Management of haemophilia

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Abstract

Haemophilia is an inherited bleeding disorder associated with a deficiency of coagulation factors VIII or IX. The bleeding tendency is proportional to the degree of deficiency. The hallmark of the severe phenotype is recurrent and spontaneous bleeding into joints which can lead to crippling joint deformity and arthritis at an early age in the absence of effective treatment. The condition is inherited as an X-linked disorder although there is no family history in approximately one-third of cases and this represents a new mutation. In the absence of effective treatment, the prognosis is poor but the development of coagulation factor concentrates in the last few decades has transformed the outlook. Recombinant products are now increasingly regarded as the treatment of choice because they are free of the risk of viral infection. Conventional treatment now consists of the administration of concentrate on a prophylactic basis to prevent bleeds and hence minimize disability in the long-term. Patients with haemophilia now live essentially normal lives and life expectancy approaches that of the normal population. Inhibitors to factor VIII arise in a significant minority of patients with haemophilia A and vigilance is required in screening children for the development of this complication. Bypassing agents such as FEIBA® and NovoSeven® may be used to control bleeding in such cases and the regular administration of large doses of coagulation factor concentrate will usually result in suppression of inhibitor production. Looking to the future, it is likely that modified molecules with enhanced properties such as increased half-life will soon be available and trials of gene therapy are also underway.

Keywords antenatal diagnosis; carrier; factor VIII; factor IX; haemophilia; inhibitors; recombinant

Clinical features of haemophilia

Haemophilia is a congenital disorder of coagulation and affects approximately 1 in 10000 males worldwide, with approximately 5000 patients with haemophilia in the United Kingdom. Haemophilia A is due to a deficiency of factor VIII in the circulating blood and haemophilia B (also known as Christmas disease) is a clinically identical disorder caused by factor IX deficiency. The genes for factors VIII and IX are both located on the X chromosome and thus haemophilia is inherited as an X-linked recessive condition. The daughters of affected males are obligate carriers but the sons are normal. The phenotype remains constant within a family, so the daughter of a man with only mild haemophilia may be reassured that she will not pass on a severe form of the condition. However, approximately one-third of all cases of haemophilia arise in the absence of a previous family history and is due to a new mutation.

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In families with a documented history of the condition the diagnosis is often made shortly after birth by measuring the factor VIII (or IX) level in a cord blood sample. Typical laboratory findings in haemophilia include normal prothrombin (PT) and thrombin times but a prolonged activated partial thromboplastin time (APTT). The platelet count and bleeding time are normal. A specific factor assay is required to confirm the diagnosis. Where there is no documented family history of the condition, the diagnosis is often delayed until the child starts to crawl or walk and the child is noted to have significant bruising or limp. In such cases, there is a distinct possibility that non-accidental injury will be considered in the differential diagnosis.

The clinical severity (phenotype) is critically determined by the level of circulating factor VIII (or IX) in the blood, and severe haemophilia is defined by a clotting factor level of less than1 IU/dl. The hallmark of severe haemophilia is recurrent and spontaneous haemarthrosis. Typically, hinge joints such as the knees, elbows and ankles are affected but bleeds may also occur in the wrist or shoulder. Bleeding into the hip joint is unusual. The affected joint is swollen and warm, and held in a position of flexion, with no external discolouration or bruising around the joint. It is unusual for an infant to suffer spontaneous haemarthroses in the first few months of life. The first joint to be affected tends to be the ankle as the child learns to crawl. The initial signs of a haemarthrosis in an infant will often be obvious discomfort and distress, accompanied by limping or reluctance to use a limb. Recurrent bleeds into a joint can result after a period of months or years to synovitis and joint damage resulting in crippling arthritis. Bleeding into muscles is also a feature of haemophilia, but this is usually a consequence of direct injury, albeit often minor. Bleeds into certain areas are particularly dangerous because of the risk of compression of neighbouring structures. Patients with inhibitory antibodies are particularly at risk in this regard, as bleeds may be more difficult to control (see below). Bleeds in the tongue can obstruct the airway, and retroperitoneal bleeding within the ilio-psoas muscle may result in femoral nerve compression, causing weakness and wasting of leg muscles. Bleeding from the gastrointestinal tract (melaena) and bleeding into the urinary tract (haematuria) may also occur. There is also a significant risk of intracranial haemorrhage in severe haemophilia which was a significant cause of mortality in the past when treatment was not so readily available. This is a particular issue for very young children and parents need to be specifically advised to seek treatment for their child if he knocks or bangs his head. Higher levels of factor VIII (or IX) above 5 IU/dl are associated with a milder form of the disease, with no spontaneous joint bleeds but a definite risk of bleeding after even relatively minor injury.

Genetic and molecular basis of haemophilia

The factor VIII gene consists of 26 exons located at the telomeric end of the X chromosome, which range in size from 69 bp (exon 5) to 3.1 kb (exon 14) in size and which encode a mature protein is made up of 2332 amino acids. Approximately half of all cases of severe haemophilia and all cases of mild and moderate haemophilia result from heterogeneous mutations which occur throughout the FVIII gene. By far the commonest single genetic defect causing severe haemophilia is an inversion in intron-22, which is encountered in as many as 45% of people with severe

haemophilia in all ethnic groups. More recently, inversions in intron 1 of the factor VIII gene have been identified as a cause of severe haemophilia and this abnormality appears to be responsible for approximately 5% of all cases of severe haemophilia. Most other cases of haemophilia are the consequence of a variety of missense mutations although a small number of cases result from gene deletions (3). The factor IX gene (*F9*) is also located on the long arm of the X chromosome at band Xq27, and is encoded by a stretch of DNA spanning 33.5 kb and which contains eight exons. Point mutations account for the vast majority of cases of haemophilia B.

Treatment of haemophilia

Haemophilia is a rare disorder and few non-specialist health care professionals will deal with such patients on a regular basis. Patients with congenital bleeding disorders are usually followed up within designated regional comprehensive care centres which can provide multidisciplinary care. Such a unit should also offer support to patients at home in the community as well as to other regional hospitals. There is now clear evidence that such a system of haemophilia care provides a better outcome.

Plasma-derived coagulation factor concentrates were developed in the early 1970s but many patients with haemophilia were subsequently infected with either HIV and/or hepatitis C. Modern plasma-derived products are much purer and are also subjected to viral inactivation procedures so that the risk of these infections has effectively been eliminated. Recombinant factor VIII and IX concentrates are now available and any clinicians now regard these as the treatment of choice for all patients with haemophilia as they offer the best possible protection from transmission of blood-borne pathogens: it has been the policy within the UK for some years now to use these products exclusively.

The articular cartilage of young children is particularly vulnerable to irreversible damage which is primarily mediated by iron release from blood which also triggers an inflammatory reaction. The administration of prophylactic infusions of coagulation factor concentrates is now generally accepted as representing the best approach to the modern management of haemophilia. Data from a recent prospective randomized controlled trial have confirmed the longstanding impression that such treatment reduces the incidence of joint bleeds and also protects against the development of joint damage. The conventional prophylactic treatment regime involves administration of 20–40 IU/kg three times weekly in the case of haemophilia A and twice weekly in haemophilia B. However, there are many variants in treatment approach and a Canadian study has suggested that once weekly treatment is a reasonable initial alternative, with escalation of the dosage if breakthrough bleeding occurs. Prophylaxis is usually embarked upon after the first or second joint bleed, which will usually be around the age of 18–24 months of age. This will initially be given by the parents at home and the child should be able to take over the task by the age of 12 years. Periodic measurement of trough levels of factor VIII is recommended as there is a clear correlation between the probability of spontaneous bleeding and time spent with a baseline level below 1%. Firm data are also available to show that prophylaxis is associated with enhanced quality of life in children. There is also evidence that the incidence of extra-articular bleeding, including intracranial haemorrhage, is also reduced among children receiving prophylactic therapy. Data also suggest that early adoption of prophylaxis may confer protection against inhibitor development. The use of implantable venous devices certainly makes early treatment of children easier although complications such as thrombosis and bacterial infection are not infrequent. Another area of active debate is whether prophylaxis should be continued in adults. Participation in sports should be positively encouraged as this is good both for social integration and also maintenance of musculoskeletal health. Suitable activities include swimming, athletics and football but rough contact sports need to be avoided.

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is a synthetic peptide analogue of the endogenous pituitary hormone, vasopressin (antidiuretic hormone, ADH). It can significantly boost levels of both factor VIII and VWF in the blood and desmopressin is therefore a valuable agent for the treatment of mild and moderate haemophilia A as well as Willebrand's disease. This product is very cheap and is completely free from the risk of transmission of viral infections. The standard dose of DDAVP for treatment of bleeding disorders is 0.3 μg/kg given by subcutaneous injection, although it may also be given by intravenous infusion. Young children seem to particularly prone to development of hyponatraemia and it is best to avoid the use of this particular agent in children under the age of 2 years. Tranexamic acid is an inhibitor of fibrinolysis and is useful as adjunctive therapy for bleeding from mucosal surfaces such as from the nose and around the teeth and gums. Aspirin and non-steroidal anti-inflammatory agents should be avoided as they will exacerbate the bleeding tendency through inhibition of platelet function. Paracetamol is a perfectly safe alternative as it has no such action. Older patients with established arthropathy in several joints often derive considerable benefit from treatment with COX-2 inhibitors such as etoricoxib. Patients with congenital bleeding disorders should not be given intramuscular injections as this may result in haematoma formation. It is, of course, important that children receive their normal vaccinations, but these should be given via the subcutaneous route.

In the future, it is likely that modified molecules with enhanced properties such as reduced immunogenicity and increased half-life will become available. Strategies for increasing the duration of activity of coagulation include covering the molecule with polyethylene glycol (PEG) and creating molecules with mutations at sites which are the natural targets for specific proteolytic inactivation. Haemophilia also provides an attractive model for correction by gene therapy and several clinical trials in both haemophilia A and B are already underway.

Inhibitors

Now that the risk of viral infection has been eliminated, the development of antibodies (inhibitors) to infused factor VIII is the major potential complication. The problem is significantly commoner in haemophilia A than in haemophilia B. Data from the UK registry indicate that around 14% of all patients with haemophilia A and 2% of those with haemophilia B will develop inhibitory antibodies at some stage. It is quite likely that this figure underestimates the true prevalence as transient and low titre inhibitors may not be detected. The development of inhibitors is typically first seen in childhood, fairly soon after a child begins to receive treatment. Periodic screening for inhibitors is an important part of haemophilia care. UK