Biochemistry 118Q

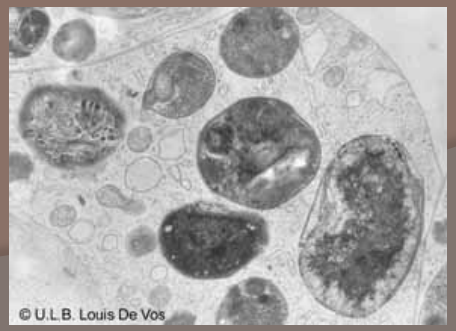
Genomics and Medicine

By: Huy Phan

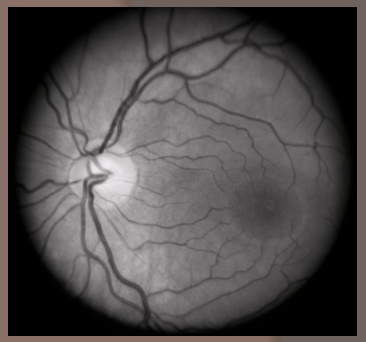
NIEMANN-PICKS DISEASE

History/Background

- 1st reported in 1914 (Niemann)
- Group of fatal metabolic disorders (A, B, C)
- Subgroup of Lysosomal Storage Disorders (LSD)
- Autosomal Recessive Inheritance
- Niemann-Pick patients show defects metabolism of cholesterol (Type C) and sphingomyelin (Type A and B)
- Ashkenazi Jewish Population (NPA/B)
- French-Canadian Population of Nova Scotia (Variant of NPC)
- Rare Genetic Disease



Symptoms

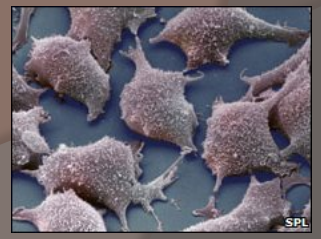


- 3 Types: Niemann-Picks A/B/C
- NPA (< 1% of ASM activity):
  - Hepatosplenomegaly, cherry-red spot of the macula of the retina
  - Death from 2-4 Years Of Age
- NPB (< 10% of ASM activity):
  - Hepatosplenomegaly with progressive hypersplenism, hyperlipidemia, Thrombocytopenia
  - Can survive into late childhood/early adulthood
- NPC (Secondary decrease in ASM activity):
  - Ataxia, vertical supranuclear gaze palsy (VSGP), dementia, hypotonia, gelastic cataplexy, and developmental delay
  - Always Fatal: Rare to live past 40; Death usually before 20

Classical Diagnostic Methods

- NPA/NPB
  - Measure level of activity of Acid Sphingomyelinase (ASM) in white blood cells
    - Measurement through blood samples
    - Specification between NPA and NPB must be through clinical evaluation

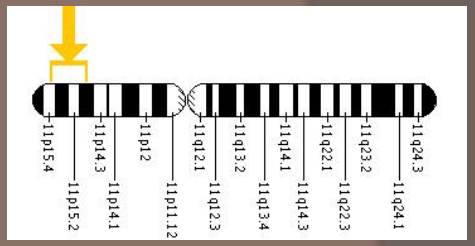
- NPC
  - Skin Biopsy done through Specialists
    - Grow Fibroblast cells in Lab and study its ability to transport/store cholesterol



Classical Treatments

- Niemann-Picks Type A/B
  - Currently no treatment for NPA
  - Only treatment to help symptoms
- Niemann-Picks Type C
  - Zavesca (Miglustat)
    - In 2009, the UK and Republic of Ireland approved Zavesca to be the 1st licensed treatment for NPC
    - Has slowed, but not stopped, neurological decline when tested on mice
    - Temper/Control symptoms using supportive Treatment

Novel Diagnoses Knowing The Causative Gene



- Causative Genes
  - SMPD1 gene:
    - Type A (acute, infantile form; most common)
    - Type B (chronic, non-neurological form; less common)
  - NPC1/NPC2 gene:
    - Type C
      - Genetically and biochemically different from Type A & B
- Research currently being done using mice:
  - Bone marrow transplantation
  - Enzyme replacement therapy
  - Gene therapy (replacing bad gene with good gene)

Novel Therapy Based on Understanding of Genetic Knowledge

- Comprehensive analysis of entire acid sphingomyelinase (ASM) gene structure used for carrier testing for partners of known Type A carriers
- Zavesca (Miglustat)
  - Only treatment to help symptom
- Lots of current research on different possibilities for Type C

Sources

- http://en.wikipedia.org/wiki/Niemann-Pick_disease
- http://www.nnpdf.org/?itool=books&referralid=gnd.section.211
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