Haemophilia A (Factor VIII Deficiency)

Description

- This is a bleeding disorder caused by deficiency of clotting factor VIII.
- The vast majority of cases are inherited but acquired forms do exist, largely in older patients, due to autoantibodies directed against factor VIII or haematological malignancy.
- Severity of disease depends upon levels of remaining factor activity, with normal range expressed as 50-200% (refer to local laboratory for reference range):

<table>
<thead>
<tr>
<th>Severity</th>
<th>Factor VIII activity level</th>
<th>Age of presentation</th>
<th>Percentage of sufferers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe disease</td>
<td>&lt;1%</td>
<td>Infancy</td>
<td>43-70%</td>
</tr>
<tr>
<td>Moderate disease</td>
<td>1-5%</td>
<td>Before 2 years</td>
<td>15-26%</td>
</tr>
<tr>
<td>Mild disease</td>
<td>&gt;5%</td>
<td>Older than 2 years</td>
<td>15-31%</td>
</tr>
</tbody>
</table>

The totals in the various categories do not equal 100%, as there is interpopulation variability due to the heterogeneity of factor VIII gene mutations and inter-laboratory variation in factor VIII activity measurement.

Aetiology

- Haemophilia A results from heterogeneous mutations in the factor VIII gene that map to Xq28.
- Carrier detection and prenatal diagnosis can be carried out by testing against the range of known mutations or indirectly by linkage analysis.
- There is marked phenotypical variability leading to a spectrum of severity as outlined above.
- Inheritance is usually X-linked recessive, affecting males born to carrier mothers.
- There is usually a clear family history but sporadic cases do occur due to novel mutations or effects of mosaicism.
- Females born to affected fathers can (rarely) have the disease due to homozygosity for the gene, where there is marriage to close relatives.
- There is a reported case of a son inheriting the gene from his father, due to uniparental disomy for the X chromosome.

Epidemiology

- It affects 1:4,000 to 1:5,000 live male births worldwide.
- It is five times as common as haemophilia B (factor IX deficiency).
- Acquired haemophilia has an incidence of 1.34 cases per million population per year, so is significantly rarer.

Presentation

Severe disease

- Neonatal bleeding in around a third to a half of cases. This may follow circumcision or other operative procedures. Neonatal intracranial haemorrhage can be a presenting feature of severe cases in about 3-4%, as can haematoma and prolonged bleeding from the cord or umbilical area.
- Intracranial haemorrhage occurs in approximately 5% of all untreated, severe cases and requires immediate intervention.
- History of spontaneous bleeding into joints, especially the knees, ankles and elbows, without a history of significant trauma. Spontaneous haemarthroses are virtually pathognomonic.
- Intramuscular haemorrhage may also occur.
- Gastrointestinal and mucosal haemorrhage do occur but are more often associated with haemophilia B/von Willebrand's disease.
- Haematuria may be a feature, which can vary from self-limiting minor episodes to gross haematuria.

Untreated cases of severe disease

This group of patients may develop the following:

- Arthropathy and joint deformity - may require replacement of affected joints.
- Soft tissue haemorrhages - common; may cause complications, including compartment syndrome and neurological damage.
- Extensive retroperitoneal bleeds - with haemodynamic compromise.
Haematoma formation - spontaneously or following trauma and may require fasciotomy.

Moderate disease
- Often presents with bleeding following venepuncture.

Mild disease
- Only bleed after major trauma or surgery, with moderate disease after minor trauma or surgery.

Differential diagnosis
- Haemophilia B (factor IX deficiency).
- Von Willebrand's disease.
- Vitamin K deficiency/antagonism with anticoagulants.
- Haemophilia C (factor XI deficiency).
- Disorders of fibrinogen or fibrinolytic production.
- Platelet disorders.
- Blood vessel disorders.

Investigations
- FBC - low haematocrit and reduced Hb if recent bleeding.
- Prothrombin time, bleeding time, fibrinogen levels and von Willebrand factor - are normal.
- Activated partial thromboplastin time (APTT) - usually prolonged but can be normal in mild disease. Mixing patient's plasma 1:1 with donor plasma should normalise APTT.
- Factor VIII:C - is reduced, and percentage activity represents severity of disease (see above).

In acute situations imaging may be required - eg, CT scan of the head and body may be used to detect haemorrhage. Joint X-rays may show little in the acute situation but there can be signs of degenerative joint disease due to previous damage. MRI and Doppler ultrasound may be better modalities for the detection of arthropathy.\[13\]

Management
Recent guidelines divide the management into prophylaxis and treatment of acute bleeding.\[14\] The following information is based on these.

Prophylaxis\[14\]
- Children with severe haemophilia should receive prophylactic infusions (once-weekly or more frequently, ideally three times a week if venous access allows) of factor VIII to prevent haemarthroses and other bleeding episodes.
- This should begin before the occurrence of a second joint bleed or significant soft tissue bleed (associated with possible reduced risk of development of haemarthrosis in later life).
- Doses should be tailored to the individual - eg, just before physical education lessons.
- Prophylaxis should be encouraged to continue until physical maturity is achieved.
- If after stopping prophylaxis further spontaneous haemorrhage occurs then prophylaxis should be reinstated. This can then be reviewed again at a later date.
- Some patients will need to have long-term prophylaxis - eg, intracranial haemorrhage with no other cause.

Acute bleeding episodes\[14\]
For acute bleeding episodes haemostasis should be aided by physical methods and transfer to hospital arranged.
- Patients who are able should administer their normal factor VIII, as advised by their haemophilia service, until they attend hospital.
- Fresh frozen plasma containing factor VIII, monoclonal-antibody purified factor VIII and recombinant factor VIII are the available sources of factor VIII used to treat acute haemorrhage, with recombinant factor VIII preferred. Fresh frozen plasma and cryoprecipitate should only be used in an emergency when the concentrates are not available because they may cause the development of antibodies to the deficient protein (an inhibitor) which greatly complicates future therapy.
- The aim is to correct factor VIII activity to 100% for severe haemorrhage (central nervous, gastrointestinal and genitourinary systems, retroperitoneal, trauma and severe epistaxis) and to 30-50% for minor haemorrhage (haemarthrosis, oral mucosal and muscular).
- Enhanced factor VIII levels are maintained for 7-10 days for severe bleeds and for 1-3 days for minor bleeds.
- Desmopressin (DDAVP®) and antifibrinolytic agents (aminocaproic acid) may be used to boost factor VIII activity and reduce factor VIII administration requirements.
- The prophylaxis regimen should be reviewed after resolution of the acute episode.

Scheduled surgical procedures
- Aim for 50-100% factor activity for 2-7 days after surgery.
- In brain or prostate surgery, nearer 100% is required.
- Desmopressin may help increase factor levels.
Prophylaxis is usually given for those with severe disease, as intermittent recombinant factor VIII injections or continuous infusion.\[^{[16]}\] Infants usually receive prophylaxis from the age of 2 years. However, if bleeding risk is high, prophylaxis at an earlier age should be considered.\[^{[16]}\]
There is strong evidence that prophylactic treatment can preserve joint function in children with haemophilia compared to on-demand treatment. However, further studies are required to confirm that prophylaxis decreases bleeding in patients with existing joint disease.\[^{[17]}\]

**Pregnancy**\[^{[18]}\]
- The management of a pregnant women known to be a haemophilia carrier should be undertaken by an obstetric team experienced in managing this condition, in conjunction with a haemophilia centre.
- Fetal sexing should be undertaken either by maternal blood sampling at around 10 weeks of gestation or by ultrasound scan at between 18-20 weeks. Third-trimester amniocentesis may be considered where confirmation of an affected male fetus will influence management at delivery.
- Mode of delivery should be informed by both obstetric and haemostatic factors; haemophilia carrier status itself is not a contra-indication to vaginal delivery.
- Invasive monitoring procedures such as placement of intrapartum scalp electrodes and fetal scalp blood sampling should be avoided.
- The diagnosis of haemophilia should be established using uncontaminated cord blood as soon as possible following delivery.
- Recombinant factor VIII should be given as soon as the diagnosis is confirmed.

**Monitoring**\[^{[14]}\]
- During the prophylaxis phases clinical and laboratory markers should be used for monitoring.
- The Haemophilia Joint Health Score should also be used in regular assessments.\[^{[19]}\]
- Adherence should regularly be determined and noted.
- Factor VIII levels should be routinely measured (trough level >1 IU/dL is used but is not always necessary in stable patients).
- Inhibitor levels should be checked at regular intervals according to the recommendations of the British Committee for Standards in Haematology (BCSH).\[^{[13]}\]
- Radiological surveillance of joints is not needed unless there is a specific indication.

**Complications**
- Degenerative joint disease due to recurrent haemarthrosis.
- Antibody inhibitor formation affects about 25–30%, reducing efficacy of therapy.\[^{[20]}\]
- Life-threatening haemorrhage.
- The use of plasma-derived factor VIII, before the availability of recombinant products, led to infection with HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) in many haemophiliacs.\[^{[21, 22]}\]
- One case of likely transmission of variant Creutzfeldt-Jakob disease (vCJD) by UK factor VIII concentrates has been reported in an elderly haemophiliac patient in the UK. The recent report of a blood test that may be used to detect vCJD has raised the possibility of a new way to identify infected individuals, perhaps even before the onset of clinical symptoms.\[^{[23]}\]
- Immune toleration induction (ITI) is recommended for patients with severe haemophilia A and a persistent inhibitor that interferes with prophylaxis or treatment of bleeds at standard doses of factor VIII inhibitor. ITI involves giving small amounts of factor concentrate irregularly over a period of time until inhibitor antibodies are no longer produced.\[^{[13]}\]
- Bleeds due to a failure to respond to factor VIII should be treated using either prothrombin complex concentrates or recombinant factor VIIa. In mild-to-moderate haemophilia, a trial of immunosuppression should be given.\[^{[13]}\]

**Prognosis**
This is much improved with modern recombinant factor VIII and approaches near-normal life expectancy. No clinical trials for gene therapy in haemophilia A are currently in progress although several improved approaches are in pre-clinical testing.\[^{[1]}\] Those infected with HIV or other blood-borne viruses carry a worse prognosis due to the effects of those diseases.

Patients should avoid competitive contact sports which will increase the risk of haemarthroses and head injuries. However, they should be encouraged to take part in other sports - eg, racquet sports, athletics or swimming.\[^{[14]}\]

**Prevention**
- Genetic screening for carrier mothers and affected families.
- Patient education helps to prevent morbidity and mortality associated with acute bleeds.
- Medical emergency identification bracelets or similar can help to identify sufferers rapidly in case of haemorrhage/trauma, etc.

**Further reading & references**
- Konkle BA, Josephson NC, Nakaya Fletcher S; Hemophilia A.
5. Hemophilia A, HEM; Online Mendelian Inheritance in Man (OMIM)
14. Valenti LA, Cooper DL, Goldstein B; Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. Haemophilia. 2011 Jul;17(4):579-89.