GAUCHER INSTITUTE
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DIAGNOSING GAUCHER DISEASE

Early diagnosis of Gaucher disease is essential in implementing the appropriate patient assessment and management plans as soon as possible.

WHAT IS GAUCHER DISEASE?

Gaucher disease is a **rare, inherited metabolic disorder** and is classified as a type of **lysosomal storage disease** known as sphingolipidosis.[1]

Gaucher disease is caused by mutations in the *GBA1* gene located on chromosome 1. Mutations in this gene lead to a marked reduction in the activity of the lysosomal enzyme glucocerebrosidase, which hydrolyses glucosylceramide into ceramide and glucose.[1] In Gaucher disease, a deficiency in glucocerebrosidase leads to an accumulation of glucosylceramide in lysosomes. Glucosylceramide then forms fibrillary aggregates that accumulate in macrophages, leading to the cell cytoplasm presenting a characteristic 'crumpled tissue paper' appearance. These cells are known as Gaucher cells and infiltrate many organs, including the bone marrow, spleen and liver, leading to the clinical manifestations of Gaucher disease.[1]

The worldwide prevalence of Gaucher disease varies by geography, but generally ranges from **0.7 to 1.75 per 100,000 individuals** and is substantially higher among the Ashkenazi Jewish population.[2,3] Males and females are equally affected by Gaucher disease because of its **autosomal recessive** mode of inheritance.[4,5]

Early diagnosis of Gaucher disease is essential in implementing the appropriate patient assessment and management plans as soon as possible.[6] However, **patients with Gaucher disease may experience a wide range of comorbidities**, which may make clinical decision-making more challenging.[7]

There is a need for greater awareness among healthcare professionals for the diagnosis of Gaucher disease. **Results from a survey of 406 haematology-oncology physicians, published in 2007, reported that 20% would consider Gaucher disease Type 1 in their differential diagnosis for a patient presenting with common disease-related symptoms**.[8] The lack of physician awareness or misdiagnosis of the disease results in diagnostic delay; a survey of 154 patients with Gaucher disease based in the US found that for 1 in 7 patients, reaching **a diagnosis of Gaucher disease took ⩾7 years**.[9]

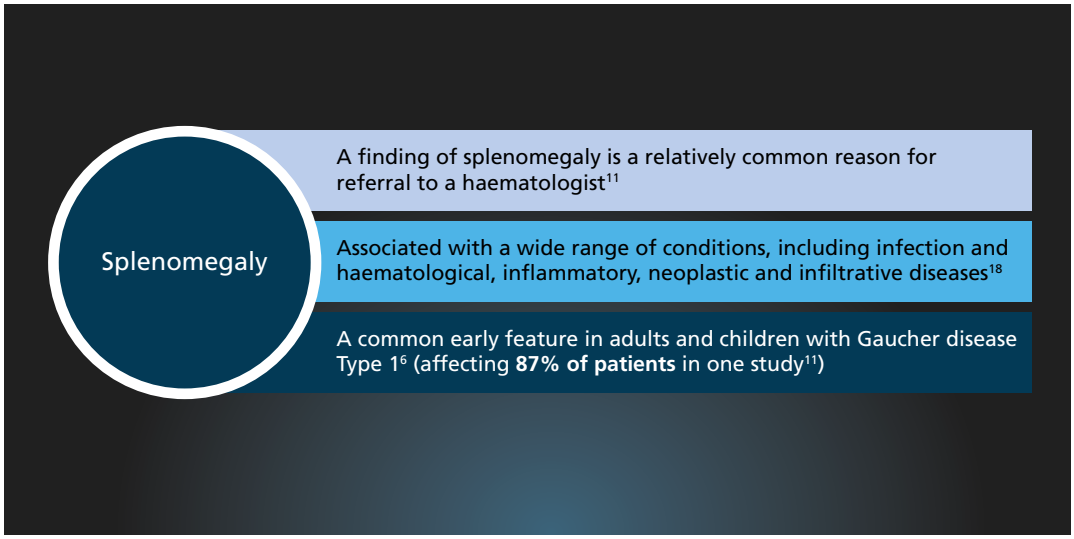
THE THREE MAIN TYPES OF GAUCHER DISEASE

	Type 1 (non-neuronopathic)	Type 3 (chronic neuronopathic)	Type 2 (acute neuronopathic)
Proportion of patients[1]	>90%	~5%	<5%
Main features	**Visceral and haematological**[1,10,11] ■ Splenomegaly ■ Hepatomegaly ■ Thrombocytopaenia ■ Hyperferritinaemia ■ Fatigue ■ Anaemia **Bone manifestations**[1] ■ Acute painful bone crises ■ Avascular necrosis ■ Osteopaenia and osteoporosis **Neurological symptoms**[12-14] ■ Peripheral neuropathy	**Visceral** ■ Similar to Type 1[1] **Neurological symptoms**[1,15] ■ Horizontal opthalmoplegia ■ Cerebellar ataxia ■ Developmental delay ■ Extrapyramidal features ■ Myoclonic or generalised seizures ■ Supranuclear opthalmoplegia ■ Supranuclear saccadic gaze palsy	**Severe neurological abnormalities**[16] **Non-neurological symptoms**[16] ■ Hepatosplenomegaly ■ Thrombocytopaenia ■ Lung disease ■ Failure to thrive ■ Fever
Major covariables[6]	Family history of Gaucher disease Ashkenazi Jewish ethnicity	Family history of Gaucher disease	
	The unexplained presence of ⩾2 signs, or one unexplained sign in conjunction with one of the covariables, should cause physicians to consider Gaucher disease in their differential diagnosis[6]		

KEY SIGNS AND SYMPTOMS: A FOCUS ON SPLENOMEGALY, HYPERFERRITINAEMIA, THROMBOCYTOPAENIA AND BONE PAIN

Splenomegaly

Splenomegaly is defined as enlargement of the spleen measured by size or weight.[17] The normal length of an adult spleen measures up to 12 cm with a weight of 70 g to 200 g; a spleen measuring >12 cm and/or weighing >400 g indicates splenomegaly.[17]

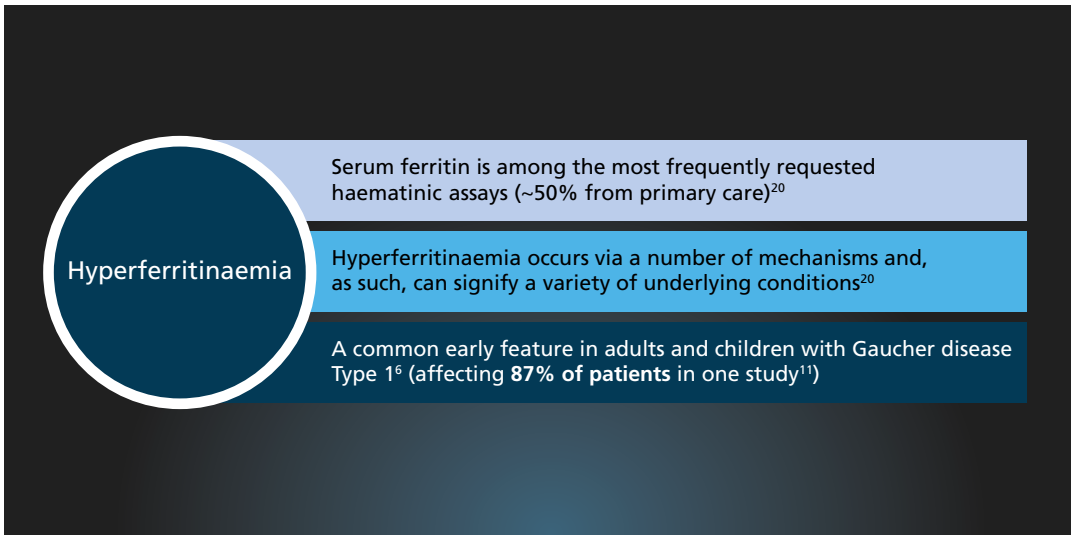


THREE STEPS TO A DIFFERENTIAL DIAGNOSIS OF SPLENOMEGALY

	Splenomegaly (haematologists and gastroenterologists)
1. Exclude infectious illnesses[18,19]	The following chronic systemic infections can lead to splenomegaly: ■ Malaria ■ Measles ■ Typhoid fever ■ Infectious mononucleosis ■ Viral illnesses
2. Exclude haematological, hepatic and inflammatory diseases[18]	■ Leukaemia ■ Lymphoma ■ Myeloproliferative disorders ■ Cirrhosis ■ Immune-mediated inflammatory disorders (e.g. systemic lupus erythematosus)
3. Check for Gaucher disease	**Gaucher disease should be included in the differential diagnosis of splenomegaly if elevated ferritin levels, thrombocytopaenia, a history of bone pain or Ashkenazi Jewish ethnicity is also present[6]**

Hyperferritinaemia

Hyperferritinaemia is defined as ferritin levels >400 µg/L in males, >150 µg/L in females; >650 µg/L in males and females aged 60 to 90 years; and >140 µg/L in children aged 6 months to 15 years.[20,21]

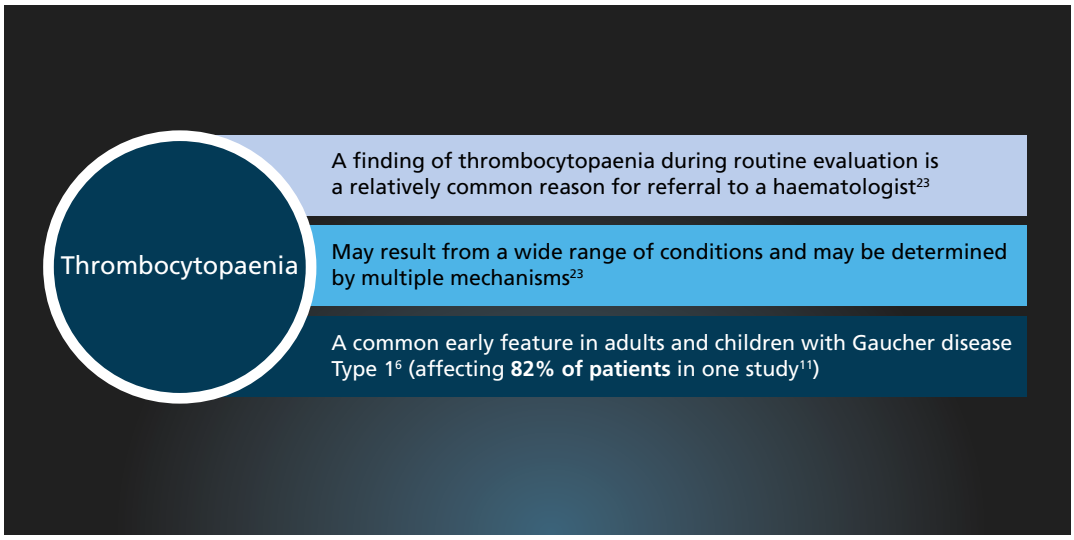


THREE STEPS TO A DIFFERENTIAL DIAGNOSIS OF HYPERFERRITINAEMIA

	Ferritinaemia (haematologists and gastroenterologists)
1. Check transferrin saturation to exclude iron-loading anaemias and genetic haemochromatosis	■ Elevated serum ferritin in combination with raised transferrin saturation may indicate iron-loading anaemias or genetic haemochromatosis[20] – Males with serum ferritin ⩾300 µg/L and transferrin saturation >50% and females with serum ferritin ⩾200 µg/L and transferrin saturation >40% overload have a 19% and 16% likelihood, respectively, of having hereditary haemochromatosis[22]
2. Exclude common causes of elevated serum ferritin with normal transferrin saturation	■ These include[20]: – Alcohol excess – Inflammatory disorders – Metabolic syndrome – Tissue damage or turnover (e.g. hepatic or malignancy) ■ Other rare causes of elevated serum ferritin with normal transferrin saturation include hereditary hyperferritinaemia with and without cataracts[20]
3. Check for Gaucher disease	**Gaucher disease should be included in the differential diagnosis of hyperferritinaemia if thrombocytopaenia, splenomegaly, a history of bone pain or Ashkenazi Jewish ethnicity is also present[6,20]**

Thrombocytopaenia

Thrombocytopaenia is defined as a platelet count below the 2.5th lower percentile of the normal platelet count distribution.[23] In adults aged >15 to 64 years, this is a platelet count of 136–436 and 120–369 x 10^9/L in males and females, respectively, and a platelet count of 165–473 x 10^9/L in children under 15 years of age.[24]



THREE STEPS TO A DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOPAENIA

	Thrombocytopaenia in adults (haematologists, rheumatologists, orthopaedists and gastroenterologists)	**Thrombocytopaenia in children** (paediatric haematologists, metabolic paediatricians, paediatric endocrinologists, paediatric rheumatologists, paediatric orthopaedists and paediatric gastroenterologists)
1. Exclude known causes	For example[23]: ■ Family history of thrombocytopaenia ■ Drug-induced thrombocytopaenia ■ Heparin-induced thrombocytopaenia ■ Viral infections ■ Pregnancy ■ Connective tissue disorders	For example[23]: ■ Family history of thrombocytopaenia ■ Drug-induced thrombocytopaenia ■ Viral injections ■ Connective tissue disorders
2. Exclude malignancy	For example[23]: ■ Acute leukaemia However, patients with any of the following may also have concurrent Gaucher disease[25]: ■ Monoclonal gammopathy of undetermined significance ■ Myeloma ■ B-cell lymphoma	For example[23]: ■ Acute leukaemia However, patients with the following may also have concurrent Gaucher disease[25]: ■ B-cell lymphoma
3. Check for Gaucher disease	**Gaucher disease should be included in the differential diagnosis of thrombocytopaenia if splenomegaly, elevated ferritin levels, a history of bone pain or Ashkenazi Jewish ethnicity is also present[6]**	

Bone pain

- Bone pain can occur in response to a variety of conditions including trauma, infection, inflammation and autoimmune disease.[26] In children, bone pain can occur in relation to growing pains.[27]
- Bone pain is a common early feature of Gaucher disease in adults and children, affecting 36% of patients in one study,[11] and manifesting as bone crises and/or bone pain in 9% and 27% of children in another study.[28]
- Bone involvement in Gaucher disease is heterogeneous and, in general, is caused by **infiltration of Gaucher cells to bone marrow**, extending from the axial to the appendicular skeleton.[29-31]

THREE STEPS TO A DIFFERENTIAL DIAGNOSIS OF BONE PAIN

1. Exclude obvious causes	■ Recent broken bone or injury	
2. Exclude osteomyelitis and Legg-Calvé-Perthes disease	Acute osteomyelitis[32] ■ Incidence is approximately 21.8 cases per 100,000 person/year ■ Occurs twice as often in males ■ Determining the causative organism is pivotal	Legg-Calvé-Perthes disease ■ A childhood disorder affecting the head of the femur, with an incidence ranging from 0.4 to 29 per 100,000 individuals[33] ■ Gaucher disease is sometimes misdiagnosed as Legg-Calvé-Perthes disease[34]
3. Check for Gaucher disease	**Gaucher disease should be included in the differential diagnosis of bone pain if splenomegaly, thrombocytopaenia, delayed growth, elevated levels of ferritin or Ashkenazi Jewish ethnicity is also present[6]**	

HOW TO RULE OUT GAUCHER DISEASE

The presence of Gaucher disease can be ruled out using an assay in dried blood spots or peripheral white blood cells, to check for glucocerebrosidase enzyme activity.[35,36]

Routine bone marrow examination is not necessary for diagnosis.[37]

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