Pediatric Grand Rounds, September 21, 2011
Gaucher Disease: A Genetic Disorder with Hematologic-Oncolologic Features
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Disclosures
None

"Unexpected abdominal mass"
• PT: E. W. B.D. 05/29/2003
• Initial consult: 08/07
• Problem: Enlarged spleen (?)
  Vs. Abdominal Mass
Pt. E. W.
• H.P.I.
  • 4 year old Caucasian “well-child”
  • General Pediatrician identified left-sided abdominal mass on routine check-up.

Pt. E. W.
• Review of Systems:
  • Normal activity, appetite, and sleep
  • Occasional fleeting abdominal pain
  • Abdomen has looked protuberant “as long as they can remember”

Pt. E.W.
• Review of systems (cont’d)
  • No Pallor
  • No Jaundice
  • No Change in Urinary Color or Frequency
  • No Musculoskeletal pain or swelling
  • No bruising or petechiae
Pt. E. W.
- **Past History:**
  - B. W. 7 pounds
  - Normal growth and development
  - Observation for closed skull fracture, age 2

Pt. E. W.
- **Family History:**
  - Parents age 30, both teachers, are well.
  - 3-year-old brother is well.
  - No consanguinity

Pt. E.W.
- **Physical Exam (P.E.)**
  - Wt. 16.4 kg, Ht. 97.4 cm, B.P. 93/51
  - Appears well, color normal
  - Oral cavity-no abnormalities
  - No adenopathy
  - Chest clear.
  - CVS-Normal pulses and heart sounds.
Pt. E.W.
- **PE (cont’d)**
  
  - Abdomen-left sided protuberance
  
  - Right side: Normal-no hepatomegaly
  
  - Left side: Large firm, smooth, non-tender “mass” → left flank, to right of umbilicus, extending down into pelvis.

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Pt. E.W.
- **PE (cont’d)**

  - Musculoskeletal: Full range of motion, no asymmetry, no swelling, no tenderness.

  - Skin: No purpura, petechiae, or rash

  - Neuro: Normal

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Pt. E.W.
- **The Problem:**

  - A left sided abdominal, flank mass in otherwise health 4 year old white girl.
Pt. E.W.

- **Differential Diagnosis:**

  - What is it?
  - From Which Organ is it arising?
  - What is the most efficient approach to finding the answer?

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Pt. E.W.

- **Lab studies:**
  - CBC
  - Hb 9.9, HCT 30, MCV 72
  - WBC 6600-normal differential
  - Platelets 80,000
  - Retic count 2%
  - Blood Smear . . .

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Pt. E.W.

- **Diagnostic Imaging**

  - Which Test?
Pt. E.W.
- High Resolution Abdominal Ultrasound
  - "Abd. Sono"
    ↓
  Massive Splenomegaly

Pt. E. W.
- Contrast – Enhanced C.T. Scan
  Abdomen and Pelvis

Yes, It’s the spleen!
Pt. E.W.

• SO, IT IS A GIGANTIC SPLEEN
• NOW WHAT?

• Leave it in?

• Ask Surgeon to remove?

• Other Diagnostic Tests

Pt. E.W.

• Well, they took it out!

• Pathology: Wt. 924 gm (normal = 49)
  • Architecture disrupted by sheets of Lipid Laden Macrophages
  • “Gaucher Cells”
Pt. E.W.

- **Diagnosis:**
  - Gaucher Disease, Type I-Non-Neuronopathic
  - Lysosomal storage disease due to congenital deficiency of glucocerebrosidase (Beta-Glucosidase)

**Consequences of Enzyme Deficiency**

Accumulation of glucosylceramide

Storage in Hematopoietic Tissues, Bone Marrow, Spleen

Infiltration by abnormal cells-take up space . . .

**Gaucher Cell vs. Megakaryocyte**
As a result of space occupation by Gaucher Cells

- Progressive Splenomegaly.
- Diminished Bone Marrow Function
  - Anemia
  - Thrombocytopenia
- Bone "Crises"
  - Disturbed Growth
Identifying Lysosomal Storage Disorders

The Importance of Early Diagnosis

Incidence of LSDs\(^1\)

- Individually rare but collectively more common
  - Individual incidence: 1:40,000 to 1:1,000,000 births
  - Collective incidence: 1:7,700 to 1:10,000 births
- Most are panethnic
- Some more prevalent in certain ethnic groups:
  - Ashkenazi Jewish descent—Gaucher, Niemann-Pick
  - African Americans—Infantile-onset Pompe disease

Relative Prevalence

CNS Involvement

- Significant or severe CNS involvement (~54%)
- No or minimal CNS involvement (~46%)

Data on file, Genzyme.

Inheritance

- Most are autosomal recessive

Father
Carrier

Mother
Carrier

1 2 3 4

Affected Individual (25%) Unaffected Carriers (50%) Unaffected Noncarrier (25%)

1 2 3 4


Overview of Gaucher Disease
Historical Timelines

- PCE Gaucher: Clinical Case
- Agoston: Glucocerebroside Accumulation
- DeDuve: Lysosome
- Brady: Glucocerebrosidase Deficiency
- Beutler; Gins: Glucocerebrosidase Gene

Date: 9/20/2011

Gaucher Disease: A Lysosomal Storage Disorder

- Inborn error of metabolism
- Most common lysosomal storage disorder
- Autosomal recessive
- Genetic defect on chromosome 1
- Enzyme deficiency
- Reticuloendothelial system
- Progressive, multisystemic, multiorgan dysfunction

Accumulation of Undegraded Substrate

Glucocerebroside (Glucosylceramide)

<table>
<thead>
<tr>
<th>Glucosyl</th>
<th>Ceramide</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Glucose and Ceramide Structures" /></td>
<td><img src="image2" alt="Glucocerebrosidase Structure" /></td>
</tr>
</tbody>
</table>

Glucocerebrosidase (Acid β-Glucosidase)

1. \( O \equiv C - CH_2 - CH_2 - (CH_2)_n - CH_3 \) 
2. \( N \equiv CH \) 
3. \( C \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \) 
4. \( OH \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \) 
5. \( H_2 O \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \) 
6. \( OD \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \) 
7. \( OH \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \) 
8. \( H_2 O \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \) 
9. \( OD \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \) 
10. \( OH \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \) 
11. \( H_2 O \equiv CH_2 - CH - CH = OH - (CH_2)_3 - CH_5 \)
Gaucher Disease

**Normal Cell**

**Gaucher Cell**

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Gaucher Disease Subtypes

**Nonneuronopathic (Type 1)**
- Panethinic (approx. 1 in 50,000)
- Prevalent in Ashkenazi Jews (approx. 1 in 500)
- Onset at any age

**Neuronopathic (Types 2 and 3)**
- Type 2 (acute)
  - Panethinic (approx. 1 in 100,000)
  - Onset in infancy
  - Life expectancy 2 to 3 years
- Type 3 (chronic)
  - Panethinic (approx. 1 in 100,000)
  - Onset in infancy/childhood

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Nonneuronopathic (Type 1)

**Most Common Symptoms**
- Splenomegaly
- Hepatomegaly
- Bone disease
- Thrombocytopenia
- Anemia
- Growth retardation
- Bruising/bleeding
- Fatigue
- Bone pain/crises
- Abdominal pain
Acute Neuronopathic (Type 2)

- Strabismus
- Retroflexion of the neck
- Cortical thumbs
- Visceromegaly
- Failure to thrive
- Cachexia

Chronic Neuronopathic (Type 3)

- Severe early onset
- Progressive developmental delay
- Oculomotor apraxia
- Anemia
- Thrombocytopenia
- Massive visceral enlargement
- Bone disease

Most Common Lab Markers

Elevated:
- Glucosylceramide
- ACE
- TRAP (tartrate-resistant acid phosphatase)
- Chitotriosidase
- Ferritin
- Gammaglobulins

Decreased:
- Total cholesterol
- HDL and LDL cholesterol
- Clotting factors
- B12
Diagnosis

Enzyme Assay
- Biochemical assay of glucocerebrosidase activity
  - Leukocytes (peripheral blood)
  - Cultured fibroblasts (skin biopsy)
- Typical adult Gaucher patient has enzyme activity between 10%-30% of normal
- Children with more severe form of Gaucher disease have less than 10% activity
- Residual activity is not always a good predictor of clinical severity

DNA Analysis
- Mutation analysis of alleles
- Reliable means of carrier testing among relatives at risk
- Particularly important for families with neuropathic subtypes

Diagnosis by DNA Analysis: Glucocerebrosidase Gene Mutations

Mutation Analysis

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>N370S</td>
<td>721</td>
<td>57</td>
</tr>
<tr>
<td>?*</td>
<td>184</td>
<td>15</td>
</tr>
<tr>
<td>L444P</td>
<td>173</td>
<td>14</td>
</tr>
<tr>
<td>84GG</td>
<td>96</td>
<td>8</td>
</tr>
<tr>
<td>IVS2</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Rare Allele</td>
<td>65</td>
<td>5</td>
</tr>
</tbody>
</table>

* "?" indicates DNA analysis of common mutations was performed, but allele remains uncharacterized.
These data are from the Gaucher Registry (CGG).
Femur: Pathology

- Hemorrhagic infarction
- Necrosis
- Osteosclerosis
- Severe osteoporosis
- Loss of cortical bone

Gaucher Bone Disease

Radiographic Lesions

Marrow Infiltration by MRI

Pulmonary Involvement

Forms of Lung Disease
- Interstitial disease
- Alveolar/lobar consolidation
- Pulmonary hypertension

Interstitial macrophage

Alveolar macrophage
Gaucher Disease: Treatment

Non-specific Care
- Hematologic
  - Iron and vitamin supplementation
  - Supportive intervention, transfusions
  - Total or partial splenectomy
- Skeletal disease
  - Pain management, bone crises
  - Joint prosthesis
  - Fracture management
  - Calcium supplementation
  - Core decompression

Specific Care
- Enzyme replacement therapy for type 1 Gaucher disease
  - Approved for treatment since 1991
- Bone marrow transplantation
  - High-risk/ethical issues

Targeted Lysosomal Enzyme Delivery

Enzyme Preparation

Cerezyme® (imiglucerase for injection)
- Generic: Imiglucerase
- Source: CHO Cell Expression
- Formulation: Lyophilized
- Additives: Citrates, Mannitol, Polysorbate 80
Therapeutic Effects of Enzyme Replacement

**Hematologic: Improvement of Anemia/Thrombocytopenia**
- ~2.5 g/dL mean Hb increase in anemic patients at 9 months
- ~50% increase in platelets in patients with thrombocytopenia at 9 months depending on presence of spleen

**Visceral: Reduction of Hepatosplenomegaly**
- ~20% decrease in liver volume in patients with hepatomegaly at 9 months
- ~45% decrease in splenic volume in patients with intact spleens at 9 months

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**Adverse Events**

<table>
<thead>
<tr>
<th>Associated With Route of Administration</th>
<th>Suggestive of Hypersensitivity</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort</td>
<td>Anaphylactoid reaction</td>
<td>Nausea</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Pruritus</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Burning</td>
<td>Flushing</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Swelling</td>
<td>Urticaria</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Sterile abscess at the site of venipuncture</td>
<td>Angioedema</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Chest discomfort</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Coughing</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Backache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia</td>
</tr>
</tbody>
</table>

*~15% of patients reported adverse events; each occurred in <4% of the total patient population.

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**Immunology of Enzyme Replacement Therapy**

- Approximately 15% of tested patients on ERT form IgG antibodies (Ab) during the first year
- Seroconversion generally occurs within 6 months and rarely after 12 months
- IgE documented in only 1 patient thus far
- Primarily nonneutralizing antibodies (<0.5% of Ab+ patients)
- Majority of Ab+ patients are asymptomatic
Conclusions

- Consider Gaucher Disease in differential diagnosis of splenomegaly—especially the "Big Spleen"

- Be aware of the spectrum of lysosomal storage disorders and the value of early diagnosis.

- Gaucher Disease, Type I, is the prototype for successful management of a genetic disorder.
Acknowledgements
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