Haemophilia: pathophysiology and management

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ABSTRACT Vidler, V. (2003) Haemophilia: pathophysiology and management. Nursing Times; 99: 41, 30–33. Haemophilia is an inherited disorder of the body’s blood clotting mechanism. Past treatments have led to the transmission of blood-borne viruses, primarily HIV and hepatitis C. Current clotting factor concentrates and treatment regimes offer patients a good quality of life. Specialist haemophilia nurses play a pivotal role in the organisation and delivery of care to this patient group.

Haemophilia is a rare inherited disorder of the body’s blood clotting mechanism. This X-linked recessive disorder occurs in 1:10,000 live male births a year and there are no variations of incidence in different ethnic groups. In the developing world many people affected by this disorder do not have access to effective treatment, which results in serious disabilities and incapacity.

Haemophilia can be divided into two categories: haemophilia A and B – characterised by a deficiency or absence of clotting factor VIII and IX respectively. This article mainly refers to haemophilia A because it is more prevalent than haemophilia B. However, the clinical features of both disorders are identical and any variations in treatment are outlined in the text.

Pathophysiology

Three mechanisms work together to facilitate healing when a blood vessel is injured (Box 1). First, the blood vessel constricts to limit the volume of blood that is lost. Second, circulating platelets form a plug at the site of injury. Finally, the blood undergoes coagulation. A number of clotting factor proteins, defined by Roman numerals, must be activated in sequence for coagulation to take place. This process allows the platelet plug to be stabilised by a fibrin matrix that is formed over its surface, thereby ensuring that the vessel wall can heal (Waugh and Grant, 2002).

Factors VIII and IX are only two of the 13 proteins that are involved in the cascade process of coagulation. If there is an absence or deficiency of any of these proteins the coagulation process will be initiated but not completed: the platelet plug will remain unstable and bleeding will continue over a prolonged period of time.

Diagnosis

A variety of elements must be considered before diagnosing haemophilia in a patient with no previous family history. A detailed history of the patient’s symptoms of bleeding, and questioning about any maternal blood relatives with symptoms of prolonged or excessive bleeding, should be considered first.

Blood samples for a clotting screen should be taken and analysed for platelet count, prothrombin time, activated partial thromboplastin time and thrombin time. Factor VIII and IX assays can be estimated if the clotting screen is suggestive of haemophilia, following which a definitive diagnosis can be made (Higgins, 1997).

After diagnosis, information and support should be offered to the patient or carer. Those with a family history of haemophilia may be unaware of current treatments and recent developments; those with no previous history will need details about the disorder, its treatment and how to access hospital services in an emergency.

Inheritance

The genes for factors VIII and IX are located on the X chromosome and display a recessive inheritance pattern. Therefore, the disease is characterised by healthy female carriers plus males affected by haemophilia (Fig 1). If the precise genetic mutation has been identified in known female carriers, chorionic villus sampling can be performed in early pregnancy to determine the haemophilia status of any male foetus, with the opportunity for a termination.

Pre-implantation genetic diagnosis is a refinement of in-vitro fertilisation that allows only those male embryos unaffected by haemophilia and female embryos to be implanted into the mother. The technique was developed specifically to offer an additional treatment option to couples affected by single gene disorders such as hae-

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**BOX 1. STAGES OF HAEMOSTASIS**

| Vessel constriction |
| Formation of platelet plug |
| Stabilisation of platelet plug |
| Healing of the vessel wall |

**BOX 2. DEGREES OF SEVERITY (HAEMOPHILIA ALLIANCE, 2001)**

<table>
<thead>
<tr>
<th>Type of haemophilia</th>
<th>Factor VIII level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild haemophilia</td>
<td>&gt;0.10–0.50IU/dl</td>
</tr>
<tr>
<td>Moderate haemophilia</td>
<td>0.02–0.10IU/dl</td>
</tr>
<tr>
<td>Severe haemophilia</td>
<td>&lt; 0.02IU/dl</td>
</tr>
</tbody>
</table>
mophilia (Klotzko, 1998).

The inheritance of haemophilia in men affected by the disorder follows a different pattern because the X chromosome will always contain a defective factor VIII gene. Therefore, all daughters born to a man with haemophilia will be haemophilia carriers but none of his sons will have haemophilia. In effect, haemophilia skips a generation and becomes an issue only when his daughter is contemplating having a family (Fig 2).

Approximately 70 per cent of babies born with haemophilia will have a family history of the disorder. It may be that the mother already has a son with haemophilia or that she has a male relative with the disease, for example a brother or maternal cousin. In these circumstances, any baby boy she gives birth to can have a sample of blood taken from the umbilical cord and be assessed for the level of factor VIII or IX. This investigation can be completed quickly so that the parents can be informed and the neonate monitored closely.

Diagnosis will be delayed if any patient with haemophilia is born as the result of a new spontaneous mutation. Individuals with mild and moderate haemophilia may present only after they have undergone a haemostatic challenge that has led to prolonged or excessive bleeding, for example surgery or dental extractions. Children with severe haemophilia tend to have few clinical problems until they become mobile, although their parents often remark on the number of large bruises on their child’s extremities. Visits to baby clinics and swimming pools can result in parents feeling acutely uncomfortable and aware of suspicious looks and implied criticisms.

It is important for nurses to be aware of, and sensitive to, the issues that families face when living with a member who has a genetic disorder that has implications well into the future. Many mothers may have feelings of guilt about passing on a defective gene to their offspring that results in their having a chronic illness requiring painful treatments or the possibility of daughters being carriers of haemophilia.

Treatment

Treatment for patients with haemophilia is determined by the clinical severity of the disease (Box 2). Those with mild and moderate haemophilia A usually require only temporary treatment to correct their clotting defect pre-operatively, following trauma and before dental extractions and conservative treatment requiring local anaesthesia. As these groups of patients already have some circulating factor VIII, administering desmopressin – a synthetic form of the hormone vasopressin – will result in stored factor VIII being released from the endothelial linings of the blood vessels (Hoffbrand et al, 2001). Desmopressin is ineffective in patients with haemophilia B and they require replacement treatment with factor IX.

The majority of clinical problems are experienced by patients with severe haemophilia A and B. The most common manifestation is spontaneous internal bleeding, usually involving the large weight-bearing joints, such as the knees, ankles and elbows (Khair, 2002). Repeated bleeding into joints has a corrosive effect on the synovium and can result in disabling and permanent damage, causing pain and disability.

Bleeding can occur at any site, either spontaneously or after a traumatic event. The only effective treatment for patients with severe haemophilia is to replace the missing clotting factor. Clotting factor concentrates are freeze-
dried preparations that require intravenous administration after reconstitution. They come in various vial sizes (250, 500 or 1000 units of factor VIII or IX), and the dose is determined by the patient’s weight and the site and severity of bleeding.

Most children and young people with severe haemophilia are treated at regular intervals (usually three times a week) with clotting factor concentrates to ensure that their clotting factor levels are always maintained above 0.03–0.04IU/dl for factor VIII or IX. This treatment means that the child or young person now has moderate rather than severe haemophilia and, therefore, is unlikely to experience disabling bleeding into his or her joints.

Such treatment is termed as ‘prophylaxis’ because it offers the greatest protection against joint damage and maximises the opportunity for children to enjoy a similar lifestyle to their peers. In addition, the clinical course of haemophilia becomes much more predictable and family life is more easily regulated.

As haemophilia is a relatively rare condition it is sensible for treatment to be delivered in centres that have accrued a degree of experience and knowledge. The optimal delivery of haemophilia treatment has been defined by the Department of Health in a Health Service Circular that is intended to ensure quality treatment for all patients (DoH, 1993).

There are 22 comprehensive care centres in the UK that offer a wide range of patient services such as genetic testing of carriers, orthopaedic surgery and the treatment of haemophilia-related complications. Additionally, a programme of national peer audit has been in place in these centres for over 10 years. There are also a number of haemophilia centres that, while not offering the full range of comprehensive services provided by the comprehensive care centres, do provide access to everyday and emergency treatment for patients with haemophilia. Importantly, this model ensures that patients have access to local services without having to travel excessive distances for routine treatment.

**Lifestyle**

The aim and philosophy of haemophilia treatment is to ensure that individuals with haemophilia have as normal a lifestyle as possible. Prophylaxis can be given in such a way as to allow participation in many normal physical and sporting activities. The only sports that are contraindicated are contact sports that involve the risk of a blow to the head because of possible bleeding within the skull. These would certainly include rugby and boxing and possibly some martial arts. Some careers are not feasible for men with severe haemophilia, for example the emergency services and the armed forces.

Other lifestyle choices, for example body piercing and tattooing, may need discussion with haemophilia health care professionals because the procedures may cause localised bleeding and subsequent swelling. Some health care professionals might consider that using clotting factor concentrates prior to these procedures is an inappropriate use of an expensive resource. The same philosophy could also be applied to extreme sports such as bungee jumping or white water rafting. The important consideration is that these issues are discussed openly, rather than the individual with haemophilia embarking on a potentially hazardous activity without prior thought and consideration of the consequences.

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**FIG 2. INHERITANCE PATTERN OF HAEMOPHILIA FOR A HAEMOPHILIC FATHER**

Adapted from *Haemophilia - a resource for healthcare professionals*; a CD produced by Wyeth Pharmaceuticals

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**REFERENCES**


Historical perspective
During the latter half of the 20th century great advances were made in the understanding of haemophilia, which led to the first effective treatments becoming available. Scientists in Oxford led the research with their discovery of techniques to quantify clotting factor levels. The type of combat in World War II meant that there was a need to provide fast and effective first aid at the front lines, and the safe transportation of blood and plasma and their appropriate use saved many lives. This development led to further treatment initiatives after the war, the most significant of which is cryoprecipitate, a component of plasma fractionation that contains many of the clotting factors needed to achieve coagulation.

During the early 1970s, clotting factor concentrates were produced from large, pooled plasma collections from blood donors. These freeze-dried preparations simply required reconstitution and bolus intravenous administration. They were able to be self-administered at home and were the single most important development in the treatment of haemophilia. Clotting factor concentrates offered an effective treatment that could be quickly and easily administered and reduced the amount of time missed from school or work. Prompt treatment of bleeding episodes minimised the risk of long-term complications and damage from repeated bleeding, particularly into the joints.

However, the introduction of clotting factor concentrates heralded a major catastrophe for the haemophilia community. As the UK was unable to achieve self-sufficiency in plasma supply, clotting factor concentrates were imported from the USA. The plasma sources for these products were often from donors whose lifestyle made them susceptible to contracting blood-borne pathogens (Star, 1998). As a consequence, in the 1970s and in the early 1980s, many people with haemophilia became infected with HIV from using contaminated clotting factor concentrates.

The distress and stigma attached to HIV infection, particularly when the disease was first identified, was profound (Susman-Shaw and Harrington, 1999). Anxieties surrounding the transmission of pathogens were heighten again when it became apparent that most haemophilia patients treated before heat treatment of clotting factor concentrates in 1985 had been exposed to hepatitis C (Makris et al, 2001).

Current concerns
Recent concerns about the theoretical risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) via blood have led to a series of measures being taken to minimise this possibility. In 1998 the DoH sanctioned the use of recombinant clotting factor concentrates for children under 16 years of age. These preparations are produced by genetic technology and do not involve the use of large collections of pooled plasma.

Although albumin is used in the production of some recombinant clotting factor concentrates, the amount is very small and often filtered out before the final product is processed. Additionally, the plasma used to produce factors VIII and IX has, since 1998, been imported from the USA, where there have been no reports of vCJD and where the collection of plasma from paid donors is now well regulated and reliable (Ironside and Head, 2003).

A further welcome initiative from the DoH in February this year will result in the use of recombinant clotting factor concentrates being extended to all adults in England over the next three years.

Role of the specialist nurse
A role for specialist nurses in the area of haemophilia care was established early in the development of specialist practice in the UK. This was fuelled by the need for a thorough coordination of home treatment programmes in the 1970s (Colvin et al, 1977).

The transmission of HIV and hepatitis C after treatment with clotting factor concentrates caused great distress and anxiety to the haemophilia community. Patients and their families and friends needed the support and understanding of health care professionals to cope with the stigma and the possible poor prognosis after contracting these viruses. To meet this need, haemophilia nurses developed counselling skills and also formed networks with other haemophilia nurses as they sought to deal with patients’ turmoil (Vidler, 2000).

As the safety profile of clotting factor concentrates has improved there has been an increase in the use of factors VIII and IX. This has mainly been as prophylaxis for children and young adults. Furthermore, the opportunity to undertake corrective orthopaedic surgery for those older patients who have suffered extensive haemophilic arthropathy can now be pursued.

Haemophilia has become a chronic illness that, with current treatment protocols, can offer an individual a good quality of life. The aftermath of HIV and hepatitis C infection is still a major issue for many adult patients. However, treatment and research into both of these viruses has moved forward, which has enabled infected patients to view their future now with some degree of optimism.

The current management of haemophilia, as with many other chronic conditions, offers specialist nurses an ideal opportunity to advance their clinical and caring skills and to provide patients with a comprehensive and holistic nurse-led service (Castedine and McGee, 1998).

Conclusion
Great advances in the treatment of haemophilia have been made over the past four decades. However, some of these improvements have brought significant morbidity and mortality, as well as considerable distress. The widespread introduction of recombinant clotting factor concentrates offers an assurance of greater safety to patients. In addition, there is the prospect of gene therapy further improving the lives of patients. The opportunity for nurses to develop and advance their clinical skills while offering patients a valuable service should be recognised and embraced.

REFERENCES