Haemophilia A

Key facts

- Haemophilia is an X-linked recessive bleeding disorder caused by partial or complete deficiency of blood clotting factors.
- The most common type is haemophilia A, which is caused by Factor VIII deficiency. Haemophilia A occurs in 1 in 5,000 male births. Haemophilia can result in prolonged bleeding and bruising after minor injury. Individuals with severe haemophilia may experience spontaneous bleeding in joints and muscles.
- All patients with haemophilia should be managed at a specialist haemophilia centre.

Clinical features

- The symptoms of haemophilia can be divided in to mild, moderate and severe.
- Boys with severe haemophilia usually present early in infancy. Individuals with mild to moderate haemophilia may not present until adulthood.
    - **Mild:** excessive bleeding after surgery, dental extractions and accidents
    - **Moderate:** bleeding into joints and muscle after minor injury
    - **Severe:** spontaneous bleeding into joints and muscles
- Bleeding into a joint can cause tightness and joint pain. The joint may be hot and swollen and difficult to move. Recurrent bleeding into joints without treatment can lead to long standing joint problems. Minor bumps to the head can lead to bleeding in the brain, which may have serious complications.

Diagnosis

- Haemophilia may be suspected in a male with a history of easy bruising or bleeding, or because of a family history of haemophilia. The diagnosis will usually be made in liaison with a haematologist.
- Abnormalities can be detected on a routine blood clotting screen that may prompt further investigations. The diagnosis can be confirmed by measuring the levels of clotting factor in the blood. Individuals with haemophilia A will have reduced levels of clotting Factor VIII. The levels of clotting factor correspond to the severity and age of onset of the disease.
- As the gene responsible for haemophilia A is known, molecular genetic testing can be used to identify the alteration in a family if appropriate.

Genetic basis

- Haemophilia is an X-linked recessive condition. This means that the gene alteration causing haemophilia is located on the X chromosome. Females have two copies of the X chromosome and males have one X chromosome and one Y chromosome.
- If a male has an altered haemophilia gene on his X chromosome, then he will be affected with haemophilia. If a woman has an altered haemophilia gene on only one of her X chromosomes, then she is said to be a carrier. Some girls who are carriers of haemophilia may have slightly reduced factor levels, which predispose to minor bleeding.
- If a female carrier of haemophilia has a son, there is a 1-in-2 (50%) chance that he will have haemophilia.

- If a female carrier has a daughter, there is a 1-in-2 (50%) chance that she will be a carrier for haemophilia.
- When men affected by haemophilia have children, all of their daughters will inherit the altered gene on the X chromosome and will be obligate carriers of the condition. Men do not pass on their X chromosome to their sons, therefore, their sons will be unaffected.

Clinical management

- Individuals with haemophilia should be managed at a specialist haemophilia centre.
- The main aim of treatment is to try to prevent bleeding, pain and joint damage. This is achieved by replacing the missing clotting factor. Clotting factor concentrate is given by intravenous infusion. Patients with more severe haemophilia may benefit from home infusions.
- Prevention of chronic joint disease is important and studies are underway to examine the long-term effects on joint outcome of prophylactic clotting factor. Most individuals with severe haemophilia A will be given prophylaxis in the first few years of life before the onset of joint damage. Even when started in later childhood or in adults, bleeding episodes are significantly reduced. 'Secondary' prophylaxis given after joint damage has occurred can also be given on a long-term basis or before surgical procedures or episodes of prolonged activity.
- In the UK all patients with haemophilia will receive artificial factor concentrates that are free from human plasma and therefore do not carry a risk of passing on blood-borne infections.
- Pregnant women who are carriers for haemophilia should be managed jointly by an obstetrician with expertise in fetal-maternal medicine and a haematologist.

Genetic testing

Genetic testing can be used to:

- Confirm the diagnosis of haemophilia.
- Provide information about the genetic status of female relatives of someone with haemophilia through carrier testing. This is particularly helpful as measuring clotting factors is not always reliable in identifying female carriers.
- Offer prenatal and pre-implantation genetic diagnosis, particularly for pregnancies at risk of severe haemophilia. Prenatal diagnosis is usually possible by chorionic villus sampling (CVS) or amniocentesis. If a couple are considering prenatal diagnosis, referral should be made to the local clinical genetics service prior to a pregnancy. This ensures that appropriate advice and investigations are undertaken and confirms whether or not prenatal diagnosis is possible. All couples considering pre-implantation genetic diagnosis must be referred to their local clinical genetics service. Fetal sex determination by non-invasive prenatal diagnosis is now available, potentially reducing the need for invasive procedures by 50%. It should be discussed with families, but needs to be facilitated by clinical genetics departments or fetal medicine units.
- Test at-risk males at birth on a cord blood sample. This is useful in guiding further management.
- It is also known that a proportion of patients with haemophilia will produce antibodies (inhibitors) to the administered clotting factor, which can reduce their response to treatment. Information about the type of genetic alteration (mutation) can sometimes provide information about whether inhibitors are likely to be produced.

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.