ANAESTHETIC MANAGEMENT OF A PATIENT WITH HAEMOPHILIA A

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Haemophilia A is an X-linked recessive hereditary disorder characterized by a deficient or defective factor VIII coagulant (factor VIII C or antihaemophilic factor). Haemophilia is more likely to occur in males rather than females. This is because females have two X chromosomes while males have only one; lacking a 'back up' copy for the defective gene, the defective gene becomes manifest more easily in males. Because females have two X chromosomes and because haemophilia is rare, the chance of a female having two defective copies of the gene is very low, thus females are almost exclusively asymptomatic carriers of the disorder. Only under rare circumstances do females actually have haemophilia.[1]

Types

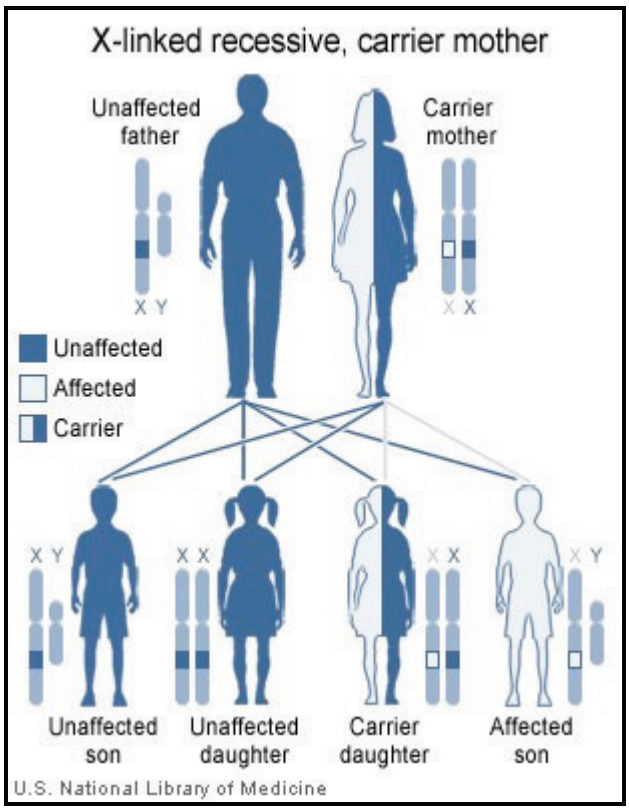
- ***Haemophilia A*** is a recessive X-linked genetic disorder involving a lack of functional clotting Factor VIII and represents 90% of haemophilia cases.[2] The incidence is about 1 in 5,000–10,000 male births.[3]
- ***Haemophilia B*** is a recessive X-linked genetic disorder involving a lack of functional clotting Factor IX. It is similar to but less common than haemophilia A. The incidence is about 1 in about 20,000–34,000 male births.
- ***Haemophilia C*** is an autosomal genetic disorder (i.e. *not* X-linked) involving a lack of functional clotting Factor XI. Haemophilia C is not completely recessive: heterozygous individuals also show increased bleeding.[4]

Acquired haemophilia is the development of Factor VIII inhibitors (auto-antibodies) in patients without a history of Factor VIII deficiency. This condition can be idiopathic (occurring in people >50 y), it can be associated with collagen vascular disease or the peripartum period, or it may represent a drug reaction (e.g. to penicillin). High titres of Factor VIII auto-antibodies may be associated with lymphoproliferative malignancies.

Genetics

Females possess two X-chromosomes, males have one X and one Y chromosome. Since the mutations causing the disease are recessive, a woman carrying the defect on one of her X-chromosomes may not be affected by it, as the equivalent allele on her other chromosome should express itself to produce the necessary clotting factors. However, the Y-chromosome in men has no gene for factors VIII or IX. If the genes responsible for production of factor VIII or factor IX present on a male's X-chromosome are deficient there is no equivalent on the Y-chromosome, so the deficient gene is not masked by the dominant allele and he will develop the illness.

Since a male receives his single X-chromosome from his mother, the son of a healthy female silently carrying the deficient gene will have a 50% chance of inheriting that gene from her and with it the disease; and if his mother is affected with haemophilia, he will have a 100% chance of being a haemophiliac. In contrast, for a female to inherit the disease, she must receive two deficient X-chromosomes, one from her mother and the other from her father (who must therefore be a haemophiliac himself). Hence haemophilia is far more common among males than females. However, it is possible for female carriers to become mild haemophiliacs due to lyonisation (inactivation) of the X chromosomes. Haemophiliac daughters are more common than they once were, as improved treatments for the disease have allowed more haemophiliac males to survive to adulthood and become parents. Adult females may experience menorrhagia (heavy periods) due to the bleeding tendency. The pattern of inheritance is criss-cross type. This type of pattern is also seen in colour blindness.



A mother who is a carrier has a 50% chance of passing the faulty X chromosome to her daughter, while an affected father will always pass on the affected gene to his daughters. A son cannot inherit the defective gene from his father.

If a male is afflicted with the disease and has children with a female who is not even a carrier, his daughters will be carriers of haemophilia. His sons, however, will not be affected with the disease. The disease is X-linked and the father cannot pass haemophilia through the Y

chromosome. Males with the disorder are then no more likely to pass on the gene to their children than carrier females and all sons will not have haemophilia (unless the mother is a carrier).

As with all genetic disorders, it is of course also possible for a human to acquire it spontaneously through mutation, rather than inheriting it, because of a new mutation in one of their parents' gametes. Spontaneous mutations account for about 33% of all cases of haemophilia A. About 30% of cases of haemophilia B are the result of a spontaneous gene mutation.

Symptoms

Affected persons have a bleeding tendency that is inversely proportional to factor VIII levels in the body. Haemophilia severity is classified according to the baseline level of clotting factor activity. Factor VIII activity levels are reported in units, with 1 U/ml corresponding to 100% of the factor found in 1 ml of normal plasma. Normal plasma activity levels usually range between 0.5 U/ml and 1.5 U/ml (50–150%):[5]

1. Severely affected patients have <1% of normal factor levels.

2. Those with moderate disease have 1–4%.

3. Patients with mild disease have 5–40%.[6]

Prolonged bleeding and re-bleeding are the diagnostic symptoms of haemophilia.[7] Haemophilia lowers blood plasma clotting factor levels of the coagulation factors needed for a normal clotting process. Thus when a blood vessel is injured, a temporary scab does form, but the missing coagulation factors prevent fibrin formation, which is necessary to maintain the blood clot. Thus a haemophiliac does not bleed more intensely than a normal person, but can bleed for a much longer amount of time. In severe haemophiliacs even a minor injury could result in blood loss lasting days, weeks, or not ever healing completely. In areas such as the brain or inside joints, this can be fatal or permanently debilitating.

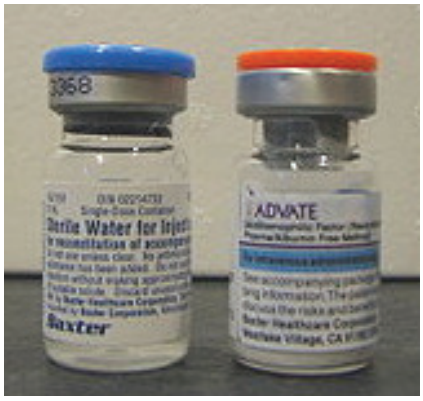
Those with <1% of normal factor VIII level are susceptible to spontaneous bleeding episodes such as haemarthrosis, soft tissue haematoma and intracranial haemorrhage.[8] All the patients with haemophilia, regardless of the severity of the disease, are at risk of excessive bleeding during surgery. Since the intrinsic limb of the coagulation system is disabled, haemostasis depends upon vascular and extrinsic mechanisms. As a result, bleeding from larger rather than small vessels poses the most serious problem.

Females who are carriers usually have enough clotting factors from their one normal gene to prevent serious bleeding problems, though some may present as mild haemophiliacs. Lyonized females (i.e. those with unequal inactivation of Factor VIII alleles and with hemizygosity of all or part of the X chromosome) may be symptomatic.

Treatment

Though there is no cure for haemophilia, it can be controlled with regular infusions of the deficient clotting factor, i.e. factor VIII in haemophilia A or factor IX in haemophilia B. Some patients develop antibodies (inhibitors) against the replacement factors given

to them, so the amount of the factor has to be increased or non-human replacement products must be given, such as porcine factor VIII.[9]



Commercially produced factor concentrates such as **"Advate"**, a recombinant Factor VIII produced by Baxter International, come as a white powder in a vial which must be mixed with sterile water prior to intravenous injection.

If a patient becomes refractory to replacement coagulation factor as a result of circulating inhibitors, this may be partially overcome with recombinant human factor VII (NovoSeven) or activated prothrombin complex concentrate.[10]

In early 2008, the US Food and Drug Administration (FDA) approved Xyntha anti-haemophilic factor, genetically engineered from the genes of Chinese hamster ovary cells. Since 1993 (Dr. Mary Nugent) recombinant factor products [which are typically cultured in Chinese hamster ovary (CHO) tissue culture cells and involve little, if any human plasma products] have been available and have been widely used in wealthier western countries. While recombinant clotting factor products offer higher purity and safety, they are, like concentrate, extremely expensive, and not generally available in the developing world.

Pre-operative Preparation

The diagnosis of haemophilia is often made from family history, laboratory findings such as greatly reduced factor VIII, and elevated PTT. The PT, bleeding time, platelet count and clot retraction will be normal in these patients, since none of these tests are dependent upon factor VIII.[11] The patient's haemoglobin may be low because of acute or chronic blood loss. When large haematomas are present, the serum bilirubin may be increased.[11]

Even for minor procedures like dental extraction, the patient should be admitted to the hospital. In preparing patients with haemophilia A for surgery, factor VIII levels are routinely raised to approach 100% of normal activity. It should be maintained for the first 3 postoperative days from the day 4 onwards it should be maintained at 80%, from 7th day onwards it is allowed to decline to 40% of normal activity. The formula used to calculate the factor VIII dose is:

N = plasma volume (ml/Kg) x weight (Kg) x % activity increase

(N is the number of units required; Plasma volume is 40 ml/Kg for adults).[12]

Since half-life of factor VIII is about 12 hours, it must be administered twice daily.

Cryoprecipitate is next choice of blood product in the management of haemophilia A, which provides 80 units of factor VIII per bag. But as cryoprecipitate contains fibrinogen, serum levels of fibrinogen may rise and increase the risk of bleeding inspite of normal amounts of factor VIII if excessively transfused.[11]

The complicating factor in management of haemophilia A is development of antibodies to factor VIII after multiple exposures to factor VIII.[13] The use of recombinant factor VIIa has been suggested as an alternative to factor VIII to avoid inhibitor development.[10] Commercially produced factor VIII can be a vector for transmission of hepatitis A and HIV.[11]

The fibrinolytic inhibitors, epsilon amino-caproic acid (EACA) or tranexamic acid are commonly administered to reduce requirement of factor VIII. The vasopressin analogue DDAVP (Desamino-VIII-Darginine vasopressin), which increases plasma concentration of factor VIII, can be administered intravenously.[11]

Surgeons, Haematologists and Anaesthesiologists should carefully plan the peri-operative management of the patient with haemophilia.

Anaesthetic Management

Intramuscular pre medication should be avoided. Vascular access itself does not cause excessive bleeding and should be appropriate for the proposed procedure. Central venous lines should ideally be placed guided by ultrasound.

If the decision is made to proceed with neuraxial anaesthesia, a subarachnoid block using a small gauge spinal needle may be preferable to epidural anaesthesia.[14]

The decision to proceed with general anaesthesia is based on a risk-benefit analysis, weighing the risk of neuraxial bleeding with a regional anaesthetic *versus* benefits of general anaesthesia. After induction of anaesthesia, extra care should be taken in manipulation or intubation of the airway as it can cause submucosal haemorrhages, which can prove life threatening. Nasal intubation should be avoided, as it can prove traumatic and bleeding from the site can lead to aspiration. Care should be taken during positioning of the extremities and pressure points should be padded to prevent intramuscular haematomas or haemarthrosis.[12]

For closure of the wound absorbable suture material like catgut should be used and local pressure should be applied.[11] Anticoagulants such as Heparin and Warfarin are contraindicated for people with haemophilia as these can aggravate clotting difficulties.

Post-operatively, analgesics such as aspirin and other NSAIDs should not be given because they are well known to have the side effect of prolonged bleeding.[11] Safe analgesics include paracetamol, oxycodone, and morphine. Patient controlled analgesia is a safe and effective alternative to intramuscular injections.[11]

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