Gaucher Disease: a multiorgan rare disease in Internal Medicine

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Rare Diseases

- Do I have as Internist the chance to deal with rare diseases?

YES
Rare Diseases: issues

- Multiorgans disorders
- Approached by “organ’s specialist” (Gastroenterologist, Hematologist, Reumatologist…)
- Inappropriate therapies

consequences

- Misdiagnosis/underdiagnosis
- Delay in diagnosis
Female 64 years old (b.1946)
She experienced acute bone pains (diagnosed as osteomyelitis) between 10 – 14 years of age

At 20 years – diagnosed with chronic hepatitis referred to hepatologist
- **Splenectomy** because of splenomegaly of unknown aetiology
- 26 years: liver cirrhosis, slight hepatomegaly and cholestasis – no viral markers

58 years (2004): anaemia, haemorrhagic episodes – referred to haematologist BM biopsy: Gaucher cells. **No action taken**
- at age 60 (2006) further findings hepatomegaly (+14-19cm), Hg 6.0-8.0g/dL, mild leucopenia, normal thrombocytes, diffuse osteopenia and coxarthrosis

GD diagnosis confirmed with enzyme assay
• Female 64 years old (b.1946)
• She experienced acute bone pains (diagnosed as osteomyelitis) between 10 – 14 years of age

• She was misdiagnosed

• Spleen was removed although “splenomegaly of unknown aetiology”

• Diagnosis of Gaucher Disease was made 44 years after the initial symptoms

• She has a very poor QoL
Mr S.B, age 36 yrs, officier in a library. Married

- Active sportman, had lack of energy, tiredness since few months leading to sport activity restriction
- No other symptoms but mild, occasional peripheral sensory loss
- **Family History:** southern italian origin. Parents apparently in good health. 3 brothers, 2 sisters
More clues......

- Hb: 12.5 g/dl ; MCV: 81 fl
- WBC: 6.2/10^9/l Neuts: 5.9; Lymph: 3.8
- Platelets: 88/10^9/l
- AST: 37 U/L, ALT: 87 U/L, gGT: 35 U/L
- Tot. Bilirubin: 1.7 mg/dl, Unconj: 1.3 mg/dl
- Iron: 84 mg/dl; Transferrin saturation: 30 %
- Ferritin: 1400 ng/ml
- HCV, HbsAg: negative
- Blood film: normo/microcytic cells; poichylocitosis
- Hb pattern; G6PD activity: normal

Liver enlargement (4 cm); spleen enlargement (3 cm)
Suspected diagnosis

- Viral neuropathy (neurologist)
- Mononucleosis
- Viral Hepatitis/Cirrhosis (Hepatologist)
- Lymphoma (Hematologist)
Bone marrow aspirate

Gaucher like cells?
Keck School staging :1a
Mr S.B, age 36 yrs, officier in a library. Married

- More than 1 year before diagnosis was made
- He visited 4 different specialists
- He underwent 2 invasive exams (BM, Liver biopsy)
- The diagnosis in presence of splenomegaly, anemia, thrombocytopenia should have been suspected and made by enzyme measurement
• 37 year old female
• She reported severe back pain at 11 years of age – wore body cast for 3 months

• When she was 26 year old one sister was diagnosed with symptomatic GD
• Family screen showed she had mild splenomegaly, Hg: 13.0g/dL, platelets: 135,000/uL
• Homozygous for N370S
• Informed – mild form of disease no need for further follow up

• At age 30 – bone crisis in distal femur: Hg 10.3g/dL, platelets: 121,000/uL, liver vol 1.4 x n, spleen 7.5 x n
• X-ray: AVN and compression fracture of T7 vertebra at site of previous back pain
• DEXA: severe osteoporosis T score: -2.8
• At age 30 years: enzyme replacement therapy initiated
• At 35 years: hip replacement surgery: bone marrow in left femur entirely destroyed by AVN
Kecking school staging : 3b
• 37 year old female
• She reported severe back pain at 11 years of age – wore body cast for 3 months

• She had the diagnosis, but because of lack of knowledges she remained untreated

• The consequences are life-long limiting
Pathophysiology of Gaucher disease

- GD caused by inherited deficiency in acid beta-glucosidase (glucocerebrosidase, GBA)

- Leads to glucocerebroside accumulation in lysosomes of macrophages

- Glycolipid laden cells (Gaucher cells) infiltrate organs to cause multisystem disease
  - Most commonly: spleen, liver, bone marrow,
  - Less commonly: lungs, lymphatic system, skin eyes, heart, kidneys, nervous system

The Enzymatic Defect in Gaucher Disease

Glucosyl

\[
\begin{align*}
\text{O} & \quad \text{CH}_2 \\
\text{O} & \quad \text{CH}_2 \\
\text{O} & \quad \text{CH}_3 \\
\text{O} & \quad \text{CH}_2 \\
\text{O} & \quad \text{CH}_2 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

Ceramide

\[
\begin{align*}
\text{O=C} & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad (\text{CH}_2)_n \\
\text{OH} & \quad \text{CH} \\
\text{N} & \quad \text{OH} \\
\text{CH}_2 & \quad \text{CH} \\
\text{CH} & \quad \text{CH} \\
\text{CH} & \quad \text{CH} \quad (\text{CH}_2)_{12}
\end{align*}
\]

Acid β-Glucosidase (Glucocerebrosidase)

Glucose

\[
\begin{align*}
\text{O} & \quad \text{CH}_2 \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

Ceramide

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\begin{align*}
\text{O=C} & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad (\text{CH}_2)_n \\
\text{OH} & \quad \text{CH} \\
\text{N} & \quad \text{OH} \\
\text{CH}_2 & \quad \text{CH} \\
\text{CH} & \quad \text{CH} \quad (\text{CH}_2)_{12}
\end{align*}
\]
The Pathophysiology of Gaucher Disease

Monocytes

Bone Marrow

Macrophages

Liver

Kupffer Cells (Hepatocytes Spared)

Bone

Osteoclasts

Lung

Tissue Macrophages

Spleen

Alveolar Macrophages
Pathophysiology of Gaucher disease

• Classified into 3 subgroups:
  – Type 1 – non neuronopathic (94%)
  – Type 2 – acute neuronopathic (1%)
    (death in infancy)
  – Type 3 – chronic neuronopathic (5%)
    (death in childhood/early adulthood)

• Phenotype affected by numerous mutations/genetic modifiers

Why a delay in diagnosis?

• Gaucher disease is a phenotypically heterogeneous disease
• There is enormous variation in:
  – Age of onset
  – Rate of progression
  – Organs affected
  – Disease severity across individuals
  – Severity of disease across organs in one individual
  – Presenting symptoms
• Even in individuals of same genotype

Gaucher Disease Type 1

Splenic Accumulation (Gross)

- White-yellow streaks show accumulated Gaucher cells and fibrotic scarring

Fibrotic Scarring
Recent Infarction
Hepatic Gaucher Cells

- Kupffer cells engorged with glucocerebroside. Hepatocytes (red staining cells) do not store glucocerebroside.
- Fibrosis and scarring are frequently present in affected livers.
Lung Gaucher Cells

Interstitial macrophages

Alveolar macrophages

- Significant lung involvement, shown here, is unusual
- Gaucher cells are present as interstitial and alveolar macrophages
- Pulmonary involvement indicates a poor prognosis
Gaucher Disease Type 1

Are you Missing the Diagnosis?

A. Type 1 patient with what appears to be mild disease expression.

B. Bone films of the same Type 1 patient demonstrating significant bone involvement.
Gaucher Disease Type 1

Asymptomatic 60-Year-Old Male

- Patient exhibits minimal signs.
- Disease should be monitored regularly for signs of progression.
- He has a high risk to develop myeloma
Gaucher Disease – Type 1

Common Presentations of Gaucher Disease - Type 1

- Painless splenomegaly, usually with hepatomegaly
- Anemia, thrombocytopenia
- Fatigability
- Easy bruising
- Excessive postoperative or postpartum bleeding

- Menorrhagia
- Aseptic necrosis of hips or humeri
- “Growing Pains” - children
- Legg-Calve-Perthes disease - children
- Growth failure - children
- Spontaneous fractures
- Bone disease
Hematological malignancies in Gaucher disease

- The relative risk of cancer in patients with Gaucher disease is 3.6
- Moreover the relative risk of a hematologic malignancy is 14.7
- The most frequent hematologic malignancy are: myeloma, chronic lymphocytic leukemia, Hodgkin’s disease, acute leukemia, non-Hodgkin’s lymphoma
Treatment of Gaucher Disease

- Enzyme replacement Therapy (ERT)
- Substrate inhibition therapy (SIT)
- Small molecules (chaperone)
- Bone marrow transplantation
- Gene therapy
- Adjunctive medication or intervention
Treatment of Gaucher Disease

- Gaucher disease
  - Chronic
  - Multisystemic
  - Highly variable (pattern, severity, progression)
- Disease heterogeneity → management cannot be homogeneous
- Patient-centered
- Goal-oriented approach is critical for individual tailoring of therapy
At Diagnosis

- Hb: 12.5 g/dl; MCV: 81 fl
- WBC: 6.2/10⁹l; Neuts: 5.9; Lymph: 3.8
- Platelets: 88/10⁹l
- AST: 37 U/L; ALT: 87 U/L; gGT: 35 U/L
- Tot. Bilirubin: 1.7 mg/dl; Unconj: 1.3 mg/dl
- Iron: 84 mg/dl; Transferrin saturation: 30 %
- Ferritin: 1400 ng/ml

After 1 year of treatment

- Hb: 13.5 g/dl; MCV: 83 fl
- WBC: 6.7/10⁹l; Neuts: 5.7; Lymph: 3.4
- Platelets: 137/10⁹l
- AST: 27 U/L; ALT: 27 U/L; gGT: 35 U/L
- Tot. Bilirubin: 1.0 mg/dl; Unconj: 0.7 mg/dl
- Iron: 118 mg/dl; Transferrin saturation: 28 %
- Ferritin: 475 ng/ml;

Spleen and liver reduced by 40%
Take home messages

• Rare diseases affect in Europe more than 35 million people
• Rare diseases must be suspected by internists
• Early diagnosis save lifess
• Rare diseases are orphan: urgent needs for improving knowledges and for investing in research