What is Hereditary Haemochromatosis?

Hereditary Haemochromatosis (HH) is a common inherited disorder where the body absorbs too much iron from the diet. The iron is then deposited in, and can ultimately damage, organs such as the liver, heart and pancreas. When a person has too much iron in their body they are said to have 'iron overload'.

The treatment of HH involves the removal of some blood at regular intervals and is called therapeutic phlebotomy; it uses the same procedure as that of a normal blood donation. When this is done the body's response is to make extra blood, using up some of the stored iron.

Early diagnosis and treatment of HH prevents complications and results in a normal life expectancy.

Ireland has the highest levels of this condition in the world. Research has shown that approximately 1 in 83 people are predisposed to develop HH.

Why do our bodies need iron?

Iron, in small amounts, is essential for the production of red blood cells which carry oxygen around the body. Our bodies have no method of getting rid of excess iron, so levels are controlled by not absorbing more iron than is needed. A person with HH absorbs a great deal more iron than is necessary.

The Signs and Symptoms

No two people are alike and symptoms will vary from person to person. Generally symptoms appear when iron levels increase but some people can have high levels of iron with no symptoms. Symptoms tend to occur after the age of 40, but may be earlier or later.

The most common symptoms include:
» Fatigue, general weakness and lethargy
» Joint pain. Knuckle and first joint of the first two fingers are commonly affected
» Abdominal (tummy) pain
» Sexual dysfunction / Loss of libido
» Discoloration or bronzing of skin
» Mood swings and irritability

Symptoms of higher levels of iron in certain organs:
» Liver: Pain in liver, enlarged liver, fatigue, jaundice (yellowness of skin)
» Heart: Irregular heartbeat, shortness of breath, swollen ankles
» Pancreas: iron overload causes diabetes resulting in thirst, increased need to urinate

Most individuals who have HH will develop at least one or two of the above symptoms.

There are a number of other reasons apart from HH that can lead to increased iron levels. These include hepatitis B, hepatitis C, excessive alcohol consumption and fatty liver disease.
Tests Involved: Iron Studies

This consists of a simple blood test to check your iron levels. It is ideally taken after an overnight fast. Both 'serum ferritin' and 'transferrin saturation' are measured.

Serum Ferritin (SF)
This is an iron storage protein. A raised result may be due to iron overload but there are other causes (such as when you are ill) that can give a high result. Therefore, the result is interpreted in combination with transferrin saturation.

A SF of > 200 µg/L in women and > 300 µg/L in men suggests iron overload. If your SF is >1000 µg/L then you will be referred onto a specialist to check your liver for damage. They may perform a liver biopsy test or fibroscan.

Transferrin Saturation
This is a protein that carries iron from the gut around the body. A transferrin saturation result above >45% is strongly suggestive of HH and should prompt a genetic test.

Diagnosis and the Tests Involved

Your GP will perform the necessary tests for diagnosing Hereditary Haemochromatosis.

Who should be tested for HH?

» If you have the above mentioned symptoms
» If you have family members with HH. If your brother, sister, child, parent or grandparent has HH then you are at increased risk of having the same condition.
» If a relative died from liver disease (but did not have Hepatitis B/C and did not drink alcohol), liver cancer at a young age (under 60 years old), heart failure where the cause of heart failure was not known, ‘bronze diabetes’ (pigmented skin and diabetes).

Your GP can order blood tests to check your iron levels. If there is a reason to suspect HH you can be tested for the genes by another blood test.

Tests Involved: Genetic Testing

Genetic testing is only performed when you have raised Transferrin Saturation. It will test for the C282Y mutation, and in some labs, will also test for the H63D mutation. Testing of patients under the age of 18 is not recommended as it is an adult onset disease. The procedure involves a blood test.

The Genetics of HH

Each person has about 20,000 - 25,000 genes. Genes control different characteristics such as eye colour and height. HH is caused by defects (mutations) in a gene called the HFE gene. HFE has many purposes, but one important role is that it helps to control the amount of iron that is absorbed from food. There are several known mutations in the HFE gene. The C282Y mutation is known to cause HH. It is still debated whether other HFE mutations, such as H63D, causes HH and there is still no established consensus.

Everyone inherits two copies of HFE, one from their father and one from their mother.

» When a person has one mutated copy, he or she is called a carrier or heterozygote
» When a person has two of the same mutated copies, he or she is called a homozygote e.g. C282Y homozygote
» When a person has two different – but mutated – copies, he or she is called a compound heterozygote e.g. C282Y/H63D compound heterozygote.

HH is a recessive disease, this means that it only develops if you receive two mutated copies of the gene, one from your mother and one from your father.
Inheritance of Haemochromatosis

Genetics can be very difficult to understand at first. What is most important is that you know which gene combination causes the greatest known risk of loading iron. See the table below for information.

<table>
<thead>
<tr>
<th>Genotype (Prevalence in Population)</th>
<th>Interpretation of result and risk of developing Iron Overload</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Homozygous C282Y (C282Y/C282Y)</strong> (1 in 83)</td>
<td>Diagnosis of Hereditary Haemochromatosis is made in the presence of iron overload. Are at risk of developing HH (i.e. not everyone with this genotype will develop HH), therefore are at risk of developing significant iron overload.</td>
</tr>
<tr>
<td><strong>Compound Heterozygous C282Y/H63D</strong> (1 in 60)</td>
<td>Excludes the diagnosis of the most common form of Hereditary Haemochromatosis. May be at-risk of developing mild to moderate iron overload in association with other factors (e.g. alcohol consumption) and may be considered for treatment via phlebotomy.</td>
</tr>
<tr>
<td><strong>Heterozygous C282Y</strong> (1 in 5)</td>
<td>At no increased risk of developing Hereditary Haemochromatosis associated iron overload. Is a carrier of Hereditary Haemochromatosis. If iron overloaded, other causes of iron overload should be considered.</td>
</tr>
<tr>
<td><strong>Heterozygous H63D</strong></td>
<td>At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.</td>
</tr>
<tr>
<td><strong>Homozygous H63D</strong></td>
<td>At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.</td>
</tr>
<tr>
<td><strong>Normal Genotype</strong></td>
<td>At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.</td>
</tr>
</tbody>
</table>

### Inheritance of Haemochromatosis

Each person has 2 copies of the HFE gene, one copy inherited from their mother and one from their father. Each copy will either be normal (n) or have the C282Y mutation (H). Therefore each person has 3 possible combinations for their HFE gene. The examples shown are averages for the whole population. However, in any particular family where both parents are carriers, it is possible for all children to be affected, all to be carriers, or all to be normal.
Management

Treatement

Treatment of HH aims to restore iron levels to a safe level. Having safe iron levels reduces the symptoms of iron overload and can help avoid complications.

Therapeutic phlebotomy, or removal of approximately 500ml of blood via a needle into the arm (same method as blood donation) is the main treatment for HH.

Phlebotomy treatment should begin when your Serum Ferritin is above the normal range (this is typically >200 µg/L in pre-menopausal women and >300 µg/L in men and post-menopausal women.)

A standard 500ml phlebotomy removes 0.25 gram of iron from the body.

Four phlebotomies remove approximately 1 gram of iron. The amount of phlebotomies you need is dependent on the amount of iron stored (ferritin) in your body.

E.g. A person with moderate iron overload may have between 4-10 grams of excess iron which will take between 16 – 40 phlebotomies to reduce to normal iron levels.

Treatment Involves Two Stages

1) Iron Unloading Stage: This involves weekly phlebotomies until your stored iron levels are in the normal range. The aim is to have your ‘Serum Ferritin’ around 50-100 µg/L. It may take many months or even years to unload excess iron.

2) Life-long Maintenance Phase: You need to maintain your Serum Ferritin at 50-100 µg/L. Therefore, your iron levels will need to be monitored usually every 3 months, at least every 12 months. You may require 3-4 phlebotomies per year to ensure your iron levels are at a safe level to keep you healthy.

Treatment for HH is ongoing for life. It is important you go for regular check-ups with your GP.

Where to get Treatment

Your GP will explain where you can get therapeutic phlebotomy in your area. It can be performed by your GP or you may be referred onto another clinic to get the procedure done. Most clinics are currently based in the hospital but there are aims to move these to the community in the future.

The Irish Blood Transfusion Service (IBTS) has a therapeutic phlebotomy programme for individuals with HH and you can be referred onto the IBTS if you meet their referral criteria. This includes having your Serum Ferritin < 600 µg/L. The service is currently available in Dublin and Cork and it is hoped to expand this service nationally. Please see https://www.giveblood.ie/ for more details.

It is important that when you attend the IBTS for phlebotomy you answer the questions honestly in order to ensure your safety and the safety of patients who may receive your blood.

Hereditary Haemochromatosis is not a blood disease. The blood can be safely used by the Irish Blood Transfusion Service providing you have no other contraindications to being a blood donor and you meet the referral criteria.

Other Tests

If your SF is elevated, you may have other tests including fasting blood glucose, HbA1c and liver tests (ALT and AST). Other tests will be ordered according to your symptoms. These tests will be explained to you by your health care provider.
Staying Healthy During Treatment

During treatment, the number of red blood cells in your blood will also be checked. This is measured by Haemoglobin (Hb). You need to have a normal Hb before phlebotomy. Having a low Hb is called anaemia.

The frequency of your phlebotomy treatments may need to be slowed down if:
- Your Hb is too low because your body hasn’t replaced your red blood cells just yet
- Your SF is too low because you are no longer overloaded
- Your blood pressure is too low.

Phlebotomy treatment will allow iron to be removed and iron stores will return to normal. However, it will not cure any clinical condition such as diabetes already present at the time treatment is started. Therefore, early diagnosis and treatment is vital.

What if I have the genetic mutations but do not have iron overload?

C282Y homozygotes and C282Y/H63D compound heterozygotes should arrange with your GP to monitor your iron levels every 12 months. You need to take no other action if they remain in the normal range.

Family Screening

If you have been diagnosed with HH it is very important that your siblings and offspring are screened for the condition. Your parents may need to be screened following an assessment by the GP on their age, sex and ferritin. If you are worried about your children, it is useful to perform genetic testing on your spouse to predict whether the children will need to be considered for genetic testing.

Diet and Lifestyle

You should eat a balanced, nutritious diet. Avoidance of dietary iron (such as red meat) has little benefit as considerably more iron can be removed in a single phlebotomy and could compromise your intake of other important nutrients. The following is advised:

- Any alcohol consumed can increase liver problems and increase iron absorption. Limit your alcohol intake to safe drinking levels. Low risk weekly alcohol guidelines for adults are:
  - up to 11 standard drinks spread over one week for women, and
  - up to 17 standard drinks spread over one week for men.

The standard drink in Ireland is 10 grams of pure alcohol which is equivalent to a pub measure of spirits (35.5ml), 100 ml of wine (12.5% volume) or a half pint of normal beer. Please note, it has been advised that the Irish Government lower these limits following reduction of UK limits in 2016. Please check www.drinkaware.ie for up-to-date guidelines.

If your liver is damaged you should avoid alcohol.

- Eat a well-balanced diet and drink plenty of water.
- Avoid iron supplements (including multivitamins and medication containing iron).
- There is no need for a patients undergoing phlebotomy to start a low-iron diet as the amount of iron removed by phlebotomy is far greater than that present in even a high-iron diet. If you do not regularly attend your appointments, restricting consumption of organ meats (such as liver) may be warranted, as these are quite high in iron
- If you are iron overloaded you should avoid raw shellfish because of the risk of vibrio vulnificus (bacterial food poisoning)
- If you are having lots of phlebotomies extra vitamin B12 and folate, either in your diet or taken as a supplement, can be very helpful. Oral supplements for vitamin B12 (5 µg daily) and folate (500 µg daily) can be taken.
- Vitamin C can increase absorption of dietary iron at meal times so should be avoided around meal times.
- HH cannot be treated by diet.

It is thought that the haemochromatosis gene originated around 40,000 years ago in Ireland in response to famine. It was spread by Vikings 'visiting' other countries.
Tips Before and After Your Phlebotomy

Phlebotomy can be hard on the body especially when you have them at high frequency. You may feel tired after treatment. It is important to look after yourself during treatment.

Before your phlebotomy, it is advised you have a balanced, nutritious meal and drink plenty of water. Drinking water helps in better flow of blood during the procedure. You should continue to drink extra fluids for 24 hours after your phlebotomy.

The procedure may be uncomfortable, but it is a simple and safe procedure which is very important for your health.

The procedure itself takes about 5-10 minutes. You will need to rest immediately after treatment for at least 15 minutes. You should avoid heavy physical activity for 24 hours after the phlebotomy.

Useful Information

This leaflet was produced following development of the Model of Care for Hereditary Haemochromatosis and Model of Care for Therapeutic Phlebotomy. Please see the HSE A-Z webpage for more details:
https://www.hse.ie/eng/health/az/H/Haemochromatosis/

For more information about HH please visit the following:

Irish Haemochromatosis Association
http://www.haemochromatosis-ir.com/

The UK Haemochromatosis Society
http://haemochromatosis.org.uk/support/handbook/

Haemochromatosis Australia
http://haemochromatosis.org.au/