Review Article

Finding and treating Gaucher Disease Type 1
The role of the haematologist

Cappellini M-D, Cassinerio E, Motta I, *et al. Eur Oncol & Haematol* 2018;14(1):50-56.

Only 20 % of haematologists consider Gaucher Disease type 1 in their differential diagnosis for patients presenting with splenomegaly and/or thrombocytopenia[1]

Gaucher disease (GD)

- Is a rare, autosomal recessive disorder caused by mutations in the *GBA* gene.[1] More than 330 mutations have been identified to date, all of which result in reduced levels of the enzyme, ß-glucocerebrosidase, which in healthy individuals hydrolyses the glycolipid, glucocerebroside to glucose and ceramide.[1]
- Is characterised by an accumulation of glucosylceramide and glucosylsphingosine in macrophages and other reticuloendothelial cells, leading to the formation of 'Gaucher cells'.[1] These lipid-laden cells gradually infiltrate the spleen, liver, kidneys, lung, brain and/or bone marrow causing progressive and heterogeneous disease.[1]
- Is the most common type of lysosomal storage disease (LSD), with an estimated prevalence if 1/75 000 births among the general population, rising to 1/600 births in Ashkenazi Jews.[1]
- Encompasses a continuum of phenotypes, ranging from a perinatal lethal form (type 2) to a mild or asymptomatic adult form (type 1).[1]

Gaucher disease type 1

- Is the most common and mildest form of the disorder.[1]
- Presents with haematological complications, including spontaneous bruising/bleeding due to thrombocytopenia and/or GD-associated coagulopathy, abdominal discomfort/swelling due to splenomegaly and/or chronic fatigue due to anaemia.[1] Hepatomegaly and abnormal liver function, increased susceptibility to infection due to suboptimal neutrophil function and neutropenia, pulmonary disease, bone pain and (in children) growth retardation and/or delayed puberty may also be present.[1]
- Is usually distinguished from type 2 and 3 GD by the absence of neurological symptoms, such as convulsions, hypertonia, mental retardation, apnoea, slow saccades and/or dementia.[1]
- Long-term complications include pulmonary hypertension, haematological malignancies (leukaemia, multiple myeloma and lymphoma) and – less frequently – solid cancers.[1] Skeletal disorders due to bone marrow infiltration (e.g. pathological fractures, osteolytic lesions and osteonecrosis) are common.[1]

In general, patients with GD type 1 who remain untreated survive through to adulthood.[1]

The importance of an early diagnosis

- The usual treatment for GD type 1 is enzyme replacement therapy (ERT).[1]
- Prompt treatment with ERT can prevent or reverse many of the clinical features associated with GD type 1, thereby improving quality of life.[1]
- In addition to enabling effective management strategies, a prompt diagnosis of GD enables early screening of at-risk relatives and timely provision of genetic counselling for affected individuals and their families.[1]

Despite the importance of early symptom management, people with GD often experience considerable diagnostic delays.[1]

Diagnostic clues

- Approximately 60 % of patients with GD type 1 have thrombocytopenia at diagnosis and 86 % (and 95 % of children) have splenomegaly.[1]
- Suspicion of GD should be further raised by the presence of hepatomegaly, fatigue (sometimes related to anaemia), leukopenia, bone pain/disease, growth retardation and/or delayed puberty.[1]

Diagnostic tests

ß-glucosidase activity tests

- A definitive diagnosis of GD can be obtained by measuring ß-glucosidase activity in peripheral blood leucocytes (normal range: 2.1-5.3 µmol/l/h).[1] However, this assay is only conducted at specialised centres and, as a result, the ß-glucosidase test may not be performed during the initial visit.[1]
- To accelerate the diagnostic process, non-invasive dried blood spot (DBS) assays have been developed for screening ß-glucosidase activity.[1] Positive results must be followed up with the traditional assay.[1]

Mutation analysis

- Molecular screening for common *GBA1* mutations is a reliable test for Ashkenazi Jews and other individuals who are at high risk for GD.[1]

Bone marrow biopsy

- Bone marrow biopsy is useful for distinguishing haematological malignancy from GD.[1]

Biochemical markers

- Abnormal levels of one or more biochemical markers (Table 1) are suggestive of GD, but similar changes can be caused by other disorders.[1]
- The most reliable and specific biomarker for GD is glucosylsphingosine (lyso-GL1).[1]

Table 1. Common laboratory markers in Gaucher disease[1]

Elevated	Decreased
Glucosylsphingosine (lyso-GL1)	Clotting factors
Chitotriosidase	Vitamin B12
CCL18	Total cholesterol
ACE	Platelet count (sometimes below 20 x 10^9/l)
TRAP	
Ferritin	
Lysozyme	
Polyclonal gammopathy and/or MGUS	

ACE = angiotensin-converting enzyme; CCL18 = chemokine (C-C motif) ligand; MGUS = monogammopathy of unknown significance; TRAP = tartrate-resistant acid phosphatase.

Algorithms for the diagnosis of GD type 1

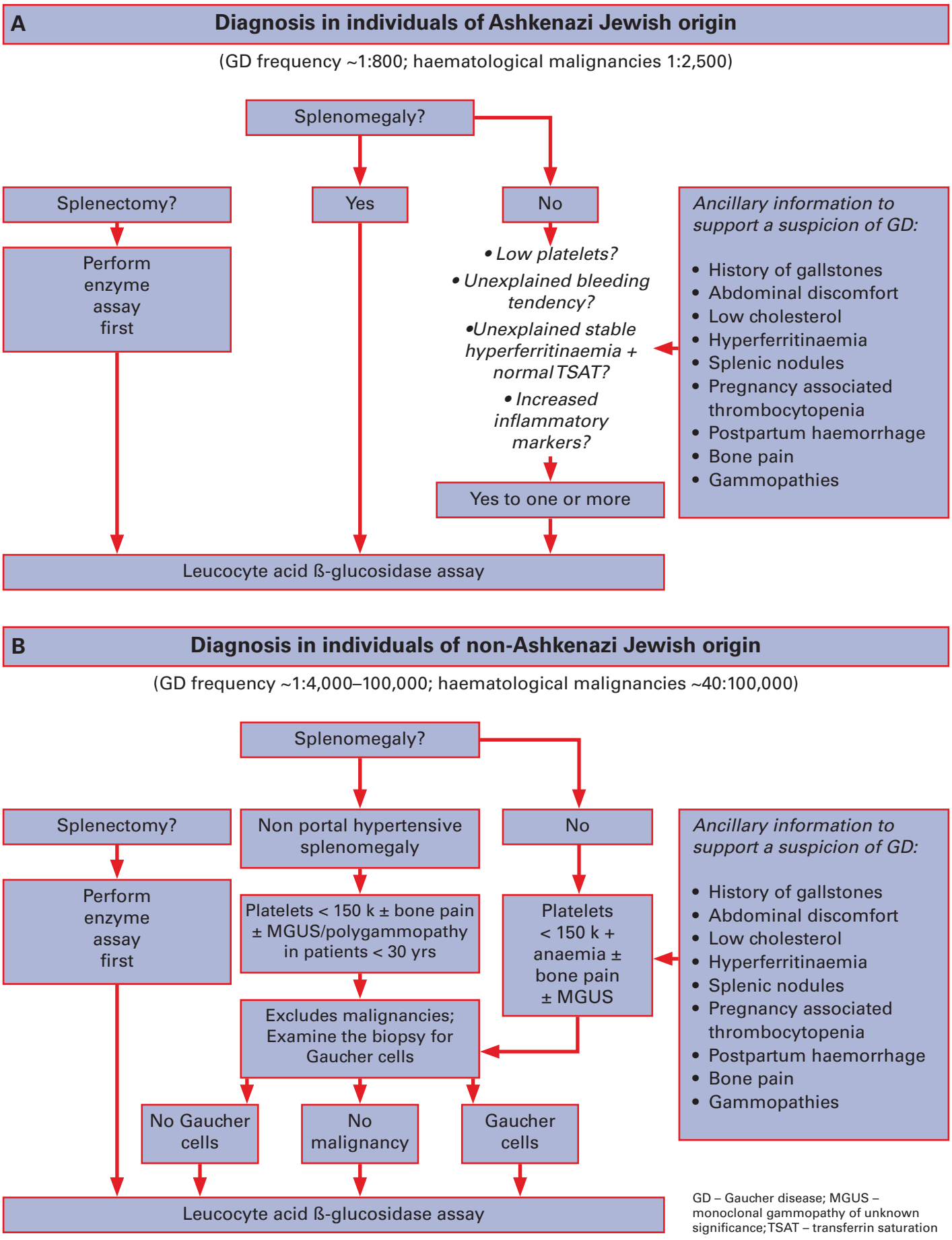
Gaucher disease diagnosis in adults

- Given the incidence of GD type 1 versus haematological malignancy in the Ashkenazi Jewish population, algorithms for the diagnosis of GD in adults suggest that ß-glucosidase activity should be routinely assessed in all high-risk individuals with thrombocytopenia and splenomegaly (Figure 1A).[1]

- In people not descended from Ashkenazi Jews, splenomegaly is more likely to be caused by haematological malignancy than by GD.[1] In these patients, it is reasonable to perform a bone marrow biopsy before GD is considered to rule out malignancy and other conditions associated with splenomegaly (Figure 1B).[1] When interpreting biopsy results, it is important to remember that malignancy and GD sometimes co-exist.[1]

Although splenectomy is indicated for a number of conditions associated with splenomegaly, it tends to worsen the clinical course of GD in the liver, skeleton and the lungs.[1]
Consequently, GD must be excluded in all patients being considered for splenectomy.[1]

Figure 1. Algorithm for the diagnosis of Gaucher disease in A: adults descended from Ashkenazi Jews and B: adults not descended from Ashkenazi Jews[1]

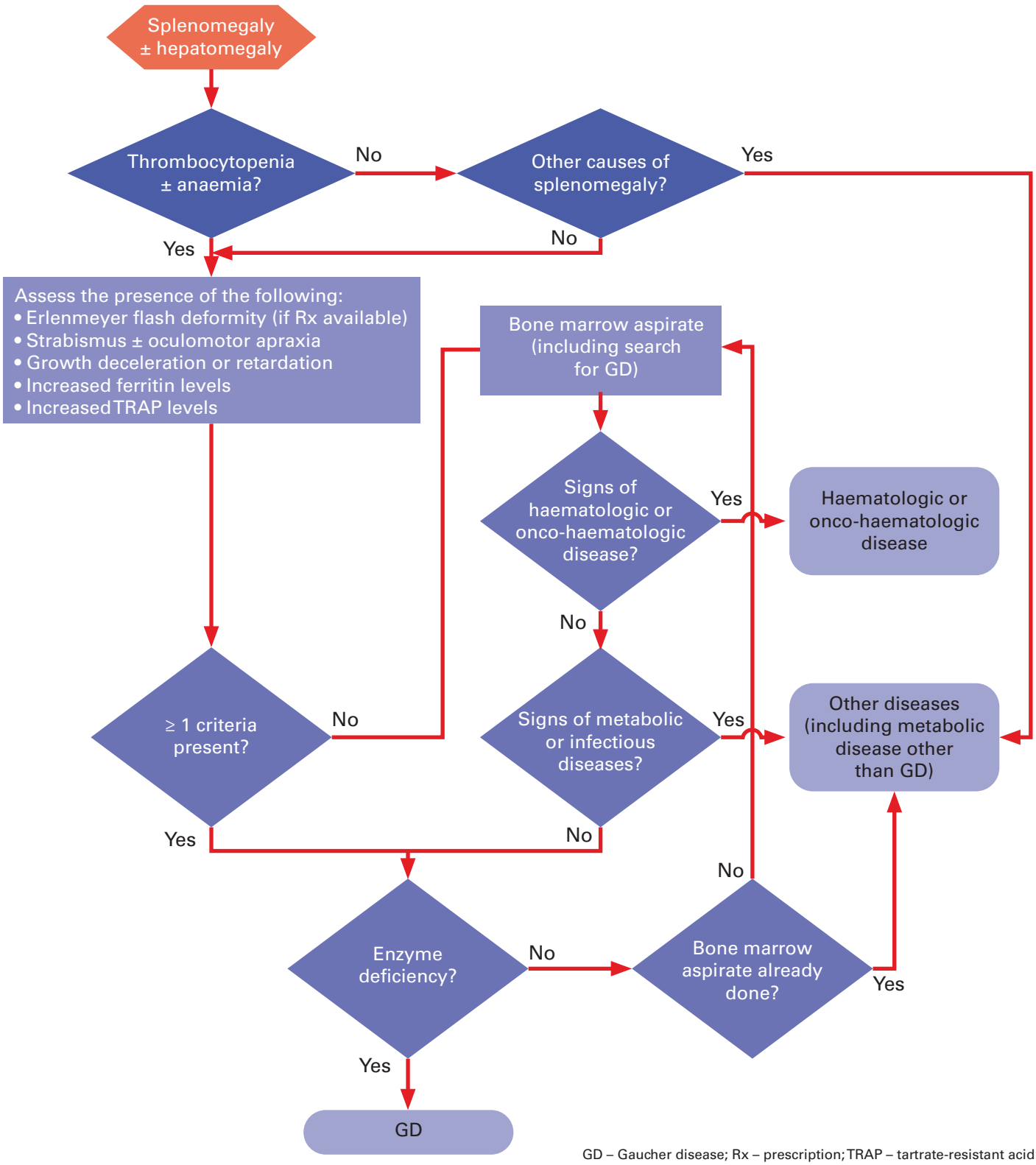


GD – Gaucher disease; MGUS – monoclonal gammopathy of unknown significance; TSAT – transferrin saturation

Gaucher disease diagnosis in children/young adults

- Algorithms for the diagnosis of GD (type 1 and 3) in children/young adults propose that GD should be considered in all children with unexplained splenomegaly, with or without thrombocytopenia, anaemia and/or hepatomegaly (Figure 2).[1]
- Where possible, GD should be confirmed using a ß-glucosidase assay, thereby avoiding unnecessary emotional trauma and/or bleeding that may be caused by bone marrow biopsy or liver biopsy.[1]

Figure 2. Algorithm for the diagnosis of Gaucher disease in the paediatric population[1]



GD – Gaucher disease; Rx – prescription; TRAP – tartrate-resistant acid

Summary

- Early diagnosis and prompt management of GD has the potential to reduce the risk of long-term GD complications while reversing many of the initial signs/symptoms.[1]
- Most patients with GD have unexplained splenomegaly and/or thrombocytopenia, and many present during childhood.[1] Consequently, most initial referrals are to haematologists and/or paediatricians.[1]
- Simple diagnostic algorithms and screening tools have been developed and validated, both in adults and in children.[1]

Reference: 1. Cappellini M-D, Cassinerio E, Motta I, *et al.* Finding and treating Gaucher disease type 1 –The role of the haematologist. *Eur Oncol & Haematol* 2018;14(1):50-56.

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