Haemophilia B (Factor IX Deficiency)

Synonym: Christmas disease

Introduction

Haemophilia B is due to a deficiency of clotting factor IX (haemophilia A is due to a deficiency of clotting factor VIII). They are both X-linked recessive conditions. By and large, haemophilia B tends to be similar to haemophilia A but less severe.

The gene locus is Xq27.1-q27.2. As is usual in such conditions, deficiency is not absolute but the lower the level of factor IX, the more serious will be the disease.[1]

There is a variation called Leyden in which factor IX levels are below 1% until puberty when they rise, possibly reaching as high as 40-60% of normal.[2] This is thought to be due to the effects of testosterone at maturity.

Epidemiology

Haemophilia B has a prevalence of around 1 in 30,000 live births (about five times rarer than haemophilia A). There are usually carrier females and affected males.[3] The reference level of factor IX is 5 μg/mL but the 'normal' range is from half to twice that level.[4]

- Severe disease occurs with a factor IX level below 1% of the reference and accounts for about 50% of cases.
- Moderate severity occurs with a level of 1-5% and accounts for around 30% of cases.
- Mild disease is with levels of 6-30% and accounts for around 20% of cases.

No race or any geographical area is exempt.

If a woman is a carrier there is a 1 in 2 chance that any son will be affected and a 1 in 2 chance that any daughter will be a carrier. If a man with the disease fathers a child, any daughter will be a carrier and any son will be unaffected and will not carry the gene. There is a report of a daughter of a man with the disease who had a factor IX level of 5% and haemarthroses and this was thought to be a manifestation due to Lyonisation, in which one of the X chromosomes is inactive. There are a few other isolated reports of females presenting with the disease.[1]

Spontaneous mutation is common in families from certain geographical areas (eg, Sweden).[5]

Presentation[4]

As a general rule, platelet deficiency causes petechial haemorrhages and ecchymoses (bruising) whilst clotting factor deficiency produces haematomas and haemarthroses. Both haematomas in muscles and bleeding into joints can result from minor trauma and be very painful.

- Patients with severe disease experience lifelong symptoms from infancy onwards, with spontaneous haemorrhages and haemarthrosis. They may even start from the trauma of delivery, especially if instrumental. Ventouse delivery may produce an enormous haematoma.
- Patients with moderate disease suffer haemorrhage from minor trauma or surgery and sometimes spontaneous haemarthrosis.
- Patients with mild disease may suffer unexpected haemorrhage after trauma or surgery, or precipitated by the use of non-steroidal anti-inflammatory drugs (NSAIDs).
- If a patient presents with a history of diagnosed haemophilia, ascertain the type and the normal level of clotting factor.

For those who have not been diagnosed, there are a number of presentations, normally in infancy, except in the mildest cases:

- There may be marked haematoma from delivery, especially after a ventouse extraction.
- Infants may bleed excessively when blood is taken, as for a Guthrie test. Circumcision may be the presenting sign of a problem. Traditional Jewish practice is to perform this on the eighth day from birth.
- Immunisations and tooth loss may lead to unexpected blood loss.
- Just the ordinary rough play of childhood, which tends to be more marked in little boys than in little girls, may produce excessive bruising or spontaneous haemorrhage. With mild disease, haemorrhage is most likely to occur with trauma or surgery.
- Musculoskeletal problems may present as warmth, pain, stiffness and refusal to use a joint due to muscle haematoma or haemarthrosis. Infants may not be able to complain in words but refusal to use a joint demands investigation.
- There may be headache, stiff neck, vomiting, lethargy, irritability and spinal cord syndromes. There can be intracranial bleeding.
- Bleeding from the gut may produce haematemesis, melaena, frank red blood per rectum and abdominal pain.
- There may be microscopic haematuria or gross bleeding into the urinary tract.
Other possible features include epistaxis, haemorrhage into the oral mucosa, haemoptysis, dyspnoea from a haematoma obstructing the airway, compartment syndromes and contusions.

**Physical signs**
- There may be heat or swelling of a haematoma or an effusion.
- There may be obvious distress on palpation or passive movement of a joint.
- Bleeding into the central nervous system (CNS) may cause neurological signs, including reduced level of consciousness.
- There may be pallor, dyspnoea, tachycardia and other features of exsanguination.

**Differential diagnosis**
- Haemophilia A.
- Von Willebrand's disease.
- Factor IX inhibitors.
- Vitamin K deficiency.
- Hepatic disease causing deficiency of clotting factors.
- Platelet disorders.
- Disseminated intravascular coagulation.

**Investigations**
It may be necessary to treat the bleeding disorder before establishing a full diagnosis. This should not be delayed. Although the treatment will probably nullify the value of coagulation tests taken soon after, curbing haemorrhage and saving the patient's life comes first. It is usually possible to take blood before any treatment is started but an accurate diagnosis may have to wait.

- Haemoglobin level may be normal for a child of that age, or low. Remember that in acute haemorrhage it takes time for haemodilution to occur.
- Note the white cell count in case the diagnosis is really leukaemia.
- Check platelets.
- Prothrombin time (PTT) will be normal.
- Activated partial thromboplastin time (aPTT) will be elevated, although in mild disease it may be within the range of normal.
- Factor IX percentage activity.
- Inhibitor levels should be checked at regular intervals according to the recommendations of the British Committee for Standards in Haematology (BCSH).[^7]
- Thromboelastography - a method of assessing clot formation characteristics - is being used in some centres to assist in determining bleeding tendency.[^8]
- Factor VIII mutation analysis should be performed to identify the specific genetic mutation once the diagnosis of congenital haemophilia has been made. This is done in specialised centres.[^7]
- Imaging of the CNS may be in order, especially if there have been neurological signs. In acute haemarthrosis, X-ray does not add much but after years of recurrent haemarthrosis there is usually evidence of joint destruction.
- Abdominal ultrasound and endoscopy may be necessary if gastrointestinal bleeding is a feature.

**Management**
The major concerns, even with recombinant products, are the possibility of transmission of infections and inhibitor formation.[^7] If patients have never been exposed to plasma products then recombinant factor IX is first-line. If this is unavailable then plasma-derived factor IX or prothrombin complex concentrates are available. The latter should be avoided if at all possible, as it has been associated with an increased risk of thrombosis.

**In the acute situation**
- Attention must be paid to trying to secure haemostasis. In the established patient, he or she may be able to self-administer factor concentrate. Get as much history as possible from the patient, who probably knows his or her disease well.
- If possible, take blood for coagulation tests before starting any therapy but do not delay therapy. Blood transfusion may be required and so group and cross-match is necessary.
- Use recombinant factor IX if available (it is first-line). For serious haemorrhage the aim is to correct the level to 100% but, for more minor haemorrhage correction to 50% will suffice. A calculation of the dose required is based on the body weight, the baseline level of factor IX and the desired level to be achieved. If it is impossible to obtain adequate recombinant factor IX in time, fresh frozen plasma and cryoprecipitate may still be used.
- A further dose should be administered 24 hours after the first and is half of the initial calculated dose. Minor haemorrhage requires between one and three doses of factor IX. Major haemorrhage needs many doses and continued factor IX activity monitoring, with the goal of keeping the trough activity level of at least 50%. Continuous infusions of factor IX may be required.
- Haematoma and haemarthrosis can be very painful and require analgesic medication. The best route is oral but NSAIDs must not be employed for fear of gastrointestinal haemorrhage.[^10] Opiates may well be needed and, if given parenterally, this must be intravenously (IV) or possibly subcutaneously (SC) but not intramuscularly (IM). IM injection will produce a large and painful haematoma.
- As the oral mucosa is rich in native fibrinolytic activity, antifibrinolytic therapy is used in addition to factor IX replacement for oral mucosal haemorrhage and prophylaxis - eg, tranexamic acid.

**In the chronic state**
New genetic tests are being developed which could aid the detection of the carrier state in women and also prenatal diagnosis. A more liberal attitude to termination than the UK reported that 18 out of 26 women given a prenatal diagnosis of fetal haemophilia opted from mother or father and the possibility of transmission of HIV if the man has been infected. More, is ethically unsound. Reproductive choices for affected families are complex. There is the question of passing on the gene either condition that is associated with a fairly normal lifestyle, with some restriction of ‘rough’ activity and a life expectancy of 60 years or may be carrying. This has two ethical objections. One is that 50% of aborted fetuses would be normal. The other is that abortion for a prevention in the area of dialysis and kidney transplantation.

The life expectancy and quality of life of patients with haemophilia have dramatically improved over a number of years, mainly due to new therapies and the awareness to the risk of HCV and HIV infections. However, new issues in terms of age-related diseases such as diabetes, hypertension, cancer and chronic viral infections are emerging. Renal diseases are a particular challenge, particularly in the area of dialysis and kidney transplantation.

Surgical considerations

- Any decision to proceed with surgery has to be a multidisciplinary one and the decision process should be aided by weighing up the risks and benefits for the patient.
- Trasexamic acid inhibits fibrinolysis, without increasing thrombosis risk in healthy individuals undergoing cardiac or orthopaedic surgery and so might be a useful adjunct.
- Liver transplant has been carried out successfully using high-purity factor IX to control peri-operative bleeding.

Prophylaxis

There are both risks and benefits from the prophylactic use of factor IX therapy rather than simply treating emergencies. Intermittent prophylactic augmentation of factor IX levels have a beneficial effect on preventing haematoma and haemarthrosis formation. The frequency of administration and the dose to be given are an individual decision between the haematologist and the patient.

The risk of transmission of HIV and hepatitis B and C infections from recombinant products has virtually been eliminated. However, there are still concerns about prions and non-capssulated viruses.

The main disadvantage of regular prophylactic administration of factor IX is the risk of inhibitors developing. They result from immune reactions as the introduced substance may present to the immune system as ‘not self’. These inhibitors are less of a problem than with haemophilia A and occur in about 1-3% of severe cases after 11 days of exposure (with a wide range of 2-180 days). In haemophilia B, inhibitor development is associated with anaphylaxis on exposure to any factor IX product (in half of the patients). Thus, first exposure should take place in a specialist centre. Unlike haemophilia A, immune tolerance induction has a poor response rate (25%) and there is a risk of nephrotic syndrome.

Lifestyle has to be adapted to accommodate the disease. Contact sports should be avoided as well as sports and pastimes in which there is significant risk of trauma. Manual labour should be avoided.

Complications

The bleeding can cause many problems, including neurological deficits; however, a very common finding is that recurrent bleeding into joints leads to destruction of the joint. The joints are painful to move and the range of movement is limited. Anyone who has taken blood from a patient with haemophilia A or B will probably have noticed that the patient is unable to extend the elbow fully.

Before the advent of recombinant factor IX, patients used to receive factor IX concentrate that was derived from the plasma of many donors. Before 1985 there was a significant risk that this product might be contaminated with hepatitis B or C or with HIV. The risk was even greater for patients with haemophilia A, partly because it is usually a more severe condition and so treatment is probably needed more often and also because they required even more donors per treatment. Because of shortages, much of the product was imported from the USA where the incidence of these diseases is much higher and where the use of paid donors tends to produce a different type of donor in terms of lifestyle. A study published in 1998 found HIV antibody in 41% of patients with haemophilia A and 6% of those with haemophilia B. For the more severely affected patients the figures were 59% and 11% respectively. In 1985 a viral inactivation process made the product much safer but the advent of recombinant ‘genetically engineered’ factor IX has made a vast difference. Without it we may still be worried about transmission of other agents such as new variant Creutzfeldt-Jakob disease.

Many people with haemophilia, including those with haemophilia B, are infected with both hepatitis C virus (HCV) and HIV and the two viruses together produce a rather worse prognosis. There continues to be a significant number of deaths from liver disease and hepatocellular carcinoma. However, those people with haemophilia who are not infected with HIV appear to have a lower death rate from cancer than the general population, a phenomenon that requires further research.

Prognosis

The life expectancy and quality of life of patients with haemophilia have dramatically improved over a number of years, mainly due to new therapeutic options and the awareness to the risk of HCV and HIV infections. However, new issues in terms of age-related diseases such as diabetes, hypertension, cancer and chronic viral infections are emerging. Renal diseases are a particular challenge, particularly in the area of dialysis and kidney transplantation.

Prevention

If a pregnant woman is known to be a carrier of the disease then it would be possible to perform selective abortion of any male fetus she may be carrying. This has two ethical objections. One is that 50% of aborted fetuses would be normal. The other is that abortion for a condition that is associated with a fairly normal lifestyle, with some restriction of ‘rough’ activity and a life expectancy of 60 years or more, is ethically unsound. Reproductive choices for affected families are complex. There is the question of passing on the gene either from mother or father and the possibility of transmission of HIV if the man has been infected. A survey in the Netherlands (which has a more liberal attitude to termination than the UK) reported that 18 out of 26 women given a prenatal diagnosis of fetal haemophilia opted for termination.
New genetic tests are being developed which could aid the detection of the carrier state in women and also prenatal diagnosis. The measurement of plasma factor activity level and information from genotyping are helpful in informing female carriers of options regarding the future of their pregnancy. For the future, this may well be an excellent disease for the use of gene therapy.

**Historical perspective**

The disease was first recognised as different from haemophilia (now called haemophilia A) by Aggler et al in 1952. However, the classical paper on the subject appeared at the end of that year. The name of the patient was Stephen Christmas. December 25 is Christmas Day, December 26th is the Feast of Stephen and the paper appeared in the Christmas edition of the BMJ on 27th December 1952. Hence haemophilia B is sometimes called Christmas disease.

The Leyden variation that improves at puberty was described in 1970. The discovery in the early 1980s that many people with haemophilia with type A and, to a lesser extent, type B, were infected with hepatitis viruses and HIV has been disastrous. However, without the treatment they would have died.

Recombinant factor VIII and factor IX have made an enormous difference. They are expensive but the cost of treatment and prophylaxis needs to be weighed against expenditure on the treatment of complications, social support and measures to improve the quality of life. Such issues can only be addressed by long-term cost-benefit analyses.

**Further reading & references**

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