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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 types1–3) 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

| Major criteria | Minor criteria | Concomitant findings |
|---|---|---|
| • Platelets below $100x10^9/L$<br>• Spleen diameter >15 cm in women and >16 cm in men<br>• Ferritin >800 mg/dL and transferrin saturation <45%<br>• Family history of the disease | • Anemia<br>• Weakness or fatigue<br>• Bone lesions<br>• MGUS or Polyclonal Hypergamma-globulinemia<br>• Prolonged bleeding time | • Osteopenia<br>• Constipation<br>• Dyspepsia<br>• Hypersplenism<br>• Coagulation disorders<br>• Ecchymosis<br>• Bone pain<br>• Recurrent infections<br>• Enlarged liver<br>• Neoplasms<br>• Thrombocytosis<br>• Parkinson-like diseases<br>• Leukopenia |

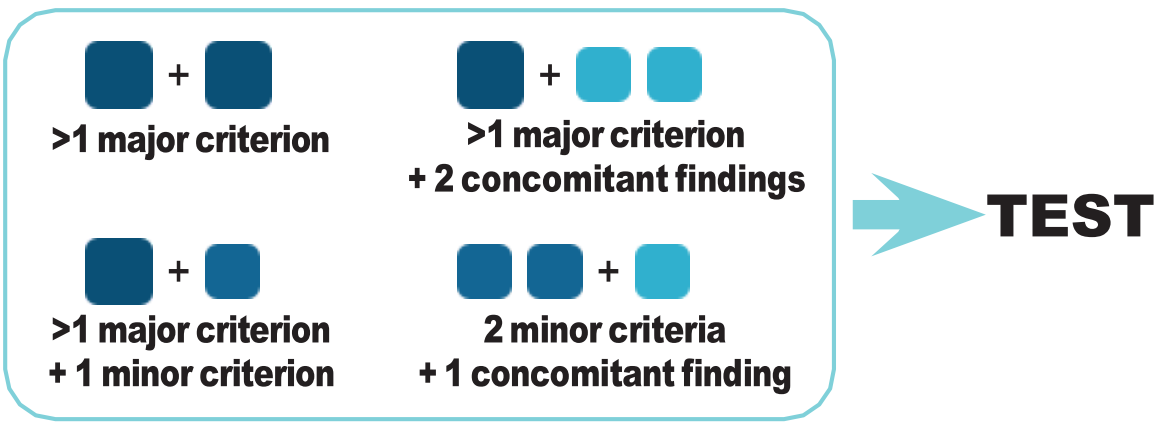
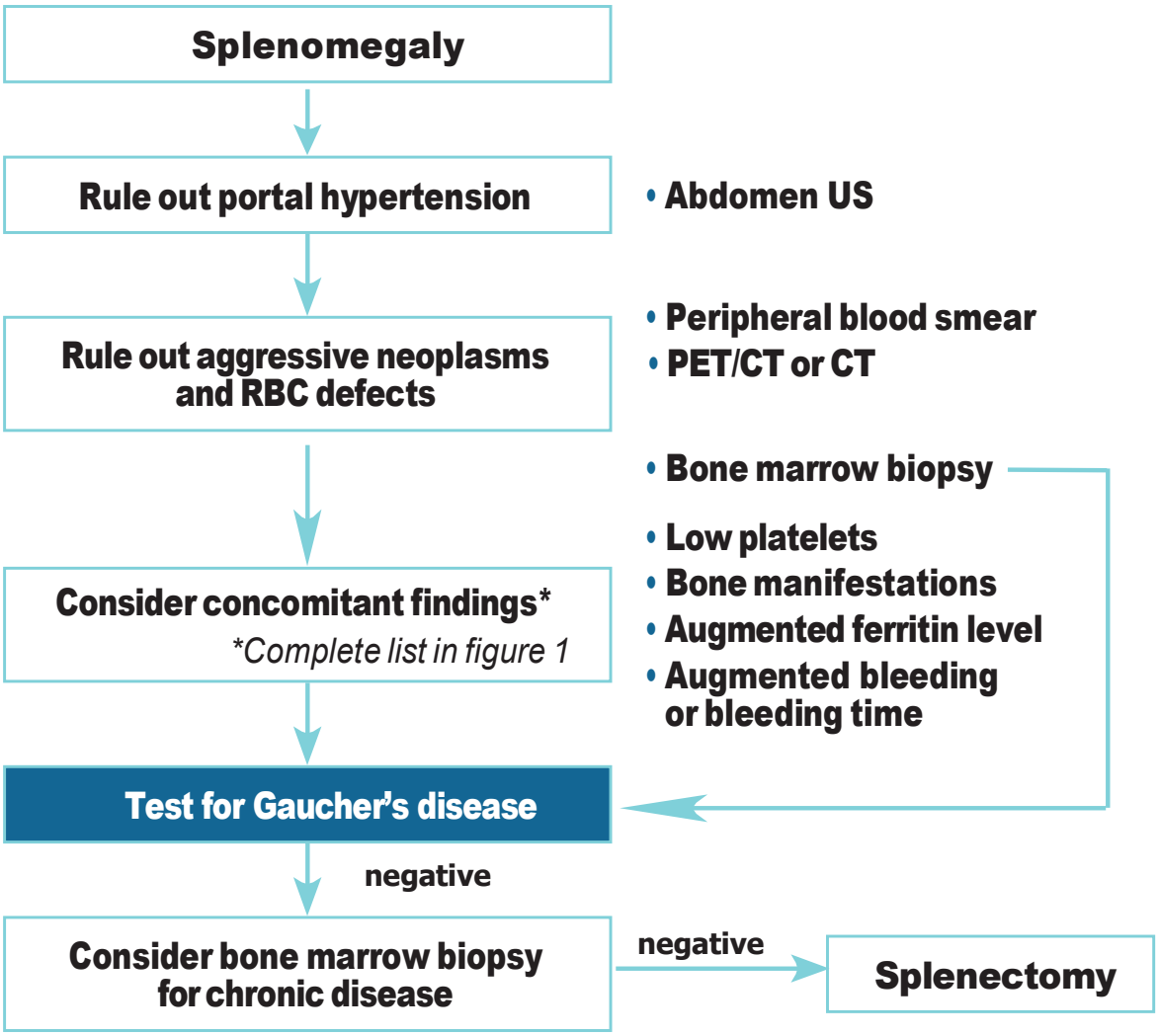


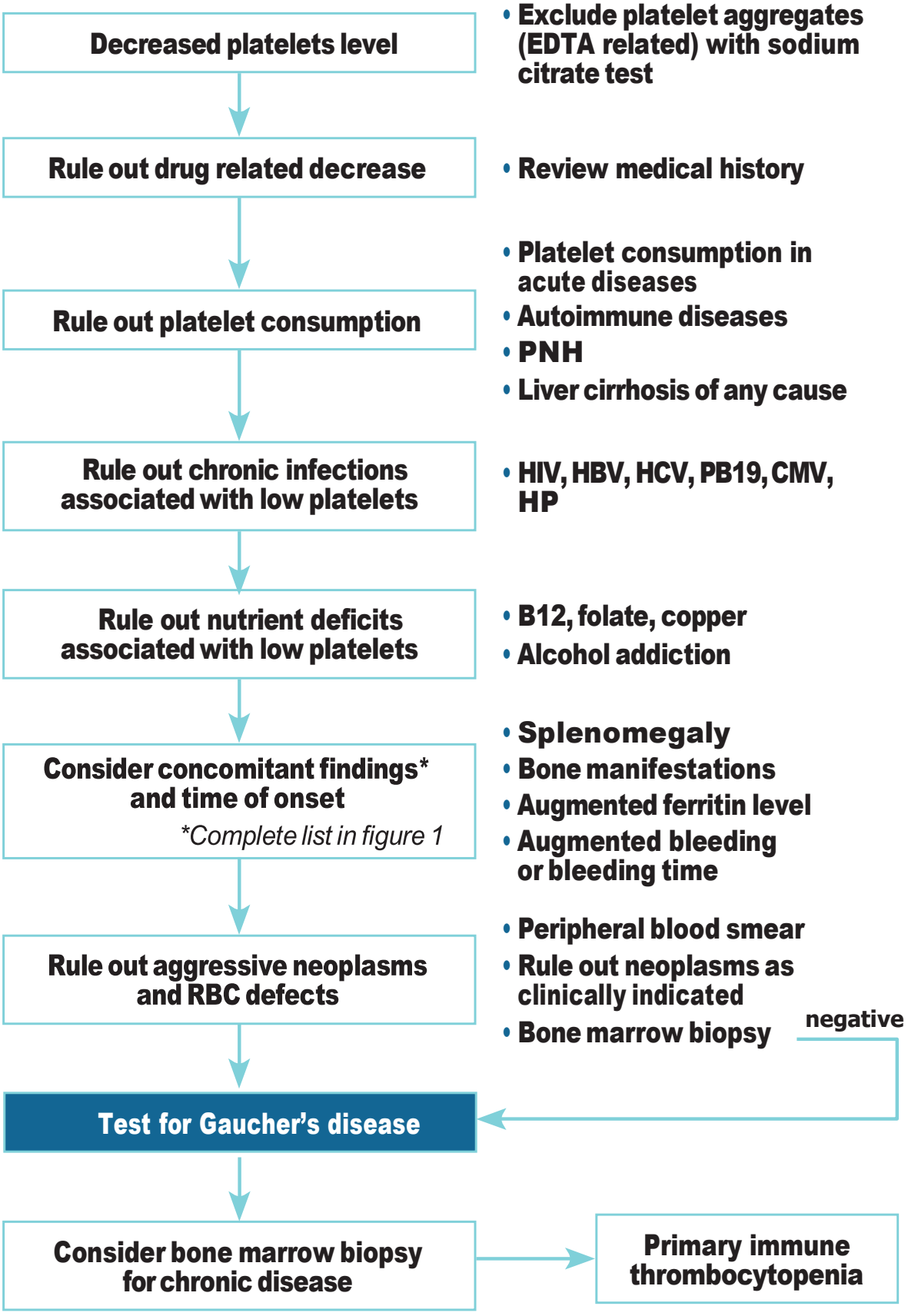

Fig 1: Screening test criteria for Gaucher's disease.
Adapted from Atul Mehta et al: Internal Medicine Journal 49 (2019) 578–591

# Algorithm for a differential diagnosis in adult patients with enlarged spleen that accounts for possible Gaucher's disease

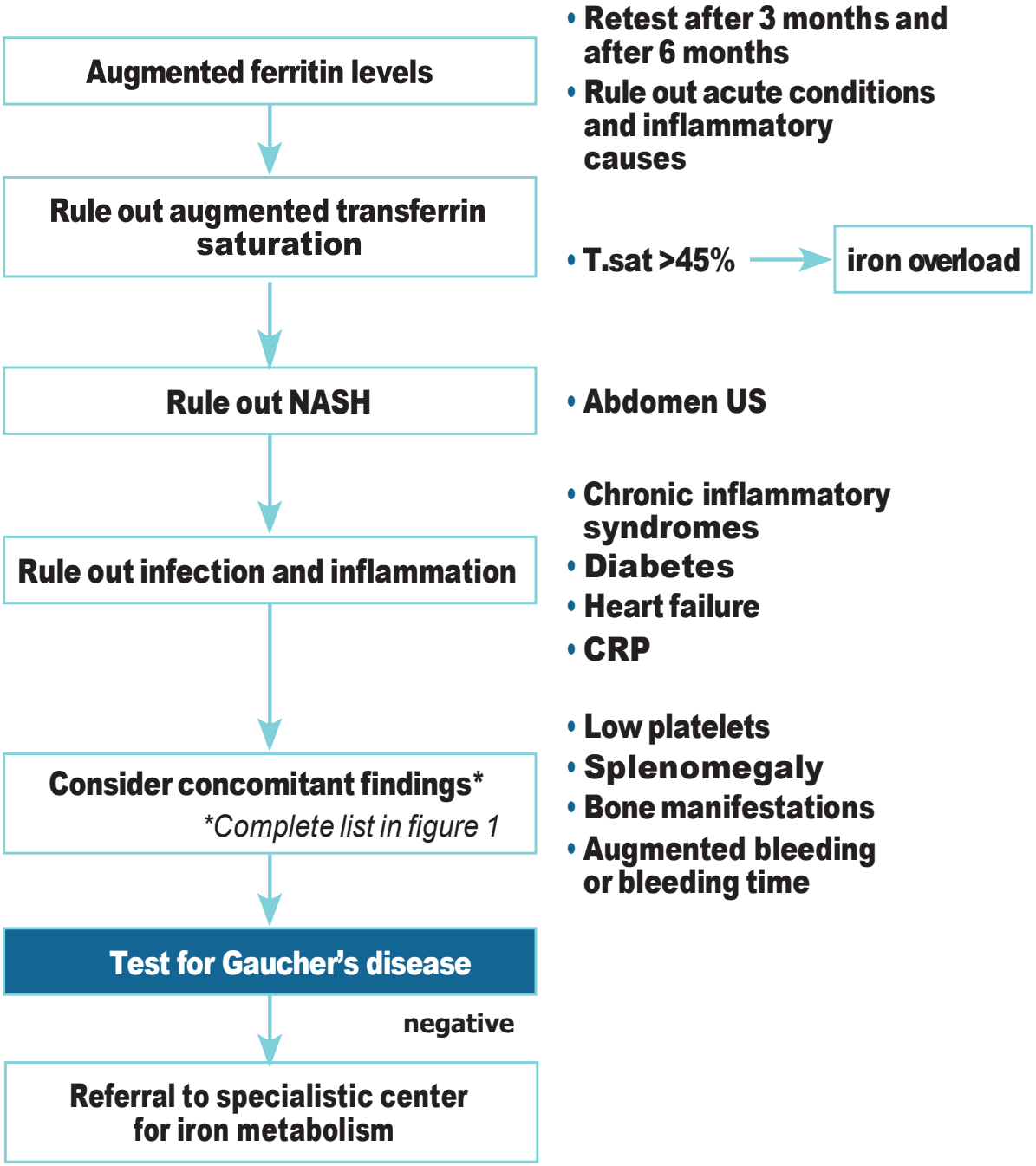



Modified from Mistry et al., Am J Hematol, 2011; 86(1): 110-115

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



# Algorithm for a differential diagnosis in adult patients with augmented ferritin levels that accounts for possible Gaucher's disease



## 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.

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