Haemophilia A and B

Key facts

- Haemophilia is a rare inherited condition that affects the body's ability to form blood clots. People affected by the condition therefore have an increased tendency to bleed.
- Haemophilia is an X-linked condition, so the majority of affected individuals are male.
- There are two types of haemophilia: haemophilia A and haemophilia B.
- Haemophilia is caused by low or absent levels of a blood clotting factor: haemophilia A is due to low levels of clotting factor VIII (FVIII), and haemophilia B is due to low levels of factor IX (FIX). As these two factors form a single functional complex, the clinical features are the same for both.

Clinical features

- Haemophilia is classified into mild, moderate or severe types depending on the blood levels of the clotting factors, FVIII or FIX. In the normal population, these levels are between 50% and 150%, but are much lower in individuals with haemophilia, ranging from 6-40% in mild cases, 1-5% in moderate cases and less than 1% in severe cases.
- The different types present with the following features:
  - » Mild: bleeding occurs only following an injury, surgery or dental extraction.
  - » Moderate: bleeding into joints and muscles may occur with minor injury or sometimes spontaneously (i.e. no obvious cause for the bleeding).
  - » Severe: spontaneous bleeding into joints and muscles.
- Individuals with mild haemophilia may not be diagnosed until adulthood.
- Individuals with severe haemophilia most commonly develop bruising and/or bleeding, leading to a diagnosis by 12 to 18 months of age.
- Bleeding into a joint leads to redness, pain and swelling. The joint may feel hot to touch and will be painful to move, with a reduced range of movement. Joint bleeds tend to occur in the larger joints, in particular the ankles and knees.

Diagnosis

- Haemophilia may be suspected in a male with a history of increased bruising or bleeding, or due to a known family history of haemophilia.
- In males with a history of bleeding, a blood test called the 'clotting screen' is often performed first. If this shows an abnormally long result, it will then be investigated further.
- The definitive diagnosis of haemophilia A or B is made by testing the blood clotting factor levels of FVIII or FIX, and confirming that these are low. This may be done straight away in families known to have haemophilia.
- A genetic test to examine the genes for FVIII or FIX will then be offered to confirm the diagnosis.

Genetic basis

- Haemophilia is an X-linked recessive condition. The genes for FVIII and FIX are found on the X chromosome, and variants in these genes can cause haemophilia.
- Females have two copies of the X chromosome and males have only one. This means that if a boy is born with a variant that results in haemophilia in his only copy of the FVIII or FIX gene, he will be affected by haemophilia; if a girl is born with the same variant in one of her copies of the FVIII or FIX genes, she will be a carrier for the condition, as she also has one normal unaffected copy of the gene.
- Carriers for haemophilia may have normal clotting factor levels, but some carriers do have lower than normal levels, and may have an increased risk of bruising and minor bleeding (such as heavy menstrual bleeding).
- Boys born to a haemophilia carrier have a 50% (one-in-two) chance of being affected by haemophilia; girls born to a haemophilia carrier have a 50% (one-in-two) chance of being a carrier for haemophilia.
- A father always passes his X chromosome to his female children, so any girls born to a man affected by haemophilia will always be carriers of haemophilia. However, fathers do not pass on their X chromosome to their male children, so any boys born to a man with haemophilia will not have haemophilia.
- Haemophilia runs 'true' in families, which means that the haemophilia is always of the same severity within one family.

Genetic testing

- Genetic testing is used to confirm the diagnosis of haemophilia in all affected individuals.
- It can also be used to test family members so that the carrier status of female relatives, who may have no personal history of bleeding, can be determined. This is particularly important in family planning for carrier women and their partners.
- Results from genetic testing can be used to offer prenatal diagnosis or pre-implantation genetic diagnosis for women wishing to manage their pregnancy.
- Patients with haemophilia A and B are at risk of developing antibodies to the factor concentrate therapy. This is more common with severe haemophilia, and is more common with haemophilia A than haemophilia B. These antibodies are called 'inhibitors', and treatments are available to try to eradicate these antibodies. Inhibitor risk is known to be linked to various gene variants in both haemophilia A and B. Genetic testing can help to predict which individuals are more likely to develop an inhibitor, and can help influence treatment choice.

Clinical management

- People with haemophilia, and carriers with low clotting factor levels, will be looked after at a specialist haemophilia centre.
- Carriers with normal factor levels will be registered with a haemophilia centre but may not be seen regularly, except during pregnancy and for delivery.
- Treatment for haemophilia depends on the clotting factor level in an individual and their history of bleeding.
- People with severe haemophilia take regular treatment (prophylaxis) to prevent bleeding. The most common treatment involves injection of the missing clotting factor into the vein using a clotting factor concentrate. This form of treatment is given frequently (for example, between once daily to once a week) with the aim to prevent joint and muscle bleeds.

- People with less severe disease will be treated only if a bleed happens, or prior to surgery or dental treatment to prevent bleeding.
- Recently, a newer therapy has become available for severe haemophilia A that can be given under the skin once a week or once a fortnight.
- Gene therapy treatments are also in clinical trial.
- Treatments for minor bleeding include tranexamic acid (a drug that helps to stabilise clot formation) that can be taken orally. For people with mild haemophilia A (but not B), desmopressin is a medication that can be used to elevate FVIII levels. It is given by injection or intra-nasally.

Direction to further reading, guidelines and patient groups

- Information for doctors: http://www.ukhcdo.org/
- Information for patients: https://haemophilia.org.uk/ and https://www.wfh.org/

This information is intended for educational use and was current in March 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and the Genetics Working Party of the UK Haemophilia Centres Doctors Organisation.