DIAGNOSING
GAUCHER DISEASE

Early diagnosis of Gaucher disease is essential in implementing the appropriate patient assessment and management plans as soon as possible.
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 \(\text{GBA1}\) 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 \(\geq 7\) years.\(^9\)

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### THE THREE MAIN TYPES OF GAUCHER DISEASE

<table>
<thead>
<tr>
<th></th>
<th>Type 1 (non-neuronopathic)</th>
<th>Type 3 (chronic neuronopathic)</th>
<th>Type 2 (acute neuronopathic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients(^1)</td>
<td>&gt;90%</td>
<td>~5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Main features</td>
<td>Viscer...al and haematomatologial(^1,11)</td>
<td>Visceral Similar to Type 1(^1)</td>
<td>Severe neurological abnormalities(^16)</td>
</tr>
<tr>
<td>Bone manifestations(^1)</td>
<td>Acute painful bone crises</td>
<td>Horizontal opthalmoplegia</td>
<td>Hepatosplenomegaly</td>
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<tr>
<td>Neurological symptoms(^1,15)</td>
<td>Cerebellar ataxia</td>
<td>Developmental delay</td>
<td>Thrombocytopaenia</td>
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<tr>
<td>Major covariables(^6)</td>
<td>Family history of Gaucher disease</td>
<td>Failure to thrive</td>
<td>Lung disease</td>
</tr>
<tr>
<td></td>
<td>Ashkenazi Jewish ethnicity</td>
<td>Fever</td>
<td>Failure to thrive</td>
</tr>
</tbody>
</table>

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**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.\(^1\)
Splenomegaly

Splenomegaly is defined as enlargement of the spleen measured by size or weight. 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.

**Splenomegaly**

A finding of splenomegaly is a relatively common reason for referral to a haematologist. Associated with a wide range of conditions, including infection and haematological, inflammatory, neoplastic and infiltrative diseases. A common early feature in adults and children with Gaucher disease Type 1 (affecting 87% of patients in one study).

**Three steps to a differential diagnosis of splenomegaly**

<table>
<thead>
<tr>
<th>Step</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Exclude infectious illnesses&lt;sup&gt;18,19&lt;/sup&gt;</td>
<td>The following chronic systemic infections can lead to splenomegaly:</td>
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<tr>
<td></td>
<td><em>Malaria</em></td>
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<td></td>
<td><em>Measles</em></td>
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<td></td>
<td><em>Typhoid fever</em></td>
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<td></td>
<td><em>Infectious mononucleosis</em></td>
</tr>
<tr>
<td></td>
<td><em>Viral illnesses</em></td>
</tr>
<tr>
<td>2. Exclude haematological, hepatic and inflammatory diseases&lt;sup&gt;18&lt;/sup&gt;</td>
<td><em>Leukaemia</em></td>
</tr>
<tr>
<td></td>
<td><em>Lymphoma</em></td>
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<tr>
<td></td>
<td><em>Myeloproliferative disorders</em></td>
</tr>
<tr>
<td></td>
<td><em>Cirrhosis</em></td>
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<tr>
<td></td>
<td><em>Immune-mediated inflammatory disorders (e.g. systemic lupus erythematosus)</em></td>
</tr>
<tr>
<td>3. Check for Gaucher disease</td>
<td>Gaucher disease should be included in the differential diagnosis of splenomegaly if elevated ferritin levels, thrombocytpoaenia, a history of bone pain or Ashkenazi Jewish ethnicity is also present&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Serum ferritin is among the most frequently requested haematinic assays (~50% from primary care)\(^\text{20}\). Hyperferritinaemia occurs via a number of mechanisms and, as such, can signify a variety of underlying conditions\(^\text{20}\). A common early feature in adults and children with Gaucher disease Type 1\(^\text{6}\) (affecting 87% of patients in one study\(^\text{11}\))

**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.\(^\text{20,21}\)

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**THREE STEPS TO A DIFFERENTIAL DIAGNOSIS OF HYPERFERRITINAEemia**

<table>
<thead>
<tr>
<th>Step</th>
<th>Differential Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Check transferrin saturation to exclude iron-loading anaemias and genetic haemochromatosis&lt;br&gt;Elevated serum ferritin in combination with raised transferrin saturation may indicate iron-loading anaemias or genetic haemochromatosis(^\text{22}): Males with serum ferritin &gt;300 μg/L and transferrin saturation &gt;50% and females with serum ferritin &gt;200 μg/L and transferrin saturation &gt;40% overload have a 19% and 16% likelihood, respectively, of having hereditary haemochromatosis(^\text{22}).</td>
</tr>
<tr>
<td>2.</td>
<td>Exclude common causes of elevated serum ferritin with normal transferrin saturation&lt;br&gt;These include(^\text{20}): Alcohol excess&lt;br&gt;Inflammatory disorders&lt;br&gt;Metabolic syndrome&lt;br&gt;Tissue damage or turnover (e.g. hepatic or malignancy)&lt;br&gt;Other rare causes of elevated serum ferritin with normal transferrin saturation include hereditary hyperferritinaemia with and without cataracts(^\text{20}).</td>
</tr>
<tr>
<td>3.</td>
<td>Check for Gaucher disease&lt;br&gt;Gaucher disease should be included in the differential diagnosis of hyperferritinaemia if thrombocytopenia, splenomegaly, a history of bone pain or Ashkenazi Jewish ethnicity is also present(^\text{20}).</td>
</tr>
</tbody>
</table>
**Thrombocytopenia**

Thrombocytopenia 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**

<table>
<thead>
<tr>
<th>Steps</th>
<th>Thrombocytopenia in adults (haematologists, rheumatologists, orthopaedists and gastroenterologists)</th>
<th>Thrombocytopenia in children (paediatric haematologists, metabolic paediatricians, paediatric endocrinologists, paediatric rheumatologists, paediatric orthopaedists and paediatric gastroenterologists)</th>
</tr>
</thead>
</table>
| 1.    | Exclude known causes                                                                             | For example\(^23\):  
- Family history of thrombocytopenia  
- Drug-induced thrombocytopenia  
- Heparin-induced thrombocytopenia  
- Viral infections  
- Pregnancy  
- Connective tissue disorders   | For example\(^23\):  
- Family history of thrombocytopenia  
- Drug-induced thrombocytopenia  
- Viral infections  
- 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 thrombocytopenia if splenomegaly, elevated ferritin levels, a history of bone pain or Ashkenazi Jewish ethnicity is also present\(^*\) |
Bone pain

- Bone pain can occur in response to a variety of conditions including trauma, infection, inflammation and autoimmune disease. In children, bone pain can occur in relation to growing pains.

- Bone pain is a common early feature of Gaucher disease in adults and children, affecting 36% of patients in one study, and manifesting as bone crises and/or bone pain in 9% and 27% of children in another study.

- 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.

**THREE STEPS TO A DIFFERENTIAL DIAGNOSIS OF BONE PAIN**

<table>
<thead>
<tr>
<th>1. Exclude obvious causes</th>
<th>Recent broken bone or injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Exclude osteomyelitis and Legg-Calvé-Perthes disease</td>
<td>Acute osteomyelitis: Incidence is approximately 21.8 cases per 100,000 person/year. Occurs twice as often in males. Determining the causative organism is pivotal.</td>
</tr>
<tr>
<td>3. Check for Gaucher disease</td>
<td>Gaucher disease should be included in the differential diagnosis of bone pain if splenomegaly, thrombocytopenia, delayed growth, elevated levels of ferritin or Ashkenazi Jewish ethnicity is also present.</td>
</tr>
</tbody>
</table>
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. Routine bone marrow examination is not necessary for diagnosis.

REFERENCES