Gaucher Disease

Most Common Lipid-Storage Disease

Chris Lemke
Biochemistry/Molecular Biology

April 23, 2001
History of Gaucher Disease

1882- French physician, Philippe Charles Ernest Gaucher (go-SHAY) described a clinical syndrome in a 32 yr. old women whose liver and spleen were enlarged.
History of Gaucher Disease

1924- German physician, H. Lieb isolated a particular fatty compound from the spleens of people with Gaucher disease.

1934- French physician, A. Aghion identified this compound as glucocerebroside.

1965- American physician, Roscoe O. Brandy demonstrated that the accumulation of glucocerebroside results from a deficiency of the enzyme glucocerebrosidase.
What is Gaucher Disease?

- The human body contains macrophages that remove worn-out cells by degrading them into simple molecules for recycling.
- Degradation occurs inside lysosomes.
- The enzyme glucocerebrosidase is located within the lysosomes and degrades glucocerebroside into glucose and ceramide.
What is Gaucher Disease?

- People with Gaucher disease lack the normal form of the glucocerebrosidase, and are unable to break down glucocerebroside.
- Instead, glucocerebrosidase remains stored within the lysosomes, preventing the macrophages from functioning normally.
- Enlarged macrophages, due to the accumulated glucocerebrosidase, are known as, Gaucher cells.
Gaucher Cell
The Enzyme

- Glucocerebrosidase
- Molecular weight = 51,637
- Number of residues = 448
- Number of alpha = 18
- Number of beta = 17
The Mutation

- Glucocerebrosidase gene locus 1q21
- Single-base mutation (adenosine to guanosine transition) in exon 9 of the glucocerebrosidase gene.
- Amino acid substitution of serine for asparagine.
- Transient expression studies following oligonucleotide-directed mutagenesis of the normal cDNA confirmed that the mutation results in loss of glucocerebrosidase activity.
Inheritance Patterns

Gaucher disease is an autosomal recessive trait.

Gaucher carriers have one normal copy of the glucocerebrosidase gene and one defective copy.

Since the trait is autosomal, Males and Females have an equal chance of inheriting the defective gene.
Gaucher Diseases

Gaucher specialists divide the disease into 3 classifications based on the particular symptoms and course of the disease.

Type 1, Adult Gaucher Disease
Type 2, Infantile Gaucher Disease (Rare)
Type 3, Juvenile Gaucher Disease (Rare)
Type 1, Adult Gaucher Disease

- Most common form.
- Defective gene for glucocerebrosidase occurs in 1 in 100,000 people in the general population.
- More common among Ashkenazi Jews, occurring in 1 in every 850 births.
Type 1 Symptoms

- General Fatigue
  - Lack of energy and stamina

- Abdomen
  - Enlarged spleen
  - Enlarged liver
  - Pain
  - Compression of the lungs
Type 1 Symptoms

Skeletal System

- Growth retardation in children
- Pain and degeneration of joints and bone-covering tissue
- Loss of bone density leading to widening of the bones along the knee joint
- Curvature of the bones
- Spontaneous fractures
- Acute bone infarctions
- Bone necrosis
Type 1 Symptoms

- **Lungs**
  - Decreased ability to provide oxygen to the blood

- **Kidney**
  - Disruption of normal function

- **Skin**
  - Yellow-brown pigmentation
  - Non-raised, round, red spots around the eyes.
Type 1 Symptoms

Blood
- Increased bleeding tendency such as nose bleeds and bruising
- Sublevels of blood platelets, RBC, WBC.
- Elevated levels of acid phosphatase and plasma proteins

Digestive
- Loss of appetite
- Intestinal complaints.
Treatment: Enzyme Replacement Therapy

Most logical, direct therapeutic approach, since people with Gaucher disease are deficient in Glucocerebrosidase.

Dr. Roscoe Brady pioneered the development of this therapy at the National Institute of Neurological Disorders and Stroke.
Enzyme Replacement Therapy

Research showed natural glucocerebrosidase infusions were ineffective!

Dr. Brady developed modified glucocerebrosidase (Ceredase) that had increased targeting and uptake by the macrophages.

Enzyme Replacement Therapy

- The production of Ceredase enzyme using a recombinant cell line has been achieved.
- New name, Cerezyme.
- Cerezyme received FDA approval in Nov. 1996.
- Ceredase has been phased out and replaced by Cerezyme for 95% of patients.
Current Research

Investigation of the biophosphonate group of drugs for osteoporosis and bone disease.
- Fosamax or Alendronate
- Didronel or Etidronate
- Pamidronate

Attempts to do gene therapy which if successful could provide a cure.

Trial of OGT 918
- A drug which acts as an inhibitor of one of the key enzymes responsible for the formation of glycosphingolipids such as glucocerebroside.
Summary

- Gaucher Disease was named after French physician, Philippe Charles Ernest Gaucher (go-SHAY)
- Most common lipid-storage disorder.
- Autosomal recessive trait
- Results from a glucocerebrosidase deficiency, causing an accumulation of glucocerebroside in macrophages.
- Enzyme replacement therapy is the most logical, direct treatment.
References


