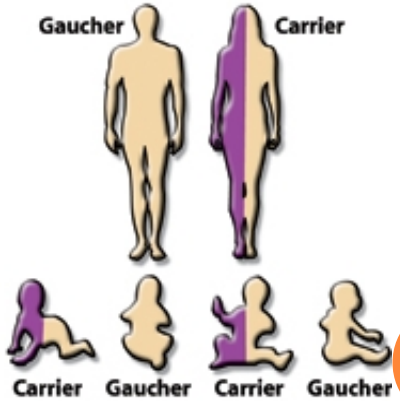
Molecular Genetics

- 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 Guacher disease
- About 200 mutations identified
- Connections with Parkinson's disease



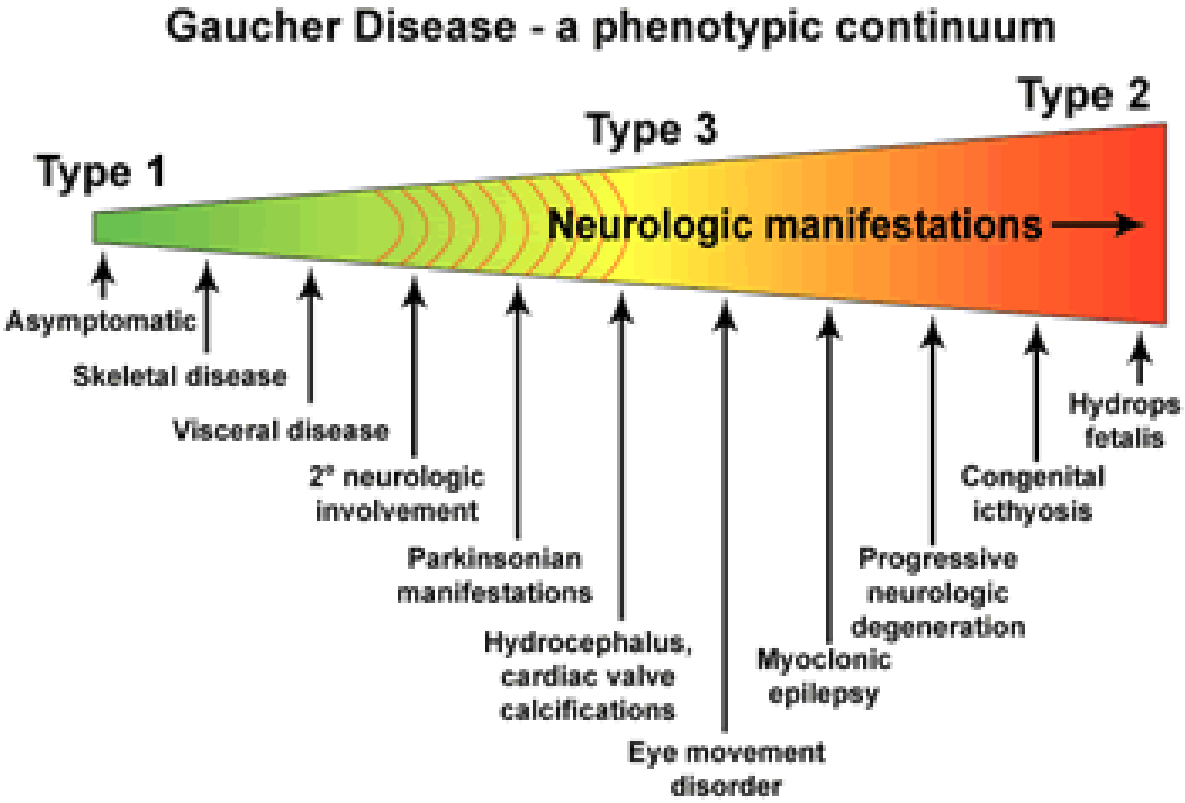






Pros and Cons of Genetic Diagnosis

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.ncbi.nlm.nih.gov/books/NBK22242/
- http://www.ncbi.nlm.nih.gov/books/NBK1269/
- http://www.genome.gov/21519714
- http://path.upmc.edu/cases/case478/images/d-4.gif
- http://path.upmc.edu/cases/case478/dx.html