Cowboys and Indians:
Navajo Neurohepatopathy and Microvillous Inclusion Disease in the Navajo

Steve Holve, MD FAAP
Tuba City Regional Health Care Corporation
Tuba City, AZ

Sadly,
I have no financial relationship with any commercial entity to disclose

“You can observe a lot by watching”
Yogi Berra

Objectives
- Understand how the American Indian wars of the 19th century have resulted in high rates of heritable illnesses in the Navajo.
- Follow the 25 year process from clinical recognition of these illnesses to identification of their unique genetic mutations in the Navajo.
- Understand the complex presentation of mitochondrial liver disease in the Navajo.
Microvillous Inclusion Disease

- Term 3160 gm AGA female infant born by NSVD
- Day 4 of life copious diarrhea and metabolic acidosis
- Stool output of 250ml/kg/d while eating
- Stool output of 200 ml/kg/d while fasting
- Stool Electrolytes in mEq/L: Na 107, K - 17, Cl - 84

Endocrine, metabolic and infectious diseases eliminated from diagnosis

Electron microscopy: villous atrophy with secretory inclusions c/w diagnosis of microvillous inclusion disease

Alive at 5 years of age

- Cholecystectomy for symptomatic cholelithiasis
- TPN related liver disease
- Recurrent central line sepsis
- Growth below 5th percentile
- Mild mental retardation

Microvillous Inclusion Disease in the Navajo

- 5 cases identified from 1990 - 1999
- Now a total of 14 cases for incidence of 1/6,000
- Both sexes
- Sibs in two families
- No known consanguinity
Hmmmm, That’s Odd

Navajo Neurohepatopathy (NNH)
- Term infant born to 27 yo G5P4 female
- Family History remarkable
  - 5 year old sib died from hepatic failure
  - 1st cousin with FTT and neuropathy

NNH Case
- 6 months - persistent jaundice and FTT
  - elevated liver enzymes including GGT
  - liver bx shows chronic active hepatitis
- 12 months - jaundice resolved but LFTs remain elevated
  - hypotonic with gross and fine motor delay

NNH Case
- 6 years old
  - nerve biopsy - loss of myelinated fibers
  - Nerve Conduction Velocity - slowing
- 8 years - progressive weakness and recurrent pneumonia
- Cirrhosis
- 11 years - death from pneumonia/ARDS

NNH Diagnostic Criteria
- Clinical presentation
  - Sensory Neuropathy
  - Motor Neuropathy
  - Corneal Anesthesia
  - Liver Disease
  - Metabolic or infectious disease derangement
  - CNS demyelination on radiologic imaging
- 4/6 or 3/6 and sibling with NN

Liver Disease in NNH
- neonatal hepatitis
- fulminant liver failure in childhood
- cirrhosis
- hepatocellular carcinoma
- common feature - elevated GGT
Work Up of NNH

- Mitochondrial DNA Depletion Syndrome by liver biopsy
- Abnormal regulation of MT DNA copy numbers as underlying defect
- 1/2,000 Navajo births
- Both sexes
- Occurred in 1/4 ratio in families
- No known consanguinity

Hepatology 34:1, 2001

Hmmm….That’s Odd!

Founder Effect

- a gene rare in the general population occurs in a small, isolated, rapidly expanding population which leads to increased gene frequency and increased frequency of the disease in that population

Examples of the Founder effect

- Religion - The Hutterites and the Amish
- Ethnicity - French Canadians and Ashkenazi Jews
- Geography - island populations
Rounded Up

The Long Walk

Fort Sumner Internment

Conditions Favoring the Founder Effect in the Navajo

- Population reduction during the Long Walk
- Geographic Isolation
- Rapid population increase
  - Navajo population increased 30 fold in 5-6 generations vs. 5 fold for U.S.

Microvillous Inclusion Disease

- Mutations in myosin Vb found in 10 patients with MVID
- Five Navajo patients all homozygous for a single base pair mutation in exon 16 causing substitution of leucine for proline
- Parents all heterozygote for this mutation
- Speculation that is area is critical for folding of protein

AJMG: 146A, 2008
NNH Mutation

- Sequenced genes associated with Mt DNA depletion Syndromes
- Homozygosity Mapping
- Positive LOD score in area of MPV 17 which is associated with known hepatocerbral form of MDS
- Single base pair mutation (R50Q) in 6/6 tested c/w founder effect

NNH Course

- Same mutation found in all patients even with different presentations
- Additional unlinked modifier genes
- Epigenetic factors
- Liver transplantation is not curative for neurologic disease which will progress and lead to death by teen years
- Dx can now be reliably done

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