Clinical Reviews

Acquired haemophilia – A diagnosis not to be missed

S J Kitson & N Grigoropoulos

Keypoints
- Non-traumatic mucocutaneous bleeding in the older people could be a first presentation of acquired haemophilia
- Underlying conditions should be actively sought
- Prompt diagnosis and treatment reduces morbidity and mortality
- Early involvement of a haematologist is advised

Abstract
Acquired haemophilia is a rare , life threatening bleeding disorder characterised by the development of auto-antibodies to coagulation factor VIII. Diagnosis is based upon the clinical history of mucocutaneous haemorrhages combined with a selective prolongation of the APTT. The condition is associated with a wide range of conditions, such as autoimmune diseases , solid and haematological malignancies. Treatment involves controlling the bleeding manifestations and eliminating the inhibitor antibodies.

Three cases from our recent practice are used to highlight the variable severity of this condition.

Keywords
Acquired; Haemophilia; Bleeding; Factor VIII; Auto-antibodies.

Introduction
Acquired haemophilia is a rare, life-threatening bleeding disorder caused by the autoimmune depletion or inhibition of coagulation Factor VIII[1] (FVIII). The presence of antibodies to the factor results in inhibition of binding to von Willebrand factor, activated factor IX and negatively charged phospholipids, thereby blocking the normal coagulation process.[2]

Three cases which recently presented to our department are presented in Box 1. These cases highlight the variable nature of the condition and the treatment options, which are discussed in more detail below.

Epidemiology and associated conditions
The incidence is estimated to be 0.2–1.0 cases per million per year, though this may be an underestimate due to difficulties in recognising and diagnosing the disease.[3] There is a biphasic age distribution with a peak in the third decade, when the disease occurs during the post-partum period, and a second peak between the ages of 68 and 80 years.[4] The two sexes are equally affected. The mortality rate associated with acquired haemophilia is 7.9–22%, depending upon the underlying aetiology and age of the patient,

Case 1: An 81-year-old man, known to have ischaemic heart disease, benign prostatic hypertrophy, diabetes and obesity, described recurrent epistaxes and the occurrence of spontaneous haematomas on his upper limbs over one week. The APTT (activated partial thromboplastin time) was prolonged and failed to correct when mixed with control serum, suggesting a coagulation factor inhibitor. Factor VIII (FVIII) activity was significantly reduced and the Bethesda assay showed an inhibitor titre of 320 units, confirming the diagnosis of acquired haemophilia. Bleeding was controlled with tranexamic acid (500mg bd) and the FVIII level rose with the addition of prednisolone and cyclophosphamide to the treatment regimen. Further investigation revealed a sigmoid colon carcinoma which may have been the underlying cause for his acquired haemophilia.

Case 2: A 74-year-old, previously healthy woman presented with recurrent fresh rectal bleeding. Upper and lower gastrointestinal endoscopy revealed haemorrhoids which were treated endoscopically. Readmission was prompted by non-traumatic haematomas with symptomatic anaemia. Clotting studies revealed a prolonged APTT with low FVIII levels in the presence of inhibitor antibodies. Steroid and cyclophosphamide treatment was unsuccessful. Bleeding was eventually controlled with recombinant FVIIa treatment, as well as tranexamic acid, vitamin K and blood transfusions. Extensive investigations have failed to reveal an underlying cause for her acquired haemophilia.

Case 3: A 75-year-old woman with known metastatic bladder carcinoma was admitted electively for a blood transfusion and found to have minor bruising. Subsequent tests confirmed acquired haemophilia. Symptomatic improvement was achieved with prednisolone and tranexamic acid.

Box 1. Recent cases from our clinical practice.

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with most haemorrhagic deaths occurring within the first few weeks following presentation[3]. The leading cause of death in these patients is often not the bleeding itself, rather the complications of treatment, including neutropenia secondary to immunosuppression and transfusion reactions.[4]

Up to 50% of cases of acquired haemophilia are associated with underlying conditions such as autoimmune diseases (including rheumatoid arthritis, systemic lupus erythematosis, myasthenia gravis), inflammatory bowel disease, psoriasis, pemphigus, asthma and COPD, diabetes, pregnancy, allergic drug reactions (to penicillins and sulfonamides) and a range of malignancies, both solid and haematological.[3,6] In the remaining instances where a cause for the development of antibodies cannot be found, the condition is considered idiopathic.

Clinical Features

Acquired haemophilia should be suspected in patients presenting with non traumatic bleeding into the skin, soft tissues, muscles or mucous membranes, gastrointestinal and genitourinary bleeds, epistaxis or retroperitoneal haematomas as well as those with prolonged post partum bleeds and excessive bleeding following trauma or surgery. This is in contrast to the congenital haemophilias, where haemarthoses are the usual presenting feature.[5]

Clinical features of the associated conditions, listed above, should also be sought.

Investigations

The diagnosis is characterised by normal platelet count and International Normalised Ratio (INR), in the presence of a prolonged Activated Partial Thromboplastin Time (APTT), which fails to correct upon mixing with normal serum. Table 1 illustrates other conditions associated with a prolonged APTT and the differences from acquired haemophilia. Confirmation requires the quantification of FVIII levels by regional laboratories as well as the presence of a FVIII inhibitor, measured with the Bethesda assay, in the absence of family or personal history of bleeding.[5] Up to 15% of healthy individuals may have low titres of FVIII inhibitor antibodies without symptoms.[1]

Further investigation should also include a search for a potential underlying cause; in most cases the nature and extent of this will be guided by the history and examination findings.

Management

Prompt fluid resuscitation, appropriate blood product support and early involvement of a haematologist are essential. The two aims of management are safe achievement of haemostasis and elimination of the inhibitor.

In 25% of cases, the antibodies will remit spontaneously and no intervention is required.[6] There is a paucity of randomised controlled trials of immunosupressants for the treatment of acquired haemophilia. However, the UKHCDO (United Kingdom Haemophilia Centre Doctors Organisation) surveillance programme suggests that the use of prednisolone at a dose of 1 mg/kg/day results in the disappearance of the inhibitor in 60–70% of cases. Between 70–80% of patients will respond to the combination of corticosteroids and oral cyclophosphamide (50–150 mg/day). However, the median time to remission, regardless of treatment, is 35 days, with overall survival unaffected by the addition of further immunosuppressive drugs.[1]

Serial measurements of the factor and its inhibitor, plus the presence of bleeding complications, are useful guides to monitor treatment.[2] Response to treatment is defined as return to normal FVIII activity and undetectable inhibitor titres. Second line agents should be considered for use when normalisation of the coagulation picture is not achieved within 6–8 weeks. Alternative agents include rituximab and cyclosporin, with immunoabsorption reserved for those with severe bleeds requiring rapid control.[8–10] It has been suggested that the selective depletion of the B cells responsible for the synthesis of the antibodies causing acquired haemophilia through the use of rituximab should increase the proportion of patients achieving remission. However, this has not yet been proven in studies.[8]

High dose intravenous immunoglobulin has been shown to be beneficial in a small proportion of patients who have failed to respond completely to immunosuppressive treatment, with a fall in inhibitor antibodies following a 2- or 5-day induction course followed by maintenance therapy, if required.[4] Administration of intravenous immunoglobulin appears to displace inhibitor antibodies temporarily through interacting with their ability to bind to receptors and preventing further antibody synthesis.[11] There is, however, a proportion of patients who fail to respond to this treatment; even for those who do respond the level of inhibitor rarely decreases to be undetectable.[11]

Bleeding may be controlled with activated prothrombin complex concentrate, porcine factor VIII, recombinant factor VIIa (rFVIIa) or, in mild cases, tranexamic acid. rFVIIa is thought to compete with the natural protein in binding to tissue factor, thereby increasing the pool of free factor VII available to activate prothrombin and initiate the clotting cascade.[12] The results available from a

Condition causing prolonged APTT	Differentiation from acquired haemophilia
Heparinisation	Accurate drug history of heparin use
Disseminated Intravascular Coagulation	Prolonged INR, low platelet count, raised fibrinogen and D-dimers
Congenital haemophilia	Family history, haemarthroses rather than mucosal pattern of bleeding
Liver Disease	Prolonged INR, raised liver enzymes
Von Willebrand's disease	Often low von Willebrand's factor (vWF) levels, reduced vWF function
Lupus anticoagulant	Presence of anticardiolipin antibodies, Exner test

Table 1. Conditions causing prolongation of APTT.

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limited number of trials are encouraging, with one study claiming that 100% of patients treated with recombinant factor VIIa, as a first line therapy, achieved good control of haemorrhage. When used as a salvage therapy, 75% of patients achieved a good response, 17% a partial response and 8% a poor response. The overall mortality rate for the treatment group was 7.9%, which is lower than that reported from other studies. However, the recombinant coagulation factor has a half-life of only two hours and repeated courses of treatment may be required.[13]

These haemostatic agents have not been compared in head to head trials, and ultimately, choice of agent should be guided by local experience. Those patients with low titres of inhibitor antibodies and measurable FVIII levels may respond to DDAVP, which promotes the production of anticoagulant factors by the liver.[1]

The use of replacement FVIII in the treatment of acquired haemophilia is limited. The autoantibodies generated in a proportion of patients with congenital haemophilia exhibit type I kinetics when binding to the FVIII molecule, i.e. there is a linear relationship between the concentration of the inhibitor antibody and the reduction in the level of the coagulation factor. At a critical autoantibody level, therefore, no FVIII can be measured. This contrasts with the autoantibodies seen in the acquired disease which demonstrate type II kinetics where the inactivation pattern is non linear, but shows a rapid initial inactivation phase followed by a slower period of equilibrium. Although this means that some FVIII is always measurable, this is often insufficient to prevent haemorrhages.[14] While the administration of FVIII to patients with congenital haemophilia can saturate the inhibitor antibodies and thereby prevent bleeding, the same is not true when used as a sole therapy in acquired haemophilia. It is only of benefit in this instance when all the autoantibodies have been removed through immunoabsorption.

Whilst combined immunosuppression regimes can result in up to 80% of patients achieving remission, follow up by haematologists is necessary as 20% of patients will suffer a relapse of the disease with a further 70% achieving a second remission. Of these, some will require long-term immunosuppression.

References

1. Hay CR, Brown S, Collins PW, *et al*. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol* 2006; **133(6):** 591–605.
2. Baggio LN, Green D. Acquired Haemophilia. *Rev Clin Exp Haematol* 2001; **5:** 389–404.
3. Franchini M, Gandini G, Di Paolantonio T, *et al*. Acquired Haemophilia: A concise review. *Am J Hematol* 2005; **80:** 55-63.
4. Schwartz RS, Gabriel DA, Aledort LM, *et al*. A prospective study of treatment of acquired (autoimmune) factor VIII with high dose intravenous gammaglobulin. *Blood* 1995;**86 (2):**797–804.
5. Cohen AJ, Kesler CM. Acquired inhibitors. *Bailleres Clin Haematol* 1996; **9:** 331–354.
6. Hay CR. Acquired Haemophilia. *Baileres Clin Haematol* 1998; **11**: 287–303.
7. Lottenberg R, Kentro TB, Kitchens CS. Acquired Haemophilia. A natural history of 16 patients with factor VIII inhibitors receiving little or no therapy. *Arch Intern Med* 1987; **147:** 1077–1081.
8. Stasi R, Brunetti M, Stipa E, *et al*. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. *Blood* 2004; **103(12):** 4424–4428.
9. Hart HC *et al*. Transplant Proceedings 1998; **20:** 323–328.
10. Zeitler H, Ulrich-Merzenich G, Hess L, *et al*. Treatment of acquired haemophilia by the Bonn-Malmo Protocol: documentation of an in vivo immunomodulating concept. *Blood* 2005; **105:** 2287–2293.
11 Sultan Y, Kazatchkine MD, Nydehgger U, *et al*. Intravenous immunoglobulin in the treatment of spontaneously acquired factor VIII:C inhibitors. *Am J Med* 1991; **91:** 35–39.
12. Hoffman M, Monroe DM, Roberts HR. Human monocytes support factor X activation by factor Viia, independent of tissue factor:implications for the therapeutic mechanism of high dose factor VIIa in haemophilia. *Blood* 1994; **83(12):** 3828–3829.
13. Hay CR, Neginer C, Ludham CA. The treatment of bleeding in acquired haemophilia with -recombinant factor VIIa: a multicentre study. *Thromb Haemost* 1997; **78(6):** 1463–1467.
14. Lusher JM. Acquired inhibitors to factor VIII in non-hemophiliac patients. In Kessler C, ed. Acquired haemophilia (ed. 2nd) Princeton NJ. 1995.

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