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Acquired Hemophilia: An Overview

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ABSTRACT

Acquired hemophilia A (AHA) is a rare disorder, having an incidence of approximately one per million per year with a one in five mortality rate**.** It is due to autoantibodies against coagulation factor VIII which neutralizes the procoagulant activity and results in severe and life-threatening bleeding. It is seen in patients with no prior history of hemophilia A. It may be associated with pregnancy, autoimmune diseases, malignancy, infections or medication. It occurs mostly in elderly. Approximately 50% of the patients have no underlying pathological conditions. Clinical manifestations include spontaneous hemorrhages in the skin, muscles or soft tissues or excessive bleeding during surgery. Hemarthrosis, hallmark of congenital severe hemophilia A is seldom seen. The diagnosis is based upon reduced FVIII levels and isolated prolongation of activated partial thromboplastintime (aPTT) which does not normalize after addition of normal plasma. The treatment involves removal of antibodies and maintaining effective hemostasis during bleeding episodes. Treatment options for removal of antibodies are immunoadsorption, immunosuppression or immune tolerance induction (ITI). Treatment of acute bleeding episodes includes use of bypassing agents like recombinant activated factor VII and activated prothrombincomplex concentrate in patients with high titer of inhibitors or antifibrinolytics, 1-deamino-8-D-arginine vasopressin (DDAVP) or FVIII concentrates in patients having low titer of inhibitors. Rituximab, an anti-CD20 monoclonal antibody can be used alone or in combination with immunosuppressive therapy in patients not responding to standard immunosuppressors.

Keywords: Acquired hemophilia A(AHA), hemophilia A

INTRODUCTION

Acquired hemophilia A (AHA) is a rare bleeding disorder seen in patients with no family history of hemophilia. It occurs due to the development of autoantibodies against endogenous factor VIII (FVIII). Clinically, it is similar to severe hemophilia A and is associated with spontaneous bleeds, which is usually mucocutaneous, soft tissue or gastrointestinal. Hemarthrosis is uncommon in AHA [1,2]. These bleeds are often difficult to predict and doesn't correlate with the inhibitor titers or FVIII levels. The reported mortality is 9.7% to 33% [1–4]**.** It is associated with prolonged APTT which does not correct on addition of normal plasma. The diagnosis is confirmed from reduced FVIII levels and detectable FVIII inhibitor. It is much more common in adults [2,4,5].

FVIII inhibitors in AHA are mostly IgG1&4 autoantibodies following second-order kinetics and react with the same regions of the FVIII molecule (i.e., A2 and C2 domains) those targeted by FVIII alloantibodies[6]. The antibodies interfere with the coagulant activity of FVIII.

Incidence

The reported incidence of AHA is 1.34–1.48 cases per million per year [1]. Increasing age attributes to poor prognosis. Up to 85% of affected individuals are older adults (60 years) with no gender predilection [2]. The age distribution for

autoantibodies is typically biphasic with an initial smaller peak between 20 and 30 years followed by a larger peak in the 8thdecade [7]. The early adulthood shows a slightly female preponderance [8].

Etiology

In 50% of cases, FVIII autoantibodies occur in patients not having any underlying medical condition. In the rest of the patients, autoantibodies may arise in the context of postpartum period, autoimmune diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), thyroiditis or may due to underlying malignancies, infections, vaccination or even medications [9–11].

The most common associated etiology is autoimmune, with the two largest series of studies displaying an autoimmune association in 17-18% [5] of the patients with AHA. In addition, skin disorders (such as pemphigus and epidermolysisbullosa) [12], drugs (including penicillin and interferon) [13-15] and even chronic graft-versus-host disease [16] have been reported as causative for AHA.

AHA should be considered early in the evaluation of cases of abnormal bleeding in the postpartum setting. Most commonly, the inhibitor develops after labor but sometimes can be found during labor, resulting in severe blood loss.

There is an added risk of transplacental transfer of the antibody and neonatal hemorrhage [17] if the inhibitor does develop during pregnancy. Postpartum AHA has good prognosis, with reported favorable outcomes in up to 97% of patients [18].

Table 1: Etiological factors associated with AHA

Category	Disease
Autoimmune diseases	SLE, RA, multiple sclerosis, Sjögren syndrome, Goodpasture syndrome, myasthenia gravis, Graves disease, autoimmune hypothyroidism, autoimmune hemolytic anemia
Drug associated	Penicillin and its derivatives, sulfa antibiotics, phenytoin, chloramphenicol, methyldopa, depot thioxanthene, interferon-α, fludarabine, levodopa, clopidogrel
Solid tumors	Prostate, lung, colon, pancreas, stomach, head, neck, cervix, breast, melanoma, kidney
Vaccination	Influenza
Hematologic malignancies	Chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, Waldenströmmacroglobulinemia, myelodysplastic syndrome, myelofibrosis, erythroleukemia
Skin disorders	Psoriasis, pemphigus, epidermolysisbullosa
Respiratorydisorders	Asthma, chronic obstructive pulmonary disease
Infection	M. pneumoniae, hepatitis B and hepatitis C infection
Others	Diabetes, surgery
Idiopathic	50% of cases

Genetic basis

The study by Oldenberg et al. comprising 57 patients with AHA, showed significantly higher frequencies of the HLA class II alleles DRB*16 (OR 10.2) and DQB1*0502 (OR 2.5) when compared with controls[(33)].In another study the CTLA-4+49G allele was found to be increased in patients with AHA (OR 2.17). However, a similar association of these alleles was not observed with congenital hemophilia and inhibitors.

Diagnosis

One should start suspecting AHA at the outset of recent onset bleeding with isolated APTT prolongation which does not get corrected by mixing studies, especially in the clinical setting of elderly patients or women in peripartum period. Investigations should include mixing studies at 0, 1 and 2 h, specific factor assays and the Bethesda assay for the quantification of inhibitors. A set of three tubes is placed at 37°C-normal plasma, patient plasma and a mixture of normal and patient plasma. APTT is performed at different time intervals to observe the presence of progressive inhibitors. However inhibitors in AHA are not always time dependent and often they can be immediate acting. According to The International Guidelines for the diagnosis of AHA[(2)], it is recommended to rule out lupus anticoagulant (LA) by a specific test. LA can sometimes mimic FVIII inhibitors resulting in decrease of most of the

coagulation factors [19]. The presence of LA can also be tested by using two APTT reagents i.e. one with low phospholipids concentration and second with higher phospholipid concentration. Shortening of APTT with high phospholipid reagent is suggestive of antiphospholipid antibodies.

The most striking differences between auto and alloantibodies inhemophilia are their inactivation patterns. Most inhibitors in congenital hemophilia are linear "type 1". These antibodies completely destroy all FVIII when present in high concentrations. "Type 2"inhibitors have a non-linear inactivation pattern and they do notcompletely inactivate FVIII, even at the highest concentrations ofinhibitor in plasma. Thromboelastography has also been used for diagnosis and also to monitor the response to treatment by rFVIIa [20].

Bleeding manifestation

Patients with AHA may present with either overt hemorrhage or anemia due to occult bleeding. Life-threatening bleeding is common, but spontaneous resolution of inhibitor occurs in approximately a quarter of cases [7]. Due to delay in the diagnosis of AHA, patients are at higher risk of bleeding-related mortalities than hemophiliacs who develop inhibitors. Mortality rates of 9.7-33% has been reported in AHA [1–4]. Death may be due to bleeding from the underlying disease or from the adverse effects of treatment. If the inhibitor is not removed, severe bleeding can occur any time. Some patients may bleed profusely until the inhibitor is removed, whereas others may live normally with detectable inhibitor levels.

Treatment

The modalities of treatment available is varied in AHA (Table 2) with the hemostatic agents being the commoner ones employed routinely to control the bleeding episodes which basically includes the replacing agents and bypassing agents (Table 3). However, the hemostatic therapy comes with a potential side effect of thrombo-embolic phenomena in certain subset of patients which have been brought out in various studies ranging form as low as nil to a stooping high figure of 55% in a study by Ingerslve et al.

Table 2: Treatment products for patients with AHA

Category	Product
Hemostatic agents	Activated prothrombin complex concentrate (aPCC), rFVIIa, FVIII concentrate (high dose), DDAVP, antifibrinolytics (tranexamic acid, EACA)
Immunosuppressive agents	Prednisolone, cyclophosphamide, Cyclosporine, intravenous immunoglobulin, vincristine, mycophenolatemofetil, azathioprine
Monoclonal antibody	Rituximab (anti-CD20)
Other inhibitor eradication procedures	Immunoadsorption, immune tolerance induction (ITI), Plasmapheresis

Table 3: First line hemostatic agents in AHA

Ser No	Agent	Recommended Dose	Comments
	Replacement Therapy		
1	Recombinant porcine FVIII (rpFVIII)	If no anti-porcine FVIII inhibitor: 50–100 U/kg initially then monitor every 2–3 h with FVIII activity and re-dose as needed If detectable anti-porcine FVIII inhibitor: 200 U/kg initially for severe bleeding 50–100 U/kg for less severe bleeding Monitor and re-dose as above	Advantage: a.Can be monitored with one stage FVIII clotting assay b. Replaces missing component c. Proven efficacy Disadvantage: a.Less effective in case of cross-reactive anti-porcine antibody b. May develop anti-porcine FVIII antibody duringtherapy and hence will require close monitoring Consider First Line when a.drug is readily available b. no underlying rpFVIII inhibitor is present c. FVIII activity measurement facilities are readily available d. life or limb threatening bleeding occurs

Table no. 3 continued.....			
	Bypassing therapy		
2	Activated prothrombin complex concentrate (aPCC)	50–100 U/kg every 8–12 h (Do not exceed 200 U/kg/d)	Advantage: a.Proven efficacy for clinical bleeding Disadvantage: a.No laboratory to monitor underdosing or overdosing b. Potential arterial or venous thrombotic risk Consider First Line when a.drug is readily available b. underlying high titer of rpFVIII inhibitor is present (>10 BU) c. FVIII activity measurement is not readily available d. bleeding is not life or limb threatening
3	Recombinant FVII activated (rFVIIa)	70–90 mcg/kg every 2–3 h until hemostasis is achieved (thereafter prolong dosing interval)	Advantage: a.Proven efficacy for clinical bleeding Disadvantage: a.No laboratory to monitor underdosing or overdosing b. Short half-life (2 h) c. Potential arterial or venous thrombotic risk Consider First Line when: a.drug is readily available b. If underlying high titer ofrpFVIII inhibitor is present (>10 BU) c. FVIII activity measurement is not readily available d. bleeding is not life or limb threatening

The treatment of AHA involves the following approach:

A. Treatment of bleeding
B. Elimination of the inhibitor.
C. Treatment of underlying disease (if applicable)

First-line treatment includes the bypassing agents. The two licensed treatment products are rFVIIa (Novo Seven®) and FEIBA® [21]. In case of low titer of inhibitors, antifibrinolytics like DDAVP or F VIII concentrates have also been used. [22,23]

Table 4: Thromboembolic risk in patients receiving bypassing agents

Study	Treatment	N	Thromboembolic events
Sumner et al	Recombinant factor VIIa	139	6 events in 4 patients (2.9%)
Ingerslev et al	Combined or alternating bypassing agents	9	55%
Baudo et al	Recombinant factor VIIa aPCC Factor VIII/desmopressin	174 63 70	2.9% 4.8% 0%
Seita et al	Recombinant factor VIIa	132	2.3%
Borg et al	Recombinant factor VIIa aPCC	28 6	0% 0%
Tiede et al	Recombinant factor VIIa Recombinant factor VIIa + tranexamic acid	63 21	5% 10%

Eradication of inhibitors

The two most common regimens proposed are corticosteroids alone or corticosteroids combined with cyclophosphamide [18]. Other regimens include steroids alone or different combination of azathioprine, rituximab, high-dose immunoglobulin, cyclosporine A, immunoadsorption, vincristine and combination chemotherapy. The recommended regimen is that the immunosuppression be initiated with either prednisolone alone at a dose of 1 mg/kg or a combination of prednisolone and cyclophosphamide (1–2 mg/kg). The median time to remission with corticosteroid treatment is about 5 weeks [24].

Intravenous immunoglobulin (IVIG)

Infusion of IVIG can also been used as treatment option. Schwartz et al. in his study in 16 patients used a total dose of 2g/kg over 2 or 5 days showing a response rate of 30%. Maximum response time was 40 days and patients with lower Bethesda

titers showed a better response [25]. Some of these patients were receiving immunoglobulin as second-line therapy, making it a reasonable option for those patients who do not initially respond to the first-line immunosuppression. There is, however, no evidence to support the use of IVIG as a single option to resolve bleeding.

Immunoadsorption / plasmapheresis

It is possible to use extracorporeal methods to remove autoantibodies to FVIII with either plasmapheresis or immunoadsorption with staphylococcal protein A [26]. This modality is useful in bleeding or presurgical patients with high titer of inhibitors who have failed to respond to bypassing agents. Following apheresis or immunoadsorption, these patients should be treated with FVIII replacement to achieve hemostasis.

Immune tolerance induction (ITI)

ITI protocols used for the treatment of alloantibody inhibitors against FVIII or FIX in patients with congenital hemophilia A or B, have been proposed for the eradication of autoantibodies against coagulation factors. Its effectiveness and safety has been demonstrated in patients treated by the Budapest protocol (human FVIII combined with cyclophosphamide and methylprednisolone)[27]**.** An aggressive protocol for the treatment of patients with AHA includes three weeks of treatment with human FVIII concentrates (30 U/kg/day for the 1st week, 20 U/kg/day for the 2ndand 15 U/kg/day for the 3rd week) along with cyclophosphamide (200 mg/day to a total dose of 2–3 g) plus methylprednisolone (100mg/day iv. for one week) and then tapering down the dose gradually over two weeks. Eradication of the inhibitor occurred in 13/14 patients in the ITI against 4/6 patients in the control group who were treated with traditional immunosuppressive therapy. Similar results (complete response of 88%) have been reported with a modified Malmo protocol (immunoadsorption, high doses of FVIII, high-dose immunoglobulin, cyclophosphamide and corticosteroids). [28]

Rituximab

Rituximab has emerged as a promising new agent for removal of inhibitors in patients with acquired haemophilia [29]. A study reported 10 patients and documented a complete remission in 8 of them. Almost similar results have been reported in two other studies [30] with 90–100% complete remission. The presence of high titers of inhibitor (>100BU/mL) was a bad prognostic factor for responsiveness to rituximab. However, the combined use of immunosuppressive therapy in most reported cases limited the evaluation of the real effectiveness of this agent. The dose is 375 mg/m^{2}per week for 4 weeks. It should be considered in patients who are resistant to first-line therapy or cannot tolerate standard immunosuppressive therapy.

Cyclosporin A

A single case report has shown complete remission with the use of Cyclosporin A in AHA patients. [31] However, its effectiveness as a single agent is yet to be confirmed and will require larger and multicentricstudies.

Summary

AHA is a rare but treatable coagulation disorder. Such patients are at a constant risk of severe hemorrhage until the inhibitors are completely removed. As they can present with life-threatening bleeding abruptly, awareness and education is critically important. Treatment options should be adapted to bleeding severity and inhibitor titers, which should always be managed jointly. Being a rare disease, it is difficult to perform randomized–controlled trials on these subjects. Concurrent with bleeding management, immunomodulation should be initiated with corticosteroid-based therapy in order to eliminate the autoantibody and restore normal hemostasis.

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