Acquired hemophilia A: pathogenesis and treatment

A P P E A R T

Acquired hemophilia A is an autoimmune disease caused by an inhibitory antibody to factor VIII. The severity of bleeding varies but patients remain at risk of life-threatening bleeding until the inhibitor has been eradicated. The cornerstones of management are rapid and accurate diagnosis, control of bleeding, investigation for an underlying cause, and eradication of the inhibitor by immunosuppression. Patients should be managed jointly with a specialist center even if they present without significant bleeding. Despite an extensive literature, few controlled data are available and management guidelines are based on expert opinion. Recombinant factor VIIa and activated prothrombin complex concentrate are equally efficacious for treating bleeds and both are superior to factor VIII or desmopressin. Immunosuppression should be started as soon as the diagnosis is made. Commonly used regimens are steroids alone or combined with cytotoxic agents. Rituximab is being used more commonly but current evidence does not suggest that it improves outcomes or reduces side effects.

Introduction

Acquired hemophilia A (AHA) is a bleeding disorder caused by polyclonal IgG1 and IgG4 autoantibodies to the factor VIII (FVIII) A2 and C2 domain. Morbidity and mortality are high secondary to age, underlying diseases, and the toxic effects of immunosuppression and bleeding, and because of this, patients should be managed by specialist centres. It is important that the disorder is recognized and diagnosed promptly; however, in 25% of patients, diagnosis is not made for more than a week after symptoms develop and this puts patients at unnecessary risk of severe bleeding. Laboratories should have systems in place that automatically investigate an isolated prolonged activated partial thromboplastin time (aPTT) so that, even if the clinician who has ordered the coagulation test has not considered AHA as a differential diagnosis, the patient is identified and treated promptly.

The incidence of AHA was 1.48 per million/year in the only two studies in which patients were linked to a defined population. Both these studies are from the United Kingdom (UK) and the incidence in other populations has not been reported. Incidence increases with age and is estimated to be 0.045/million/year in children under 16 compared with 14.7/million/year in people over 85 years. It is likely, however, that AHA is under diagnosed, especially in elderly patients. The literature on AHA has recently been significantly expanded by data on 501 patients prospectively reported to the European Acquired Haemophilia Registry (EACH2).

Pathogenesis

AHA is associated with autoimmune diseases, such as rheumatoid arthritis, polyarthritis rheumatic, and systemic lupus erythematosus; malignancy; pregnancy and dermatological disorders, such as pemphigoid. The apparent association with commonly used drugs, such as penicillin, is almost certainly due to chance rather than a genuine association. In about half of cases, no underlying cause is found.

Non inhibitory anti-FVIII antibodies are found in healthy people. The cause of breakdown in peripheral tolerance to FVIII appears to be due to a combination of environmental and genetic factors and may differ depending on the underlying disease. It is unclear, for example, why AHA is often diagnosed long after the presentation of an underlying autoimmune disease and at a median of 3 months postpartum rather than during the pregnancy. The importance of T cell interactions in the pathogenesis of AHA is supported by associations found with polymorphisms in the cytotoxic T-lymphyocyte-associated protein 4 gene and specific HLA class II molecules, such as DRB1*16 and DRB1*0502. Polymorphisms in the FVIII gene that do not cause low FVIII levels have been found in patients with AHA, and these may be associated with a loss of tolerance. The potential role of antibodies that inactivate FVIII and activate factor IX by hydrolysis is also of current interest but the precise role in the pathogenesis of AHA is unclear. More information is needed on the pathogenesis of AHA to help understand the biology of the disease and to design more effective and less toxic treatment regimens.
Diagnosis

Clinical features

Patients usually present with subcutaneous bruising, mucosal, and soft tissue bleeds, such as intracranial hemorrhage, muscle bleeds, and retroperitoneal hematoma (Figure 1 and Figure 2). Bleeding following invasive procedures is almost inevitable but hemarthroses are uncommon.1,2,4,20 The severity of bleeding is very variable, and 25-33% of patients do not require haemostatic therapy.1,10 Despite this, patients remain at risk of life threatening bleeding until the inhibitor has been eradicated.3

Laboratory diagnosis

Investigation reveals a prolonged activated partial thromboplastin time and a normal prothrombin time (Figure 1 and Figure 3). Anti-FVIII antibodies are time and temperature dependent and so the aPTT corrects less after 1-2 hours incubation with normal plasma than after an immediate mix. The diagnosis is confirmed by a low FVIII and a raised inhibitor titre on Bethesda assay. Acquired inhibitors often exhibit complex kinetics and residual FVIII can be measured, this makes establishing an accurate inhibitor titre difficult. It is common practice to report the titre based on the dilution in the Bethesda assay closest to 50% inhibition. The anti-FVIII antibody may interfere with the measurement of other intrinsic factors. Dilution experiments will demonstrate a progressive increase in these apparently decreased coagulation factors whilst FVIII remains low. A lupus anticoagulant may also interfere with coagulation factor assays, potentially leading to diagnostic difficulties. An ELISA assay may be useful in complicated cases.5,21 There have been reports of anticoagulant and anti-platelet drugs either masking or being associated with AHA, and it is important to measure the aPTT, as well as the INR when patients on warfarin present with abnormal bleeding.5,33

Pregnancy related acquired hemophilia

AHA is a very rare complication of pregnancy13,26-28 but accounts for most cases of AHA in people below the age of 40 years.13 It affects about 1 in 350,000 births in the UK and a similar incidence has been reported in Italy.1,13 Diagnosis is made a median of 3 months postpartum although AHA may present up to a year after delivery. Abnormal bleeding at the time of delivery is also common. One of 42 cases in the EACH2 registry presented ante-partum although there was evidence for undiagnosed ante-partum inhibitors in a further seven.

Retrospective reviews have suggested a longer time to remission in pregnancy-related AHA compared with other aetiologies,26-28 although this was not seen in the 42 patients reported to EACH2 and spontaneous remissions are recognized. Choice of immunosuppression has influenced the potential side effects of cytotoxic drugs in women of childbearing age. Rituximab has been used successfully in postpartum AHA but data do not support that it is superior to other immunosuppression.11,28

The risk of relapse in subsequent pregnancies is not known. In one study, AHA recurred in four of six subsequent pregnancies in three patients;34 however, no relapses were reported in nine subsequent pregnancies in another study, and the Italian Registry reported no relapses amongst four patients.13 The antibody may affect the FVIII level of the fetus, and this should be anticipated at the time of delivery.10,32

Treatment

Treatment should arrest hemorrhage, eradicate the inhibitor, treat underlying disease, and protect against trauma and non-essential invasive procedures (Figure 1). Patients should be managed by an experienced hemophilia center even if the initial presentation appears benign. Invasive procedures should be avoided, and venepuncture and blood pressure monitoring should be kept to a minimum (Figure 2). Patients should be educated to recognize and report symptoms early.5,13

Haemostatic management

Bleeds may be very severe, and prompt haemostatic control is important to reduce morbidity and mortality. Available haemostatic agents do not have predictable efficacy and so regular clinical review supported by appropriate imaging and measurement of hemoglobin level is required. In contrast, many patients do not need haemostatic treatment, and subcutaneous bleeding, even if extensive, can be managed conservatively (Figure 3).5,33

The current options for haemostatic control are the use of bypassing agents, human FVIII (potentially with immunoadsorption), and DDAVP. Haemostatic therapy often needs to be continued at a reduced dose, and frequency after the bleeding has stopped to prevent recurrence. Mucosal bleeds benefit from concomitant therapy with an anti-fibrinolytic agent.

Bypassing agents

At the time of writing, the available bypassing agents are Novoseven (rFVIIa) and the activated prothrombin complex concentrate Factor Eight Inhibitor Bypassing Activity (FEIBA). A retrospective report of 139 patients treated with rFVIIa described 182 bleeds. In the 103 episodes where rFVIIa was used as first line therapy, it was effective or partially effective in 95%.14 A similar first line efficacy was reported to the EACH2 registry.29 When used as second line therapy, rFVIIa was reported to have 80% efficacy and in 57 surgeries, an effective or partially effective response was reported in 86% of cases.34

In the EACH2 registry, 64 bleeds were treated with FEIBA with 94% efficacy.10 Similar results were found in a retrospective study of 34 severe and moderate bleeds. A median of six infusions were needed for moderate bleeds with 100% haemostatic efficacy at a median of 36 hours compared with ten infusions for severe bleeds with 76% haemostatic control at a median of 48 hours.35

Although rFVIIa and FEIBA have not been directly compared in AHA, a rigorous analysis of data in the EACH2 registry suggests the two agents have indistinguishable haemostatic efficacy.35 The choice of agent should depend on considerations, such as the patient’s previous response, dosing schedule, use of plasma-derived products, and cost. If first line therapy fails, the alternative bypassing agent may be successful and should be tried at a relatively early stage.
Both agents are associated with thrombotic events in AHA. Analysis of 139 AHA patients treated with rFVIIa reported 12 (8.6%) thrombotic events, mainly arterial, in ten patients, four of whom died, although the direct relationship with rFVIIa is not clear and the study methodology would tend to overestimate the incidence. Each2 reported eight thrombotic events associated with haemostatic therapy with a bypassing agent out of 237 (3%) patients. These events were seen with both rFVIIa and FEIBA. Inevitably, the risk of arterial thrombosis in patients with AHA treated with bypassing agents will be higher than in congenital hemophilia because of the additional cardiovascular risk factors in elderly patients and the complex clinical situation of many patients. Treatment of significant

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**Figure 1. Overview of the management of acquired haemophilia A.**

- **Suspected AHA**
  - Spontaneous subcutaneous bruising, muscle and retroperitoneal bleeds and unexpected bleeding after invasive procedures
  - Elderly patients or those with autoimmune disease, malignancy or pregnancy within the last year

- **Screening tests:** FBC, prothrombin time, activated partial thromboplastin time and fibrinogen.
  - Suspect diagnosis if aPTT is prolonged and PT normal.
  - Perform aPPT correction test but if clinical symptoms are suspicious proceed to further investigation even if full correction is seen.
  - See figure 3

- **Further Investigations**
  - aPTT correction studies immediate and after 2 hour incubation
  - Assay FVIII, FIX, FXI, FXII
    - May need to repeat with diluted samples
  - Inhibitor titre by Bethesda assay
  - Test for Lupus anticoagulant
  - See figure 3

- **Management of bleeds**
  - Treat bleeds early:
    - Use bypassing agent (rFVIIa or aPCC)
    - Subcutaneous bleeds are unlikely to need haemostatic treatment even if extensive
    - Protect against further bleeding
      - Minimise venepuncture and blood pressure monitoring. Only essential surgery can be considered and must be in a specialist centre

- **Inhibitor eradication**
  - Auto-immune disease: Anti-nuclear antibodies, double stranded DNA, rheumatoid factor
  - Malignancy: Chest X-ray, body CT scan, tumour markers, prostate specific antigen
    - In cases resistant to immunosuppression consider occult malignancy

- **Prevent thrombosis**
  - Start venous thromboprophylaxis for in-patients as soon as FVIII is above 100 IU/dL
  - Consider using bypassing agents above licensed doses only in exceptional cases

- **Relapse seen in up to 20% of cases**
  - Regular follow up for at least 12 months to detect relapse early
  - Consider further investigation for malignancy at time of relapse
  - Check FVIII and inhibitor before any invasive procedure
bleeding should not be withheld because the benefits clearly outweigh the thrombotic risk. However, minor bleeding, such as subcutaneous, should not be treated without careful consideration of the risk involved because these bleeds will usually resolve spontaneously. The approach of using up to 270 µg/kg rFVIIa should be considered only in exceptional circumstances in patients with AHA because this dose has not been shown to be safe in this patient group or efficacious for treating the types of bleeds associated with AHA. Furthermore, the use of combined rFVIIa and FEIBA should be avoided except in life-threatening situations unresponsive to each agent alone.

**Human FVIII**

Human FVIII will usually be inadequate haemostatic therapy unless the inhibitor titre is low. FVIII is less effective than rFVIIa or FEIBA for the treatment of bleeds in AHA. The dose of FVIII required will need to be sufficient to overcome the inhibitor and provide an adequate haemostatic level. Although formulae have been suggested for calculating the dose, the inaccuracies inherent in the laboratory measurement of inhibitor titres in AHA make these at best very rough approximations, and regular monitoring of plasma FVIII level and clinical response is required.

The use of human FVIII in combination with immunoabsorption is more likely to result in haemostatic FVIII levels despite higher anti-FVIII inhibitor titres. This treatment strategy may be useful as first line therapy or if bypassing agents have failed, although it is available in only a very limited number of centres.

**Porcine FVIII**

In AHA, the inhibitor titre to porcine FVIII is usually 5-10% of the human titre and so porcine FVIII may achieve haemostatic levels in situations where human FVIII is ineffective. Porcine FVIII is no longer available, and a recombinant B-domain deleted porcine FVIII is under investigation and trials in AHA are awaited.

**Desmopressin**

Some patients with a low titre inhibitor and baseline FVIII above 5 IU/dL may respond to a desmopressin infusion; however, response is unpredictable and haemostatic efficacy is not as good as that seen with bypassing agents.

**Management of surgery**

Invasive procedures are associated with significant risk of severe bleeding because hemostasis cannot be guaranteed. Only procedures that are absolutely unavoidable should be considered and even then, the benefits carefully weighed against the risks of delaying until the FVIII level has increased. Treatment options include the use of bypassing agents, immunoabsorption with FVIII infusion, and previously porcine FVIII.

**Inhibitor eradication**

Patients should be immunosuppressed to eradicate the inhibitor as soon as a diagnosis has been made (Figure 1). There are numerous reports in the literature but data are often difficult to interpret because different endpoints and definitions are used and studies are almost invariably reports of cohorts without controls. The majority of papers are case reports, single centre cohort studies, or retrospective surveys from specialist centers and so are likely to reflect more severely affected patients; publication bias of good outcomes is inevitable. About 25% of patients have a spontaneous remission, although the associated morbidity is significant. The literature, therefore, must be treated with caution, and the conclusions drawn from many studies are limited.

Options for immunosuppression are steroids, cytotoxics (cyclophosphamide, azathioprine, vincristine, or combination therapy), rituximab, cyclosporin A, plasmapheresis or immunoabsorption, and FVIII immune tolerance. Regimens needed to be compared with regard to the proportion of patients achieving complete remission (CR) and the time this takes, the relapse rate, and the morbidity associated with the treatment. Recent studies with adequate follow up have reproducibly reported a relapse rate of 10-20% and some patients require long term immunosuppression to prevent relapse. The absence of any reported relapses in many published studies suggests the results need to be interpreted with caution. Meta-analyses have identified older age and underlying malignancy as risk factors for mortality whilst achieving a CR is protective.

**Steroids and cytotoxic agents**

The only prospective randomized study performed to date enrolled 31 patients. This study is often misinterpreted as providing evidence to support the addition of cyclophosphamide to steroids if a CR has not been achieved by 3 weeks. The study data, however, do not provide any evidence that this strategy is superior to any other. Patients were treated initially with prednisolone 1 mg/kg for 3 weeks after which ten patients were in CR. Four patients were randomized to continuing treatment with prednisolone alone and this led to CR in three (75%). Of the ten patients randomized to adding cyclophosphamide, five (50%) achieved CR and of those in whom cyclophosphamide was substituted for prednisolone, three out of six (50%) achieved CR. There was no difference between the treatment arms.

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**Figure 2. Typical bleeding in acquired haemophilia. The disorder in this patient was associated with Castlemann’s disease and treatment with α interferon. The bleed was caused by venepuncture.**
A non-randomized, prospective national consecutive cohort study compared patients treated with steroids versus steroids and cytotoxics. The design of this study makes it less prone to selection bias than other cohort studies. The 34 patients treated with steroids had 76% CR at a median (95% confidence interval) of 49 (31-62) days compared with 78% CR at 39 (34-57) days for the steroids and cytotoxics group. There was no statistically significant difference between the treatment arms and mortality was not different. A meta-analysis of 20 studies reported that the use of steroids and cyclophosphamide resulted in more patients achieving CR compared with steroids alone. A more recent meta-analysis of 32 non-randomized studies (that included the 20 reports used by Delgado et al.) found that patients receiving combination chemotherapy had reduced odds of persistent hemophilia (OR 0.04, CI 0.01-0.23) compared with steroid therapy alone (OR 0.38, CI 0.14-0.94).

The most robust analysis available to date comes from the EACH2 registry of 331 patients. Patients treated with prednisone alone were compared with those treated with prednisone and oral cyclophosphamide. The groups were matched for age, gender, inhibitor titre, FVIII level, and underlying etiology by logistic regression and propensity score. The study reported an odds ratio (95% confidence intervals), 3.25 (1.51-6.96), \( P < 0.001 \) in favor of combined therapy despite the prednisone alone arm receiving a higher dose of steroids. Despite the different CR rates after first line therapy, the final outcome in terms of survival and sustained remission was the same for both treatments in all large studies. Interpretation of the current data suggests that the combination of steroids and cyclophosphamide is more likely to result in a stable remission than steroids alone but the final outcome is not better.

Regimens involving combination chemotherapy have been reported to have high success rates but without comparative groups, the results must be treated with caution because numbers are very small. Whichver regimen is used, 3 weeks appears to be too short a time to assess outcome because the median time to remission has been reproducibly been shown to be about 5 weeks.

**Intravenous immunoglobulin**

The available evidence strongly supports the view that intravenous immunoglobulin (IVIG) as a single agent or in combination with steroids and cytotoxics is not useful in inhibitor eradication in AHA. Although a study of 16 patients treated with IVIG reported that three subjects with an inhibitor titre less than or equal to 1 BU/mL achieved an undetectable inhibitor titre and normal FVIII level; one patient also received concomitant steroids. This means that for patients treated with IVIG alone, 2/16

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**Figure 3. Investigation for possible acquired hemophilia A.**
(12.5%) responded, a rate lower than that seen for spontaneous remission (25%). A study of six patients treated with steroids and IVIG reported a CR rate of 66%, similar to other reports of steroids alone. A larger study that compared non-randomized patients who either did or did not receive IVIG, the EACH2 registry (unpublished data) and a literature review all show no benefit of IVIG.

**Rituximab**

Rituximab has become a popular treatment for AHA but case reports, patient cohorts, and reviews of the literature have not demonstrated that it is superior to other regimens. A literature review of 71 patients treated with rituximab and a variety of immunosuppressive agents found a response rate of over 90% but the authors were cautious about interpreting the results and suggested that rituximab should be used as a second line agent in combination with steroids. Another literature review suggested that 42 patients treated with rituximab had similar outcomes to 44 control patients treated with cyclophosphamide and steroids. Data from EACH2 support these findings, 30/51 (59%) patients treated with a rituximab-based regimen achieved a stable remission and this was less than for patients treated with steroids and cyclophosphamide. The 12 patients treated with rituximab alone had only a 42% response rate.

Rituximab does not result in more rapid remission and may be associated with slower remissions. The 51 patients in the EACH2 registry had a median (inter-quartile range) time to a negative inhibitor of 65 (29-144) days, a slower response compared with other regimens. This finding is supported by other reports.

The current data on rituximab are difficult to interpret, however, there is no published evidence to support the hypothesis that rituximab-based regimens result in more patients achieving CR or a more rapid response. Some patients resistant to standard first line regimens respond to second line rituximab. There is no evidence to support the use of rituximab in patients with high titre inhibitors as some authors have suggested.

**Cyclosporin A**

A number of cases have been reported in which cyclosporin A has induced CR following failed first line therapy.

**Immune tolerance**

The use of FVIII in conjunction with immunosuppressive agents in AHA has been reported. The rationale is that FVIII may stimulate antibody producing cells into division, making them more susceptible to cytotoxic agents. The lack of adequate controls in these studies means that direct assessment of the role of FVIII cannot be made.

A report of patients treated with three weekly infusions of FVIII combined with vincristine, cyclophosphamide and steroids resulted in a 92% complete remission rate in 12 patients after one to three courses. The same group, however, later published a report in six patients who were treated with vincristine, cyclophosphamide, and steroids without FVIII and found 83% remission after one to seven courses. These data are difficult to interpret, the remission rates are similar to other studies, given the number of patients involved, but the time to remission appears to be relatively short. The effect of FVIII is unclear because the intensity of immunosuppression was greater than for many other protocols.

Infusion of FVIII on a daily basis (30 IU/kg/day for one week, 20 IU/kg/day for a second week, and 15 IU/kg/day for a third week) combined with intravenous cyclophosphamide and methylprednisolone reported complete remission in 93% of 14 patients after a median of 4.6 weeks, compared with 67% remission at a median of 28.3 weeks in six historical controls treated with steroids-cyclophosphamide. Although this is a relatively high CR rate, the median time to response is similar to studies that did not use FVIII and the median time of 28.3 weeks to CR in the controls is long. Taken together, these reports are insufficient to conclude that immune tolerance with FVIII is beneficial in AHA, and the high cost of FVIII in these protocols should be taken into account. Controlled studies appear to be the only way that this question can be answered.

**Immunoabsorption**

A cohort of 35 patients with severe bleeding was treated with a combination of oral cyclophosphamide 1-2 mg/kg daily, prednisolone 1mg/kg daily, immunoabsorption on day 1-5 weekly, IVIG 0.3 g/kg day 5-7 weekly, and FVIII 100 IU/kg daily. Rapid control of bleeding was reported with an undetectable inhibitor at a median of 3 days (95% CI 2-4) and CR in 88% of patients at a median of 14 days (95% CI 12-17). The same team has now published data on 67 patients with similar outcomes. Although no control patients are reported and the cost of the FVIII is very high, this treatment appears to rapidly control bleeding and induce CR in those that respond. It should be considered in severely bleeding patients, especially those unresponsive to bypassing agents.

**Venous thromboprophylaxis**

Remission of AHA is often associated with high FVIII levels, and because patients are likely to have other risk factors for venous thrombosis, they should be treated with appropriate venous thromboprophylaxis.

**Relapse**

Relapse has been reported in 20% of 102 patients at a median of 7.5 months (range 1 week to 14 months). This finding has been confirmed by data from the EACH2 registry, which reported relapse in 18% of those treated first line with steroids, 12% for steroids and cyclophosphamide, and 1% in those treated with first line rituximab after a median of 4 months. Patients, therefore, require prolonged follow up and should be advised to report symptoms of bleeding or bruising early (Figure 1).

**Conclusions on inhibitor eradication**

There is consensus that immunosuppression aimed at eradicating the inhibitor should be started as soon as the diagnosis of AHA has been made. Available data suggest that a combination of steroids and cyclophosphamide may result in a higher remission rate than steroids alone. Rituximab-based regimens have no advantage over other treatment; however, long-term outcome is not affected by the choice of first line therapy. Until further data become available, it is not possible to make definitive recommendations, and first line therapy is at the discretion of the cli-
niciation based on the clinical circumstances and taking into account the potential side effects of each treatment. If a patient does not respond to first line steroids then a cytotoxic agent or rituximab can be added. Similarly, if a patient fails first line rituximab then steroids and cytotoxic agents may be successful. Cyclosporin A is a useful second line option. A regimen based on high dose FVIII and immunoadsorption can be considered for patients with severe bleeding.

Future developments

Clinical progress in AHA is hampered by small numbers of patients and difficulties in performing randomized studies. In the area of bleed control, it is recognized that the haemostatic efficacy of all agents is unpredictable. Understanding why the bleeding phenotype in AHA differs from congenital haemophilia may lead to a better understanding of the mechanism of haemostatic failure and possibly translate into improved haemostatic management. Access to new haemostatic agents is important, and studies on the safety and efficacy of recombinant B-domain deleted porcine FVIII and longer or enhanced acting rFVIIa molecules are awaited.

Studies in the field of inhibitor eradication are a major challenge, demonstrated by the fact that the literature contains only one randomized prospective clinical trial, which was unable to recruit sufficient patients to provide interpretable data. Trials that compare conventional steroid and cytotoxic agents with rituximab or investigate the role of FVIII would be useful. These trials will need to recruit hundreds of patients to be adequately powered and require international collaboration and significant resources to perform. It must be recognized that these trials may not be feasible and that registry data will be the best available data for the foreseeable future.

References