Gaucher

Introduction

An introduction to Gaucher disease.

Gaucher disease is an inherited, genetic disorder which results in a lack of the enzyme ‘glucocerebrosidase’. To understand the implications of this it is useful to know a little about this enzyme’s normal activity. The human body contains many different types of cells. A basic cell has many components as you can see from the diagram below, including the nucleus which contains chromosomes. Within the cell there is a small compartment called the lysosome - this contains all the enzymes the cell needs to manage its recycling of waste products. Macrophages are a type of cell that are particularly important in Gaucher disease. The macrophage is responsible for the recycling of old red blood cells (red blood cells carry oxygen around the body and are constantly being made, used and recycled) and part of this process requires the enzyme glucocerebrosidase.

Macrophages engulf the products they need to recycle. The enzymes in the lysosome then begin the process of breaking them down into small units. In Gaucher
disease this process is ineffective and the cell becomes full of stored material (glucocerebroside). Eventually the macrophage swells and becomes misshapen and is unable to function effectively. These macrophages are then called Gaucher cells which are stored mainly in the liver, spleen and bone marrow.

**Inheritance**

Gaucher disease is an inherited genetic disorder described medically as an ‘autosomal recessive disease’. Each person has 23 pairs of chromosomes which contain genes – they receive 1 set from each parent. Genes contain the necessary information to allow our body to be formed and to function. It is estimated that every human being has 8 -10 genes that have changes within them (called mutations) however only some can cause disease. Gaucher disease only produces symptoms when both copies of the gene are affected. This may well have occurred when both parents have 1 copy of the genetic mutation (carriers) and passed it on to their offspring.

If you would like further information about the inheritance pattern in your personal circumstances or to know whether it is likely that any other members of your family are affected please discuss this with your physician or specialist nurse.

**Symptoms**

The signs and symptoms of Gaucher disease are related to the accumulation of Gaucher cells in the body. The main sites for storage are the liver, spleen and bone marrow. Storage however can also occur in the nervous system, lungs and heart.
There are currently thought to be 3 main types of Gaucher disease:

- **Type 1** – this is the most common form and is not thought to include the nervous system. The progression of the disease is variable – from very mild to severe (non-neuronopathic).
- **Type 2** – this is the most severe, although rarer form of the disease often resulting in early death before the age of 2. There are considerable neurological and systemic complications (acute neuronopathic).
- **Type 3** – this form of the disease includes systemic and neurological complications although less severe than type 2. It presents in childhood and is moderate to severe (chronic neuronopathic).

In more recent years Gaucher disease has been considered to be a continuum from mild disease through to severe neuronopathic disease.

Most people with Gaucher disease do not develop all of the possible symptoms. In addition, the severity of the disease varies enormously. Some of the symptoms are listed below:

**Liver**

<table>
<thead>
<tr>
<th>Hepatomegaly – large liver</th>
<th>Enlarged abdomen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis – scarred liver</td>
<td>Abnormal liver tests, jaundice &amp; other signs of liver disease</td>
</tr>
<tr>
<td>Predisposition to gall stones</td>
<td>Often no symptoms – sometimes abdominal pain</td>
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</tbody>
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**Spleen**

<table>
<thead>
<tr>
<th>Splenomegaly – large spleen</th>
<th>Enlarged abdomen</th>
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<tbody>
<tr>
<td>Anaemia – low haemoglobin (red blood cells)</td>
<td>Fatigue, reduced energy &amp; stamina</td>
</tr>
<tr>
<td>Thrombocytopenia – low platelet count</td>
<td>Frequent/ heavy nosebleeds, bleeding gums, easy bruising.</td>
</tr>
<tr>
<td>Neutropaenia – low white cell count</td>
<td>Increased risk of infections</td>
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</tbody>
</table>
Splenectomy – surgical removal of the spleen | Need life long prophylactic antibiotics & regular immunisations

Bones

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<tr>
<th>Bone crisis</th>
<th>Bone pain – sometimes described as a “heart attack” of the bone (usually acute – sudden)</th>
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<tbody>
<tr>
<td>AVN – avascular necrosis – areas of dead bone</td>
<td>Bone pain (often chronic – long term), possible need for joint replacement surgery, reduced mobility</td>
</tr>
<tr>
<td>Osteopenia – weak bones</td>
<td>Risk of fractures</td>
</tr>
<tr>
<td>Radiological changes – abnormal bone visible on Xray</td>
<td>May or may not produce pain</td>
</tr>
<tr>
<td>Delayed growth</td>
<td>In children</td>
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</tbody>
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Neurological

Neurological symptoms are usually associated with type 3 gaucher disease.

| Neurological | Hearing loss, eye movement problems, poor co-ordination, poor mobility, seizures & tremor |

Treatment

There are currently two licensed treatments available for Gaucher disease in the UK - ERT (enzyme replacement therapy) and SRT (substrate reduction therapy). To receive either of these in England you are required to attend one of the National Centres.
Enzyme replacement therapy (ERT)

Enzyme replacement therapy is the direct replacement of the missing enzyme. Genzyme corporation developed Cerezyme, an intravenous infusion that is usually given once per fortnight, long term. Initially this needs to be administered in hospital but treatment can subsequently be managed at home. The UK is supported by homecare companies who can co-ordinate drug supply and delivery, education and support for patients to self-cannulate and infuse, and a long term home infusion service where necessary.

Side effects are infrequent, but include:

- Infusion reactions – pruruits (itching), burning, swelling & abcess.
- Hypersensitivity reactions – pruritis, flushing, urticaria (rash), angiodoema (swelling around the face/eyes), chest discomfort, breathing difficulties and hypotension (low blood pressure). NB anaphylaxis has been reported in a few cases.
- Additional reactions – nausea, abdominal pain, diarrhoea, rash, fatigue, headache, fever, dizziness, chills, backache and tachycardia (fast heart rate).

This treatment is considered to be an “orphan drug” and as such prescribing in the England is restricted to NCG centres. In Scotland, Wales and Northern Ireland, permission has to be sought from the devolved NHS authorities in each region.

Substrate reduction therapy (SRT)

Substrate reduction therapy is an oral preparation thought to slow the production of
glycosphingolipids (the precursors to glucocerebroside – the substance that builds up in gaucher disease). The drug is called Zavesca (miglustat) and is marketed by Actelion. It currently has a licence for the treatment of mild to moderate Gaucher disease in patients for whom ERT is deemed unsuitable. Zavesca may be prescribed by your specialist centre if it is appropriate and the same homecare companies used to deliver ERT will also supply SRT.

Like all medicines, Zavesca can have side effects, including:

- most common - diarrhoea, flatulence (wind), nausea, dizziness, weight loss, tremor and headache. The diarrhoea can usually be controlled by dietary management and you should discuss this with your physician before starting this treatment.
- other more rarely reported – peripheral neuropathy (tingling/numbness in hands/feet) and memory impairment.

If you have any questions/concerns about the information you have read here please discuss them with your Doctor.