Acquired Hemophilia A: Experience of a Tertiary Care Institute from North India

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Abstract Acquired hemophilia A (AHA) is an uncommon bleeding disorder infrequently reported among Indians. The present retrospective data comprises eight cases of AHA over a period of 15 years. The mean age of patients was 59.7 years. The activated partial thromboplastin time was prolonged in all cases and the inhibitor screen showed the presence of inhibitors. Factor VIII: C assay was performed in 7 cases and all cases demonstrated low levels. Lupus anticoagulant was negative. Six patients were managed with steroids and symptomatic supportive care. These patients were followed up for a mean period of 3.5 years (range 1–5 years). Of these, there was one fatality prior to initiation of therapy and one patient continues to have inhibitors.

Keywords Activated partial thromboplastin time · Acquired hemophilia · Immunosuppression · Inhibitor screen · Inhibitor assay

Introduction

Acquired Hemophilia A (AHA) is an uncommon bleeding disorder that occurs due to autoantibodies against coagulation factor VIII (FVIII) in non-haemophilic patients [1].

FVIII inhibitors are time-dependent [2]. The estimated incidence of AHA is between 1.3–1.5 per million per year and the incidence increases with age [2, 3]. There are no significant sex differences in AHA distribution at any age except around 20–40 years, where AHA is increasingly pregnancy associated [4]. The most common presentation is in the form of a hemorrhage in the skin, muscles or soft tissues. Severe bleeding occurs in most of the patients and the mortality reported in the literature ranges from 8 to 33% [5]. The management includes corticosteroids with or without cytotoxic drugs [6]. The literature pertaining to AHA from the Indian subcontinent is sparse. The present series is an analysis of the presentation, testing, and management in a tertiary care centre.

Patients and Methods

Laboratory records of patients with bleeding manifestations who reported to, and were worked up in the coagulation laboratory of the Department of Hematology were retrospectively analyzed for the previous 15 years. A total of 8 cases were diagnosed as AHA, based the clinical details (Bleeding manifestation, older age group, no history of inherited bleeding disorders and no history of treatment by anticoagulant as provided by the treating clinician in his referral notes), and the data for screening coagulation tests, mixing studies with incubation, factor assays and Bethesda assay. Additional clinical details, where required, were obtained from the treating clinician. The clinical details are provided in Table 1. The study was approved by the ethics committee of the Institute (Reference No.INT/IEC/2017/52/dated 23.02.17).

Venous blood was collected in 3.2% sodium citrate anticoagulant and platelet-poor plasma was prepared for

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Table 1 Clinico laboratory details and outcome of patients

No	Age	Sex	Presenting symptoms	Platelet count (lakhs/ μ L)	APTT in secs	Type of inhibitor	Factor VIII level (IU/dL)	Inhibitor titre in BU/mL	Lupus anticoagulant	Management	Follow-up	Outcome
1	50	F	Oozing following tooth extraction	2.02	55	Time-dependent	–	1.4	Negative	Symptomatic treatment (tranexamic acid)	2 years	APTT within normal range, lost to follow-up thereafter
2	52	M	Hematoma, ecchymosis	2.73	74	Time-dependent	10	4.4	–	IVIg (2gm/Kg), prednisolone 1 mg/kg $\times$ 2 months followed by tapering and increasing dose (total duration 2.5 years)	4 years	No symptom till 4 years. Then lost to follow-up
3	68	M	Hemarthrosis	–	71	Time-dependent	11	27	–	Prednisolone 1 mg/kg $\times$ 2 months followed by tapering (total duration 4 months)	5 years	Asymptomatic. APTT within normal range
4	45	F	Vaginal bleed and pelvic hematoma following laparoscopic hysterectomy for multiple fibroids	1.80	74	Time-dependent	39	–	–	Prednisolone 0.5 mg/kg OD $\times$ 2 months followed by tapering (total duration 3 months)	5 years	Asymptomatic after 4 months. APTT within normal range
5	78	M	Multiple cutaneous bleeds, intramuscular hematoma	3.28	64	Immediate acting (strong)	<1	–	Negative	Prednisolone 1 mg/kg $\times$ 3 months	4 years	Asymptomatic after 3 months. APTT within normal range
6	28	F	Leiomyosarcoma uterus with vaginal bleeding	–	120	Time-dependent	10	–	–	Supportive	Expired	Died within a week due to haemorrhage
7	77	M	Hematoma thigh	1.46	81	Time-dependent	1	46.4	–	Not done	–	Lost to follow-up after the first visit
8	80	M	Ecchymosis thigh and forearm	3.65	65.8	Immediate acting (strong)	<1	448	Negative	Prednisolone 1 mg/kg $\times$ 1 month followed by tapering, however, the treatment was stopped in-between.	1 year	Tests and bleeding responded to steroids, which could be given intermittently because of a purulent infection in between. Currently off steroids, and asymptomatic, APTT at the last follow-up was prolonged

the coagulation tests. The following coagulation tests were performed: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen assay, inhibitor screen, FVIII: C assay and Bethesda assay. All assays, other than inhibitor screen and Bethesda assay, were performed on automated coagulation analyzers {Stago Compact & Stago STA-R Evolution (Diagnostic Stago, France) and ACL TOP 500 CTS (Instrumentation Laboratory, USA)} using commercially available reagents and the manufacturer's instructions. The inhibitor screen was performed manually and the inhibitor was quantified by the Bethesda assay. The platelet count was retrieved from the patient's clinical records.

In all patients, the coagulation screen (PT, APTT and fibrinogen assay) was performed. In cases with isolated prolongation of APTT, the APTT based mixing study (Inhibitor screen) with patient plasma (PP) and normal pooled plasma (NPP) in 1:1 dilution was performed. One tube, that contained a mixture of PP and NPP, was kept for 2 h at 37 °C. The next two tubes containing only PP and only NPP were kept separately. The fourth tube was made using NPP and PP after 2 h and APTT of all four tubes was performed. The result of the fourth tube was interpreted as '0' hour while the result of the first tube was interpreted as '2' hours incubation.

The cases showing correction at '0' hour and prolongation at '2' hours were considered as time-dependent inhibitors and were worked up for FVIII inhibitors. Cases with FVIII deficiency (but not Factor VIII inhibitors) are expected to show correction at both '0' hour and at '2' hours. The cases with no correction at '0' hour and 2 hours incubation were considered to have immediate acting

inhibitors. In such cases with suspected AHA, first lupus anticoagulant (LA) was excluded. If LA was negative, then factor assays (FVIII and FIX) were performed in multiple dilutions with buffer, to lower the concentration of inhibitor. As a result of dilution, the inhibitor level gets diluted in the PP and the FVIII present in FIX-deficient plasma (used for FIX assay) is less affected due to dilution. On the other hand, FVIII deficient plasma (used in FVIII assay) does not have FVIII and the inhibitor neutralizes the available FVIII present in PP. As a result of this, the FIX assay shows normal FIX level and FVIII assay shows a low level of FVIII (due to the presence of inhibitor in PP). The inhibitor level was quantified by the Bethesda assay. A flowchart for investigations in AHA is labeled as Fig. 1.

Testing for heparin contamination of the sample was not performed. As these patients presented with bleeding, therapeutic heparin was unlikely, and samples contaminated by heparin from indwelling lines could not be excluded by direct testing as the modalities for heparin testing were not available in our laboratory.

Results

In the last 15 years, 2000 patients were investigated in detail for suspected bleeding disorders. All patients had bleeding manifestations and were referred for establishment of a diagnosis for the bleeding diathesis. Of these, a total of 8 cases were diagnosed as AHA. The patients' age ranged from 28 to 80 years (median age-60 years) with the male to female ratio 1.6:1. Spontaneous bleeding occurred in 6 patients, whereas in 2 patients, it followed surgical

Fig. 1 Algorithm for workup in a case with suspected acquired hemophilia A

procedures. Five out of 8 patients received fresh frozen plasma transfusion prior to testing; however, there was no improvement of symptoms.

The APTT was prolonged in all cases and ranged from 55 to 120 s (normal range 27–32 s). The PT and fibrinogen levels were normal in all cases. The platelet count was available in 6 cases and was within the normal range. The inhibitor screen was performed in all cases. Six cases (6/8) showed the presence of time-dependent inhibitors. The FVIII assay was performed in 5/6 cases and it ranged from 1 to 39% (normal range 60–160%). The Bethesda assay was done in four cases (4/6) and the titres ranged from 4.4 to 448 BU/ml. The case wise details are depicted in the table. Data for Factor VIII was not available in a single case (case no. 1). Two cases (case no. 5 and 8) had immediate acting inhibitors. The LA and FIX assay was performed and both these cases were LA-negative and FIX levels were 89 and 69%. The vWF antigen levels in these cases were 187 and 194 iu/dl. The FVIII levels in these cases were less than 1% suggesting strong FVIII inhibitors.

Treatment and Follow-Up

The follow-up details are available in seven cases. Case no. 7 was lost to follow-up after the first visit. Case no. 6 was managed with supportive transfusions and expired within the 1 week due to severe bleeding and shock. The remaining six patients received treatment and were periodically reviewed. The mean follow-up of these six patients was 3.5 years (range of 1–5 years). None of these patients relapsed after completion of therapy or during the follow-up. Two patients were treated symptomatically with mainly supportive care, while four patients received steroids. Among these, 5 cases (including case no. 1 and 3) showed improvement clinically and laboratory wise (APTT returned to the normal range). One patient (case no. 8) continued to exhibit inhibitors in his last visit and is still on follow-up. The details of treatment and follow-up are shown in Table 1.

Discussion

Data on AHA in the literature is mainly from western countries and case series from China. AHA from India finds mention as an occasional case series or a few case reports [7–13]. This bleeding disorder occurs predominantly in adults. AHA can occur in association with other diseases/situations—autoimmune disorders, malignancy, skin diseases, and post-partum state whereas in nearly half of them no cause is evident [1–3]. In the present series one case had a history of a leiomyosarcoma while in the rest of the cases, no etiology was identified. The median age of the

AHA patients reported in the literature is approximately 75 years [4]. Our patients are somewhat younger than those reported from other parts of the world but are relatively older than those from our region (median 60 years, range 53.8–56.3 years) [7–13].

The laboratory trigger for workup was a prolonged APTT seen universally. The inhibitor screening test with 1:1 dilution of NPP and PP was performed in all cases. A time-dependent inhibitor was detected in 6 cases, which was confirmed by FVIII assay and the Bethesda assay. Two cases showed immediate acting inhibitors with very low FVIII levels. As lupus anticoagulant is an immediate acting inhibitor it was first excluded in these 2 cases. As per international recommendations on the diagnosis and treatment of AHA, an immediate prolongation does not exclude AHA, as high-titre FVIII inhibitors may be fast acting and neutralize FVIII [6] resulting in prolonged APTT after mixing. After exclusion of LA, testing for FIX and FVIII assay on multiple serial dilutions with buffer was performed. These results showed that the inhibitor was against FVIII and not against FIX. Immediate acting FVIII inhibitors are less common but have been reported. A stepwise protocol is helpful in determining the nature of these types of inhibitors. The diagnosis of AHA in two cases was suggested by the negative LA testing and results of factors assay in multiple dilutions. The immediate acting FVIII inhibitors usually occur in cases with a high titre of inhibitors. One of the two cases, with immediate acting inhibitors that we encountered, had a high titre of inhibitors. The reason for the immediate inhibition at low titre in the second case is not clear, though it was negative for LA.

These inhibitors can be asymptomatic or may lead to life-threatening bleeds. The aim of therapy is to eradicate the autoantibody and to increase FVIII to a level that minimizes the risk bleeding. The patients presenting with severe bleeding during the course of disease require hemostatic treatment. Recombinant activated FVII or activated prothrombin complex concentrate is usually recommended, however, these are not economically viable options in most of the Indian patients [3, 6]. None of our patients had received these therapies.

First line immunosuppressive treatment in AHA includes corticosteroid therapy (prednisone, 1 mg/kg/d for 4–6 weeks) or in combination with cytotoxic agents (e.g., cyclophosphamide, 1.5–2 mg/kg/d for up to 6 weeks) [6, 14]. The level of inhibitors significantly decreased in 58–76% of the patients with steroids alone and in 77–89% of the patients with steroids and cytotoxic drugs [5, 15].

Inhibitors can resolve with minimal or no therapy [16, 17], nevertheless treatment can be challenging in a patient with inhibitors. In the present series, five patients received steroids and four of them responded within 3 months. In one patient symptomatic treatment was

effective and the bleeding stopped with no further recurrences. In a series of 16 patients by Lottenberg et al., 4 patients did not receive any immunosuppressive therapy and became asymptomatic following infusion of FVIII. Among these, one patient showed the disappearance of inhibitors after 3 months while the other 3 patients the patients became asymptomatic for several months, despite persisting inhibitors. The treatment of patients with AHA depends on the natural history of any concomitant pathology and the clinical presentation [18–20]. Few cases with post-partum or drug induced inhibitors may require no treatment other than close clinical observation since these inhibitors tend to disappear spontaneously within a few months after delivery or drug discontinuation [18]. In other cases, the eradication of the associated disease may lead to the disappearance of the inhibitor [17]. In the present series, only one case received symptomatic treatment, however, no associated disease was evident.

Treatment with corticosteroids can be fraught with difficulties. One patient (case no. 8) who received corticosteroids developed a purulent skin infection. Following this, the steroids were withdrawn. He developed ecchymosis and his APTT was prolonged along with the presence of inhibitors. Restarting corticosteroids lead to the normalization of the prolonged APTT and the steroids were gradually stopped again. This resulted in the recurrence of APTT prolongation, but he remains asymptomatic.

The mortality in AHA is high and the causes are multifactorial [5, 21, 22]. In our series, only one patient expired due to bleeding following leiomyosarcoma of the uterus, and the death occurred within few days of diagnosis of AHA. The fatality in the current series is 12.5% as against the reported worldwide mortality rate in AHA, which is estimated to be around 8–33% [23].

In summary, Acquired Hemophilia A is a rare acquired bleeding condition. Our data has shown a total 8 cases over a period of 15 years. As has been reported the world over, it is a disease of older people. The clinical findings were varied ranging from ecchymotic patches, deep hematomata, mucosal bleeds to even hemarthrosis. The APTT, inhibitor screen, and FVIII assay are necessary for the diagnosis, while the inhibitor assay is essential for management and prognosis. Our patients demonstrated a wide range of inhibitor titres. Immunosuppressive treatment with regular follow up with APTT testing was beneficial in most cases.

Compliance with Ethical Standards

Conflicts of interest The authors have no conflicts of interest to declare.

Human and Animal Rights Statement This retrospective analysis was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its

later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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