# Rare but important haematological conditions: Gaucher disease

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## Abstract

Gaucher disease is a rare autosomal recessive disorder of sphingolipid metabolism. Deficiency of β-glucocerebrosidase results in the accumulation of glucosylceramide in cells of the reticuloendothelial system, with consequent organomegaly and bone marrow failure. Recent research has suggested that defects exist beyond the macrophage, for example in immune and mesenchymal-derived cells. Patients often present to haematologists and, despite the availability of an enzyme assay, diagnosis is often made incidentally on bone marrow biopsy. Specific therapy is available by enzyme replacement or substrate reduction, resulting in an improvement of haematological parameters and bone disease. Patients with Gaucher disease suffer a higher incidence of haematological malignancy, and although understanding is incomplete, recent research suggests a role of antigenicity of lysolipids both in Gaucher and non-Gaucher-related myeloma.


**Keywords** Enzyme replacement therapy; Gaucher; macrophage; substrate reduction therapy

## Key points

- Gaucher disease is a rare but treatable metabolic condition with a wide range of haematological and osseous manifestations; it often presents first to haematologists
- Patients display symptoms of bone marrow failure, hepatosplenomegaly and bone pathology, and have a higher incidence of haematological malignancy, especially multiple myeloma
- Patients continue to experience delays in diagnosis, and delays in initiation of therapy appear to affect the likelihood of continuing bone complications
- Early diagnosis can facilitate supportive care and the initiation of Gaucher-specific therapy for appropriate individuals, and can reduce the potential for long-term disabling complications

## Introduction

Gaucher disease (GD) is an autosomal recessive disorder owing to deficiency of β-glucocerebrosidase and accumulation of glucosylceramide in cells of the reticuloendothelial system (Figure 1). The gene coding for β-glucocerebrosidase (*GBA*, also known as *GBA1*) is located on chromosome 1q21, and approximately 300 mutations of the *GBA1* allele have been reported. The reported incidence of GD is 1 in 57,000, but GD is more common in Ashkenazi Jews, in whom the incidence is 1 in 850, with a carrier frequency of 1 in 10 to 1 in 17.5.

## Haematological presentation

Clinically, GD is divided into non-neuronopathic (type 1) and neuronopathic (types 2, 3) types. Type 1 GD is the most prevalent and presents with clinical features related to the effects of substrate accumulation in macrophages, including fatigue, easy bruising, anaemia and bone pain. The most common laboratory feature at presentation is thrombocytopenia caused by splenomegaly in combination with bone marrow infiltration. Data from the International Collaborative Group on Gaucher Disease registry show a median platelet count in non-splenectomized patients of 85 $\times$ $10^9$/litre. Low platelets combined with abnormalities of platelet function result in a bleeding tendency, which can be spontaneous or can become obvious during dentistry, surgery or parturition. A variety of coagulation factor deficiencies including acquired von Willebrand's disease have also been described, and might in part be due to low-grade disseminated intravascular coagulation or, in the case of factor XI genetic deficiency, be associated with Ashkenazi heritage.

Severe anaemia at presentation is less common and suggests more severe bone marrow infiltration by glucosylceramide-laden Gaucher macrophages. Iron and vitamin $B_{12}$ deficiency and autoimmune haemolysis have also been described. Fatigue is often out of proportion to the haemoglobin concentration and is likely to be multifactorial in the context of a generalized inflammatory state and cachexia in the most severe cases.

Splenomegaly is common and can result directly in abdominal pain or early satiety. The enlarged spleen can be massive and contain circumscribed accumulations of Gaucher cells (gaucheroma) (Figure 2). Hepatomegaly is usually less marked, but in severe cases cirrhosis can occur and a number of cases of hepatic transplantation have been reported. Abdominal pain can also be due to gallstones, which are more frequent, especially in splenectomized patients.

## Bone disease

Most patients have radiographic evidence of bone involvement, with features that include local or generalized osteopenia, osteosclerosis, infarction, remodelling abnormalities, such as Erlenmeyer flask deformities, and fractures.[1] Patients experience

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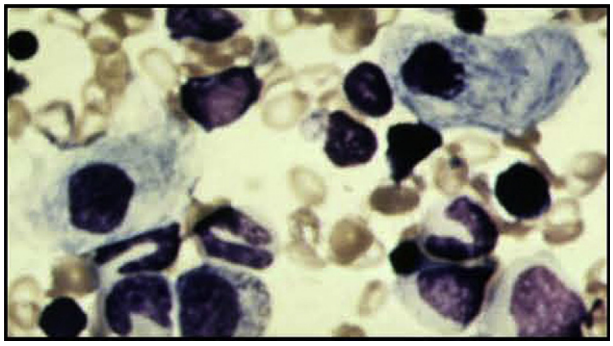

**Figure 1** Glucosylceramide engorged macrophage.

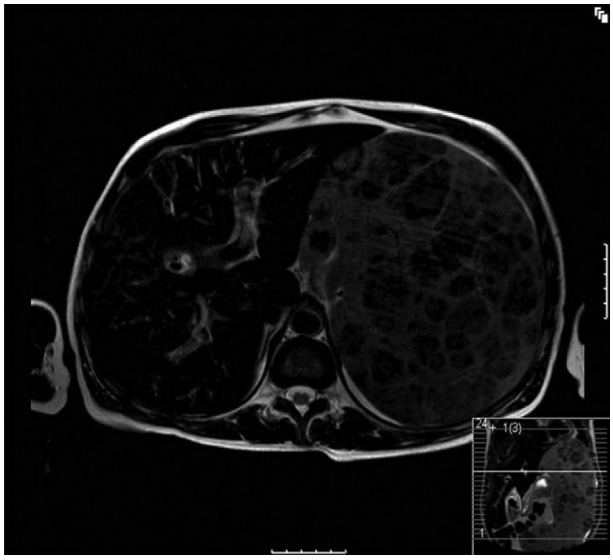

**Figure 2** MRI scan of liver and spleen of 55-year-old man with Gaucher's disease, demonstrating enlargement of the liver and spleen with multiple focal mass lesions.

severe episodes of localized bone pain with raised inflammatory markers and sterile blood cultures (bone crises) on a background of chronic pain and disability. Spontaneous fractures can occur, and many patients require early joint replacement. The aetiology of osseous manifestations is not completely understood. Raised pressure in the marrow compartment from excess storage cells causing vascular occlusion may contribute to infarction and avascular necrosis. However, remodelling abnormalities and reduced bone density are likely to be more complex, involving abnormalities of osteoblast and osteoclast lineages.

Several small cohort and large database studies have indicated an increased risk of malignancy, particularly haematological, in GD. The risk of multiple myeloma has been suggested to be up to 50 times the background rate. Recent evidence has suggested this may be related to antigenicity of lysolipids including glucosylceramide resulting in stimulation of clonal B cells, and that this mechanism may also be relevant to non-Gaucher myeloma patients.[2]

## Diagnosis

A recent retrospective analysis of referral routes to a UK specialist centre found that, despite the availability of specific therapies for GD, there are still significant delays between the onset of symptoms and diagnosis.[3] In most patients, GD is diagnosed by haematologists, usually by bone marrow trephine biopsy. This is probably a haematological default pathway for patients presenting with splenomegaly and cytopenias, and results in an incidental finding of bone marrow Gaucher cells. However, there is a differential diagnosis for Gaucher cells (Table 1).

The diagnosis of GD must therefore be confirmed by finding reduced β-glucocerebrosidase enzyme activity. This is a simple fluorometric assay that can be performed on leucocytes from whole blood, cultured fibroblasts (rarely necessary) or blood spots. Raised awareness of the condition and the availability of this assay can expedite diagnosis and avoid the need for bone marrow biopsy. Sequencing of the glucocerebrosidase gene allows definition of the pathogenic mutations, which can assist in prognostication and genetic counselling, but is not essential for diagnosis. GD should be considered in the differential diagnosis for a patient presenting with unexplained thrombocytopenia, anaemia or splenomegaly with or without accompanying bone pain.

## Assessment and monitoring

Following diagnosis, patients should be assessed for the extent and severity of their symptoms. Magnetic resonance imaging (MRI) of the axial skeleton provides information on the degree of bone marrow infiltration and skeletal abnormalities, including bone infarction/avascular necrosis and remodelling abnormalities. Bone density should be assessed using dual-energy X-ray absorptiometry. In a limited number of centres, quantitative chemical shift imaging reveals the percentage of bone marrow fat, an indicator of bone complications. Several scoring systems have been developed, more recently incorporating quantitative assessments of organ volume and bone disease. The utility of a number of biomarkers correlating with baseline disease severity and treatment effects has been evaluated. The activity of serum chitotriosidase enzyme is increased in GD patients. Other markers found to be elevated include tartrate-resistant acid phosphatase, angiotensin-converting enzyme and macrophage inhibitory protein (MIP)-1α and MIP1β.

### Differential diagnosis of 'foamy' macrophages in the bone marrow

| Lysosomal storage disorders | Haematological disorders (pseudo-Gaucher cells) |
|---|---|
| Gaucher's disease | Multiple myeloma |
| Fabry disease | Hodgkin's lymphoma |
| GM1 gangliosidosis | Non-Hodgkin's lymphoma |
| Wolman/cholesterol ester storage disorder | Chronic myeloid leukaemia myelodysplasia |
| Niemann–Pick A and B (sea blue histiocytes) | B cell acute lymphoblastic leukaemia |
| | Thalassaemia |
| | Sickle cell disease |

**Table 1**