DON'T LET IT SLIP
Gaucher’s disease

Gaucher’s disease (GD) is an autosomal recessive, genetic disorder that reduces levels of the enzyme glucocerebrosidase in the lysosome. Glucocerebrosidase is a key enzyme in the catabolism of the sphingolipid glucosylceramide, and deficiency of this enzyme results in accumulation of glucosylceramide in macrophages, which then accumulate in the bone marrow, liver, lungs, spleen and brain.

At least 200 pathogenetic variants of the glucocerebrosidase gene have been identified. Patients with GD may present with a broad range of signs and symptoms, and a spectrum of disease severity is observed. The three disease phenotypes (GD types 1–3) are also diverse, ranging from cases that are lethal within a few months from birth, to mild or asymptomatic forms in which symptoms may not appear until as late as the eighth decade of life. Most patients present with the non-neuronopathic type 1 form (with a prevalence of 1 in 40,000–60,000 in the general population rising to approximately 1 in 850 among individuals with Ashkenazi Jewish ancestry), and may experience clinical problems, including bone pain, bone fracture, osteoporosis, anemia, thrombocytopenia, reduced growth, bleeding and hepatosplenomegaly. Neurological complications are rarely seen in type 1 disease, but are more common in types 2–3.
### Criteria to perform Gaucher screening test

<table>
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<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Concomitant findings</th>
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<tbody>
<tr>
<td>• Platelets below 100x10⁹/L</td>
<td>• Anemia</td>
<td>• Osteopenia</td>
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<tr>
<td>• Spleen diameter &gt;15 cm in women and &gt;16 cm in men</td>
<td>• Weakness or fatigue</td>
<td>• Constipation</td>
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<tr>
<td>• Ferritin &gt;800 mg/dL and transferrin saturation &lt;45%</td>
<td>• Bone lesions</td>
<td>• Dyspepsia</td>
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<td>• Family history of the disease</td>
<td>• MGUS or Polyclonal Hypergamma-globulinemia</td>
<td>• Hypersplenism</td>
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<td>• Prolonged bleeding time</td>
<td>• Coagulation disorders</td>
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</table>

**TEST**

- >1 major criterion + 2 concomitant findings
- >1 major criterion + 1 minor criterion + 1 concomitant finding
- 2 minor criteria + 1 concomitant finding

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Fig 1: Screening test criteria for Gaucher’s disease. Adapted from Atul Mehta et al: Internal Medicine Journal 49 (2019) 578–591
Algorithm for a differential diagnosis in adult patients with enlarged spleen that accounts for possible Gaucher’s disease

- Splenomegaly
  - Rule out portal hypertension
    - Abdomen US
  - Rule out aggressive neoplasms and RBC defects
    - Peripheral blood smear
    - PET/CT or CT
    - Bone marrow biopsy
    - Low platelets
    - Bone manifestations
    - Augmented ferritin level
    - Augmented bleeding or bleeding time
  - Consider concomitant findings*
    *Complete list in figure 1

- Test for Gaucher's disease
  - negative
    - Consider bone marrow biopsy for chronic disease
      - negative
        - Splenectomy

Algorithm for a differential diagnosis in adult patients with low platelets that account for possible Gaucher’s disease

1. Decreased platelets level
   - Exclude platelet aggregates (EDTA related) with sodium citrate test

2. Rule out drug related decrease
   - Review medical history

3. Rule out platelet consumption
   - Platelet consumption in acute diseases
   - Autoimmune diseases
   - PNH
   - Liver cirrhosis of any cause

4. Rule out chronic infections associated with low platelets
   - HIV, HBV, HCV, PB19, CMV, HP

5. Rule out nutrient deficits associated with low platelets
   - B12, folate, copper
   - Alcohol addiction

6. Consider concomitant findings* and time of onset
   *Complete list in figure 1
   - Splenomegaly
   - Bone manifestations
   - Augmented ferritin level
   - Augmented bleeding or bleeding time
   - Peripheral blood smear
   - Rule out neoplasms as clinically indicated
   - Bone marrow biopsy

7. Rule out aggressive neoplasms and RBC defects

8. Test for Gaucher’s disease

9. Consider bone marrow biopsy for chronic disease

   - Primary immune thrombocytopenia
Algorithm for a differential diagnosis in adult patients with augmented ferritin levels that accounts for possible Gaucher’s disease

- Augmented ferritin levels
  - Rule out augmented transferrin saturation
    - Rule out NASH
      - Rule out infection and inflammation
        - Consider concomitant findings*
          *Complete list in figure 1
            - Test for Gaucher’s disease
              - negative
                - Referral to specialistic center for iron metabolism
  
- Retest after 3 months and after 6 months
- Rule out acute conditions and inflammatory causes

- T.sat >45% → iron overload

- Abdomen US

- Chronic inflammatory syndromes
  - Diabetes
  - Heart failure
  - CRP

- Low platelets
  - Splenomegaly
  - Bone manifestations
  - Augmented bleeding or bleeding time

- Referral to specialistic center for iron metabolism

*Complete list in figure 1
Coagulation disorders

Coagulation disorders are also frequently found at diagnosis in Gaucher’s disease and multiple clotting abnormalities of variable severity have been described. The detection of prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) should prompt assaying the plasma levels of single coagulation factors. In one of the largest studies including 30 type 1 GD patients, at diagnosis, PT was prolonged in 42% and aPTT in 38% of them. The most common coagulation factor deficiencies are factor V, factor X, and factor II, but the reduction of all circulating clotting factors has also been reported. The reduction of clotting factors is due to different pathogenetic mechanisms: liver disease may reduce their synthesis, an enlarged spleen can increase their clearance, and the elevated concentration of circulating glucocerebroside or the presence of antiphospholipid antibodies may interfere with the clotting cascade. Clotting factor defects may also be due to their consumption by an ongoing low-grade intravascular coagulation and fibrinolysis, possibly triggered by cytokines secreted by the Gaucher cells.

Although coagulation defects are a frequent sign at diagnosis, we did not consider it useful to include them in our diagnostic algorithm, due to the presence of different confounding factors. Acquired defects of clotting factors can have different and also concurrent etiologies and inherited deficiencies may have a high prevalence in some ethnic groups. Factor XI deficiency has a high prevalence in the Ashkenazi Jewish population, with a heterozygosity as high as 9%, while von Willebrand factor deficiency has a prevalence of up to 1% in Caucasian population.


10) Serratrice, C.; Cherin, P.; Lidove, O.; Noel, E.; Masseau, A.; Leguy-Seguin, V.; Jaussaud, R.; Marie, I.; Lavigne, C.; Maillot, F. Coagulation Parameters in Adult Patients with Type-1 Gaucher Disease. J. Hematol. 2019, 8, 121-124


