Diagnosi differenziale della splenomegalia: Gaucher ed altro

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Disclosures

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- Sanofi-Genzyme
- CRISPR
- Protagonist
- La Jolla
- Alnylam
Hepatosplenomegaly

• Enlarged liver and spleen are common findings in several hereditary and acquired diseases
• Splenomegaly alone or associated to hepatomegaly is a diagnostic challenge for any physician
• Spleen has interesting structure and function
A normal spleen weighs 150 g and is approximately 11 cm in craniocaudal length.

The normal spleen is usually not palpable, although it can sometimes be palpated in adolescents and individuals with a slender build.

Poulin et al defined splenomegaly as moderate if the largest dimension is 11-20 cm, and severe if the largest dimension is greater than 20 cm.

Considerable variation in how massive splenomegaly is defined.

In recent publications describing techniques for laparoscopic splenectomy, massive splenomegaly has been described as ≥17 cm craniocaudal length, >20 cm, or splenic margin below the umbilicus or anteriorly extending over the midline.
The differential diagnosis of splenomegaly is extensive

- Most often, the etiology is evident in light of historical and the concurrent presence of familiar, often pathognomonic, physical or laboratory findings (e.g. lymphadenopathy, stigmata of chronic cirrhosis or rheumatoid arthritis, abnormal blood morphology suggestive of hematological malignancies hemoglobinopathies or red cell cytoskeletal disorders).

Weinreb NJ & Rosenbloom BE 2013
Differential diagnosis of splenomegaly

• Less commonly, there may be no relevant past or family history and accompanying findings may be non-specific (e.g. hematologic cytopenias without abnormal morphology), rare and unfamiliar (e.g. “gray” platelets), or simply not present. It is this scenario that so often leads to diagnostic error or delay in patients with splenomegaly that ultimately proves to be attributable to rare hereditary genetic diseases with which many physicians are unfamiliar.

Weinreb NJ & Rosenbloom BE 2013
Sustained diagnostic uncertainty is particularly stressful (for patient and physician) when splenomegaly is “massive”, overtly symptomatic and sometimes accompanied by fear of an underlying malignancy.

In such circumstances, clinicians, who are sometimes unaware of available biochemical or genetic testing possibilities, may feel pressed to seek a quick answer through invasive procedures such as bone marrow and liver biopsy or even total splenectomy that they may regard as not only diagnostic but also therapeutic.

Weinreb NJ & Rosenbloom BE 2013
A partial differential diagnosis of splenomegaly

- Hematological
- Portal hypertension
- Storage diseases
- Systemic diseases
- Infections
- Tropical splenomegaly syndrome
- Cryptogenic syndrome
Hematological

Massive splenomegaly

- fairly common

- CML, PMF, HCL, NHL, amyloidosis, Langherans hystocytosis, splenic hystocytic sarcoma, thalassemia major or intermedia, hereditary hemorrhagic teleangiectasia, Gray platelet syndrome

Massive splenomegaly

- less common

- CLL, Acute leukemia, PV, hereditary spherocytosis and related syndromes, other hemolytic anemias (very rare: congenital dyserythropoietic anemias, glutathione synthetase or transferase deficiencies)
Hematological

Massive splenomegaly

- fairly common

Massive splenomegaly

- less common

- CML, PMF, HCL, NHL, amyloidosis, Langherans hystocytosis, splenic hystocytic sarcoma, thalassemia major or intermedia, hereditary hemorrhagic teleangiectasia, Gray platelet syndrome

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A partial differential diagnosis of splenomegaly

• Hematological
• **Portal hypertension**
• Storage diseases
• Systemic diseases
• Infections
• Tropical splenomegaly syndrome
• Cryptogenic syndrome
Portal Hypertension

- **Cirrhosis**, including hemochromatosis, cystic fibrosis, familial Mediterranean fever, Wilson’s disease (possible confusion with Niemann-Pick C)
- **Hepatic, portal, splenic venous thrombosis** (hereditary thrombophilias)
A partial differential diagnosis of splenomegaly

- Hematological
- Portal hypertension
- Storage diseases
- **Systemic diseases**
- Infections
- Tropical splenomegaly syndrome
- Cryptogenic syndrome
Systemic Diseases

- Sarcoidosis
- Secondary amyloidosis
- Systemic lupus erythematosus
- Rheumatoid Arthritis (Felty Syndrome*)
- Systemic mastocytosis
- Autoimmune lymphoproliferative syndrome (ALPs)

*RA + splenomegaly + neutropenia
A partial differential diagnosis of splenomegaly

- Hematological
- Portal hypertension
- Storage diseases
- Systemic diseases
- Infections
- Tropical splenomegaly syndrome
- Cryptogenic syndrome
Infections

• **Acute**: septicemia, sub-acute bacterial endocarditis, typhoid, infectious mononucleosis, hemophagocytic lymphohistiocytosis

• **Chronic**: tuberculosis, brucellosis, syphilis, malaria, leishmaniasis, schistosomiasis
A partial differential diagnosis of splenomegaly

- Hematological
- Portal hypertension
- Storage diseases
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- Cryptogenic syndrome
Benign and malign masses found incidently

• **Splenic cysts (true*, false)**
• **Benign tumors**
  1. Hemangioma
  2. Hamartoma
  3. Litoral cell angioma
  4. Lymphangioma
  5. Inflammatory pseudotumor
• **Malign tumors**
  1. Angiosarcoma
  2. Metastases

Splenic cysts (true)
1. parasitic
2. non parasitic
A partial differential diagnosis of splenomegaly

- Hematological
- Portal hypertension
- **Storage diseases**
- Systemic diseases
- Infections
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- Cryptogenic syndrome
Lysosomal Storage Disorders (LSDs)

- LDSs are a heterogeneous group of inherited diseases resulting from the deficiency in one or more enzymes or transporters that normally reside within the lysosomes.
- They are characterized by progressive accumulation of uncleaved lipids, glycoproteins and/or glycosaminoglycans in the lysosomes.
- The consequences are organ damages and several forms have severe liver and spleen enlargement.
Malattie da accumulo lisosomiale

Prevalenza stimata di circa 1:8000 nati vivi

Classe di malattie metaboliche causate da mutazioni codificanti per proteine fondamentali per la funzione lisosomiale

Attualmente si conoscono più di 45 malattie lisosomiali

Monogeniche, ereditarietà autosomica recessiva o X-linked

Patogenesi, da difetto genetico per:
• uno o piu’ enzimi lisosomiali specifici
• proteine di attivazione
• proteine di membrana

Attività enzimatica deficitaria
Malattie da accumulo lisosomiale

Attività enzimatica deficitaria

Accumulo progressivo del relativo substrato

Interferenza sulla normale attività cellulare

Morte cellulare

• It is the most common inherited lysosomal storage disease
• Gaucher Disease is 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

# Gaucher Disease: Clinical Types

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>Childhood/Adulthood</td>
<td>Infancy</td>
<td>Childhood</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+ → +++</td>
<td>++</td>
<td>+ → +++</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+ → +++</td>
<td>++</td>
<td>+ → +++</td>
</tr>
<tr>
<td>Skeletal disease/bony crises</td>
<td>- → +++</td>
<td>-</td>
<td>++ → +++</td>
</tr>
<tr>
<td>Primary CNS disease</td>
<td>Absent</td>
<td>+++</td>
<td>+ → +++</td>
</tr>
<tr>
<td>Lifespan</td>
<td>6 to 80+ years</td>
<td>~2 years</td>
<td>2 to 60 years</td>
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<tr>
<td>Ethnicity/</td>
<td>Panethnic</td>
<td>Panethnic</td>
<td>Panethnic</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td></td>
<td></td>
<td>Norrbotttnian</td>
</tr>
<tr>
<td>Frequency</td>
<td>1/60000</td>
<td>&lt; 1/100,000</td>
<td>&lt; 1/50,000</td>
</tr>
<tr>
<td>~ 1/500 to 1/1,000 (AJ)</td>
<td></td>
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</tr>
</tbody>
</table>
Organs Involvement

- Enzyme deficiency
- Macrophages
  - Lungs
    - Alveolar macrophages
  - Spleen
  - Liver (Kuppfer cells)
  - Bone marrow
  - Bones
Key manifestations in adult Gaucher type 1

- **Splenomegaly**: abdominal discomfort, satiety
- **Thrombocytopenia**: tendency to bleed (+/- coagulation abnormalities)
- **Anaemia**: chronic fatigue
- **Leucopenia**: increased susceptibility to infections (+/- compromised neutrophil function)
- **Bone disease**: pain, acute bone crises, avascular necrosis, bone deformation, osteopenia, osteoporosis, fractures, joint collapse
- **Hepatomegaly**: often affecting liver function
Splenomegaly

- Present in more than 90% of GD patients at diagnosis
- Defined as spleen greater than 0.2% of total body weight in Kg
- Because of high incidence of GD in Ashkenazim, GD should be considered in any individual of Ashkenazi origin presenting with mild, moderate or severe splenomegaly
- However... the absence of splenomegaly does not exclude GD

Pastores et al 2004 Semin Hematol;41(4 Suppl 5):4-14
Gaucher Disease tipo 1
Unnecessary splenectomy

• Undiagnosed patients may undergo diagnostic splenectomy or other inappropriate splenectomy. Where possible splenectomy should be avoided in GD

• Splenectomy is a risk factor for exacerbated disease
  – More aggressive bone disease
  – Increased risk of cancer
  – Increased risk of portal hypertension
  – Increased risk of pulmonary hypertension
  – Infections

• Awareness of consequences of splenectomy important as splenomegaly and hypersplenism can be controlled with treatment

Cox et al 2008: J Inherit Metab Dis:30(5): 768-82
Haematologists/Internists/Pediatricians

key in diagnosis

• Presenting signs and symptoms often related to the haematological manifestations of disease:
  – Thrombocytopenia
  – Anaemia
  – Bleeding

• Other haematological signs may include
  – Hyperferritinemia
  – Vitamin B12 deficiency
  – MGUS
  – Coagulopathies
  – Increased risk of haematological malignancy

• When and why a diagnostic algorithm makes the difference?
Adult Gaucher Disease

• Gaucher disease is rare:
  – Incidence: 1 in 50,000-100,000
  – 1 in 1000 in individuals of Ashkenazi Jewish background
Diagnostic algorithm for individuals of non-Ashkenazi origin

Non portal hypertensive splenomegaly?

- + Platelets <150k and/or
  + bone pain and/or
  + MGUS/polygammopathy in patient <30 yrs

Exclude malignancies
Examine BM biopsy for Gaucher cells

- No Gaucher cells
- No malignancy
- Gaucher cells

Beta-glucocerebrosidase assay

Splenoectomy?
PERFORM ENZYME ASSAY FIRST

Ancillary information to support a suspicion of Gaucher disease:
- History of:
  - Gall stones/cholelithiasis
  - Abdominal discomfort
  - Low cholesterol
  - Hyperferritinemia
  - Splenic nodules
  - Pregnancy associated thrombocytopenia
  - Post partum haemorrhage
  - Bone pain
  - Gammopathies

Diagnostic algorithm for individuals of Ashkenazi origin

**Splenomegaly?**

- Yes
  - Low platelets?
  - **Bleeding tendency?**
  - Unexplained stable hyperferritinemia with normal transferrin saturation?
  - Increased inflammatory markers?
  - **Yes to one or more**

- No

  *Simultaneously exclude coagulopathies*

**Beta-glucocerebrosidase assay**

**Splenectomy?**

- Perform enzyme assay first

Ancillary information to support a suspicion of Gaucher disease:

- History of:
  - Gall stones/cholelithiasis
  - Abdominal discomfort
  - Low cholesterol
  - Hyperferritinemia
  - Splenic nodules
  - Pregnancy associated thrombocytopenia
  - Post partum haemorrhage
  - Bone pain
  - Gammopathies

Study Feasibility Assessment

- We developed a questionnaire to assess in advance the feasibility and validity.
- It was e.mailed to 105 Italian hematology centres.
- It included 4 simple questions to verify the assumptions of the numerical study and to assess the interest of the Italian Centres to participate.
Questions

- How many first hematological visits/year?

- What percentage of patients has the first visit for thrombocytopenia and/or splenomegaly?

- What percentage of such patients remains without a definite diagnosis?

- Are you interested in participating in a study on Gaucher disease
Study Feasibility Assessment: results

- 33 Centres returned the questionnaire
- Median hematologic visits/years: 1000
- Patients attending with Thrombocytopenia/splenomegaly: around 18%
- Patients with no clear diagnosis: around 11%
- All Centres were wishing to participate
RESULTS

DBS 196

- POSITIVE 7
  - Enzyme
    - Confirmed molecular analysis 3
  - Heterozygous 1

- BORDERLINE 27
  - Enzyme
    - Confirmed molecular analysis 4
    - Repeated 18

- NEGATIVE 161
  - Repeated 18

7/196 DIAGNOSIS OF GAUCHER (4.11%)  
REVIEW
Early Diagnosis of Gaucher Disease in Pediatric Patients: Proposal for a Diagnostic Algorithm

Maja Di Rocco, MD,1* Generoso Andria, MD,2 Federica Deodato, MD,3 Fiorina Giona, MD,4 Concetta Micalizzi, MD,5 and Andrea Pession, MD6

Gaucher disease (GD) is caused by an enzyme deficiency that leads to the accumulation of glycolipids in various organs. Although the signs and symptoms of GD emerge in childhood in the majority of patients, the disease often remains unrecognized for many years with delay of benefits of therapy or development of irreversible complications. Based on published data and data from the International Collaborative Gaucher Group Registry, an algorithm has been drafted for early diagnosis of GD in pediatric patients. It will help hematologists in promoting a timely diagnosis and early access to therapy for pediatric patients with GD. Pediatr Blood Cancer © 2014 Wiley Periodicals, Inc.

Key words: algorithm; Gaucher disease; pediatric age
Splenomegaly ± hepatomegaly

Thrombocytopenia and/or anemia?

Yes

Assess the presence of the following:
• Erlenmeyer flask deformity (if RX available)
• Strabismus and/or oculomotor apraxia
• Growth deceleration or retardation
• Increased ferritin levels
• Increased TRAP levels

≥1 criteria present?

Yes

Bone marrow aspirate (including search for Gaucher cells)

Signs of hematologic or onco-hematologic disease?

Yes

Hematologic or onco-hematologic disease

No

Signs of infectious or other diseases?

Yes

Other diseases (including metabolic diseases other than Gaucher disease)

No

Enzyme deficiency?

Yes

Gaucher disease

No

Bone marrow aspirate already done?

Yes

No

Comments

• A simple diagnostic algorithm based on splenomegaly and/or thrombocytopenia can be used to identify subjects potentially affected by Gaucher Disease

• This approach may impact on the early diagnosis and therapy
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