BRIEF REPORT
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Real-World Clinical Outcomes and Prognostic Factors in Acquired Hemophilia A: A Single-Center Retrospective Analysis

Edinsel Hemofili A'da Klinik Sonuçlar ve Prognostik Faktörler: Tek Merkezli Retrospektif Bir Gerçek Yaşam Analizi

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Abstract
Objective: Acquired hemophilia A (AHA) is a rare but potentially life-threatening bleeding disorder. Our single-center retrospective study aimed to assess clinical features, treatment strategies, and prognostic indicators in adult AHA patients.
Materials and Methods: Eleven patients diagnosed between 2008–2024 were reviewed. Clinical data, laboratory findings, treatments, and outcomes were analyzed. Survival estimates and prognostic factors were evaluated using Kaplan–Meier and univariate analysis.
Results: Median age was 41 years; 54.5% were female. Pregnancy-associated AHA (36.4%) had excellent outcomes with steroid monotherapy and no relapse. Idiopathic and autoimmune cases required combination therapy and had higher relapse rates. The median follow-up duration was 27 months. All patients achieved remission (median response: 62 days), though 36.4% relapsed. High inhibitor titer (>20 BU) predicted delayed response (p=0.038); male sex and major bleeding were linked to shorter relapse-free survival.
Conclusion: Baseline inhibitor burden and disease etiology influence AHA prognosis. Tailored therapy and multicenter validation are needed to refine management strategies.
Key words: acquired hemophilia A; bleeding disorder; inhibitor; bypassing agents; immunosuppressive therapy

Özet
Amaç: Edinsel hemofili A (EHA) nadir görülen ancak yaşamı tehdit edebilen bir kanama bozukluğudur. Bu tek merkezli retrospektif çalışmamızın amacı, erişkin EHA hastalarında klinik özellikleri, tedavi stratejilerini ve prognostik göstergeleri değerlendirmektir.
Gereç ve Yöntemler: 2008-2024 yılları arasında tanı konulan 11 hasta incelendi. Klinik ve laboratuvar verileri, tedaviler ve klinik sonuçlar analiz edildi. Beklenen sağkalımlar ve prognostik faktörler Kaplan-Meier yöntemi ve tek değişkenli analiz ile değerlendirildi.
Bulgular: Medyan yaş 41 idi; %54,5'i kadındı. Gebelikle ilişkili EHA (%36.4) steroid monoterapisine çok iyi yanıt verdi ve nüks gözlenmedi. İdiyopatik ve otoimmün hastalık ilişkili olgularda kombine immünsupresif tedavi gerekti

ve nüks oranı daha yüksekti. Ortanca takip süresi 27 aydı. Tüm hastalarda remisyona ulaşıldı (medyan yanıt: 62 gün), ancak %36,4'ünde nüks görüldü. Yüksek inhibitör titresi (>20 BU) gecikmiş yanıtla (p=0.038); erkek cinsiyet ve majör kanama daha kısa relapssız sağkalımla ilişkilendirildi.
Sonuç: Tanıdaki inhibitör yükü ve hastalık etiyolojisi EHA prognozunu etkilemektedir. Yönetim stratejilerini iyileştirmek için kişiselleştirilmiş tedavi ve çok merkezli validasyon gereklidir.

Introduction

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by autoantibodies against factor VIII (FVIII). It typically affects older adults but may occur postpartum [1,2]. Its incidence is approximately 1.5 per million annually [3]. Management involves prompt diagnosis, bleeding control with bypassing agents, immunosuppressive therapy (IST) for inhibitor eradication, and evaluation for underlying conditions to guide treatment [1,4,5].

We conducted a single-center, retrospective study to assess clinical features, treatment modalities, and outcomes in adult AHA patients, focusing on prognostic indicators affecting treatment response, relapse, and survival.

Methods

The study included patients aged ≥18 years diagnosed with AHA at the Cerrahpaşa Faculty of Medicine between January 2008 and December 2024, based on international criteria [6]. Ethical approval was obtained (Date: 05-03-2025, No: 2025/156). Data on demographics, bleeding features, comorbidities, FVIII activity, inhibitor titers, treatments, and outcomes were retrospectively collected.

Major bleeding was defined by involvement of vital organs, ≥2 g/dL hemoglobin drop, or ≥2 units RBC transfusion; others were classified as minor. Response definitions followed published guidelines [7]. Follow-up extended from diagnosis to last visit or death. Categorical variables were compared using chi-square or Fisher's exact test. Mann–Whitney U test was applied for non-parametric continuous variables. Kaplan-Meier estimates were used for overall survival (OS) and relapse-free survival (RFS).

Results

Eleven patients (54.5% female) with a median age of 41 years (range: 26–79) were analyzed. In 36.3%, no underlying cause was found; postpartum period was the most common identifiable etiology (Table 1). Three patients had connective tissue disorders (bullous pemphigoid or rheumatoid arthritis) (Table 1, 2).

FVIII activity was <1% in 81.8% and inhibitor titers >20 Bethesda Units per milliliter (BU/mL) in 63.6%. All patients presented with bleeding, with 45.4% having major hemorrhages (Table 1).

Patient characteristics, treatment approaches, and disease course are summarized in Table 2. Recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) were used in six patients each to control the initial bleeding episode, accounting for 81.8% of the cohort. Combination or switch between agents occurred in three cases. Desmopressin, high-dose FVIII, and emicizumab were not used. One patient underwent plasmapheresis and right femoral artery embolization (Table 2).

Median hemostasis duration was 7 days (range: 2–45). Patients with minor bleeding had shorter bypassing agent use (p=0.027). Number of bleeding sites did not significantly affect hemostasis duration (p=0.47).

All patients received IST. Steroid monotherapy was first-line in 90.9% (Table 2). Due to regulatory delays in Türkiye, the first-line usage of rituximab often impossible. In our hands, rituximab is usually added to the corticosteroid therapy in patients who fail to respond to first-line steroid monotherapy, or who have recurrent clinical bleeding and/or prolongation of APTT during steroid tapering after initial response.

Three patients (all pregnancy-associated) with inhibitor titers ≤20 BU achieved complete remission (CR) with steroids alone, without relapse. A fourth postpartum case with inhibitor titer >20 BU also achieved CR with added rituximab (Table 2).

Of three patients with autoimmune disorder-associated AHA, one achieved CR with cyclophosphamide, while two required rituximab addition to steroid monotherapy. One of these relapsed and was re-treated (Table 2). Among idiopathic AHA cases (36.3%), only one patient sustained CR with steroids alone. The remaining three initially responded to combination therapy but relapsed in two cases (Table 2).

All patients achieved CR with a median time of 62 days (range: 44–160). Inhibitor titer >20 BU was associated with longer time to CR (p=0.038). Pregnancy-associated cases had significantly shorter time to CR (p=0.022), whereas idiopathic cases required longer (p=0.013). Baseline FVIII activity and bleeding severity were not significantly associated with treatment duration (p=0.075 and p=0.168, respectively). There was no significant relationship between the type of bypassing agent used and time to remission (p = 0.783).

Median follow-up was 27 months (range: 3–173). Four patients (36.4%) relapsed; two had multiple relapses without sustained response (Table 2). One developed popliteal vein thrombosis during relapse under aPCC (Patient #4). Two patients (Patients #1 and #6) died: one from trauma-induced hemorrhage, another from unknown causes.

In univariate analysis, male sex and major bleeding at presentation were associated with shorter RFS (p=0.015 for both). No factor reached significance for survival, although age >50, hemoglobin <10 g/dL, and non-pregnancy-associated AHA trended toward significance (p=0.062). Inhibitor titer, APTT, and type of bypassing agent were not predictive for either RFS or OS (Table 3).

Discussion

AHA is a rare and serious bleeding disorder caused by neutralizing autoantibodies against FVIII, requiring prompt diagnosis. The management of AHA involves both the control of acute bleeding episodes and the eradication of inhibitors through IST [1,8]. Our single-center study provides valuable insights into the clinical characteristics, treatment responses, and outcomes of patients with AHA, thereby contributing to the current understanding of this uncommon condition.

In our cohort, bypassing agents were administered in 77.8% of patients to achieve bleeding control, consistent with the EACH2 registry (70.5%) [9]. Both rFVIIa and aPCC were effective, aligning with prior studies reporting 80–90% efficacy [10].

Currently, no laboratory parameters reliably predict or monitor the efficacy of bypassing agents; thus, treatment response must be evaluated clinically [1]. This limitation can create uncertainty regarding the optimal duration of therapy. One patient developed popliteal vein thrombosis during receiving aPCC, underscoring the need for thrombotic risk monitoring, especially when agents are combined.

Steroid monotherapy was the initial IST in 90.9% of patients, achieving CR in all, with a median response time of 62 days—slightly longer than the 5–6 week timeframe reported in previous cohorts [3,8,9]. In the EACH2 and Lindahl et al. studies, corticosteroid monotherapy yielded CR rates of 57–72% [9,11], while regimens incorporating rituximab reported CR rates up to 90% [8]. In our cohort, four patients received rituximab as first-line therapy, all achieving CR.

Pregnancy-associated AHA, accounting for 36.4% of cases, showed a particularly favorable course: three of four patients responded to steroids alone and none relapsed. These patients had significantly shorter response times (p=0.022) and low inhibitor titers, supporting existing data suggesting a transient, self-limiting postpartum immune dysregulation [3,6,12]. In contrast, idiopathic and autoimmune-associated cases more often required combination IST and showed higher relapse rates and delayed remission (p=0.013).

High inhibitor titer (>20 BU) was significantly associated with delayed IST response (p=0.038), consistent with previous studies demonstrating that higher inhibitor levels are associated with a more protracted treatment course [13–15]. Neither FVIII activity >1% nor initial bleeding severity predicted time to remission.

Relapse occurred in 36.4% of patients—higher than the 14% reported by Lindahl et al. [11]. This may reflect early IST tapering or discontinuation. Additionally, patients with multiple relapses posed treatment challenges, highlighting the need for alternative or intensified IST strategies in refractory cases.

Compared to the only multicenter AHA study from Türkiye (Davulcu et al.) [16,17], our cohort had comparable initial characteristics but higher aPCC utilization, longer median follow-up, and a higher relapse rate.

Limitations include the retrospective design and small sample size.

Our study underscores the clinical heterogeneity of AHA and highlights the prognostic significance of baseline inhibitor titers and underlying disease etiology. Individualized treatment approaches are crucial, particularly for high-risk subgroups. Larger multicenter studies are needed to validate prognostic markers and optimize therapeutic strategies for sustained remission and reduced complications.

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Table 1. Demographic and clinical characteristics of patients.	
Parameter	**Total (n: 11)**
Sex, n (%)	
Female	6 (54.5)
Male	5 (45.5)
Age at diagnosis, years	
Median (range)	41 (26 – 79)
Age categories, n (%)	
≤ 70 years	8 (72.7)
> 70 years	3 (27.3)
Underlying disorder	
İdiopathic/None	4 (36.3)
Connective tissue disorders	3 (27.3)
Pregnancy	4 (36.3)
Hemoglobin level at diagnosis (g/dL)	
Median (range)	11.7 (5.8 – 14.7)
APTT at diagnosis (s)	
Median (range)	82 (53.9 – 121)
FVIII level at diagnosis (IU/dL)	
Median (range)	0.6 (0.1 – 5)
FVIII inhibitor titer at diagnosis (BU/mL)	
Median (range)	36.95 (2 – 130)
Severity of bleeding at diagnosis, n (%)	
Major	5 (45.4)
Minor	6 (54.5)
Number of bleeding sites at diagnosis, n (%)	
1	3 (%27.2)
≥2	8 (%72.7)
Number of bleeding sites (all), n (%)	
Skin and subcutaneous tissue	8 (72.7)
Joint	2 (18.1)
Muscle	5 (45.4)
Gastrointestinal system	1 (9)
Genitourinary system	3 (27.2)
BU: Bethesda unit; FVIII: Factor VIII.	

Table 2. Clinical features, treatments, and outcomes in acquired hemophilia A patients.

Patient No	Age at Dx, Sex	Underlying Disorder	Inh titer (BU/mL)	Major/ Minor Bleeding	Bypassing Agent Used	IST	Time to achieve CR (days)	Duration Until Relapse	Second Line Bypassing Agent Choice	Second and Subsequent IST	Treatment Response	Follow Up Duration (months)
1¥	77, F	Bullous Pemphigoid	60	Major	rFVIIa rFVIIa + aPCC	CTX	140	None				15
2	41, M	Idiopathic	104	Major	rFVIIa	MP	160	2 months	rFVIIa + aPCC	MP + CTX CTX RTX	No Response	173
3	30, F	Postpartum period	2	Minor	None	MP	60	None				27
4	56, M	Idiopathic	78	Major	aPCC rFVIIa	MP + CTX	150	50 months	aPCC	MP + RTX MP + RTX	No Response	116
5	26, F	Postpartum period	32	Minor	aPCC	MP + RTX	60	None				19
6¥	78, M	Bullous Pemphigoid	40	Major	aPCC *Plasmapheresis *Embolization	MP + RTX	48	1 Months	aPCC	MP + CTX	CR	11
7	34, F	Idiopathic	34	Minor	aPCC	MP + CTX	160	None				24
8	39, F	Postpartum period	3	Minor	rFVIIa	MP	44	None				35
9	41, F	Postpartum period	2	Minor	aPCC rFVIIa	MP	44	None				51
10	54, M	Idiopathic	NA	Major	rFVIIa	MP + RTX	78	18 months	rFVIIa	MP + RTX	CR	36
11	77, M	Rheumatoid arthritis	130	Minor	None	MP + RTX	62	None				3

aPCC: activated prothrombin complex concentrate; BU: Bethesda unit; CR: complete remission; CTX: cyclophosphamide; Dx: diagnosis; F: female; IST: immunosuppressive therapy; Inh: inhibitor; M: male; MP: methylprednisolone; rFVIIa: recombinant activated factor VII; RTX: rituximab.
¥ Patient deceased.

Table 3. Factors affecting relapse-free survival and overall survival in acquired hemophilia A.		
Variable	**RFS (*p*-value)**	**OS (*p*-value)**
Age at diagnosis >50 years	0.161	0.062
Male sex	**0.015**	0.695
Major bleeding at diagnosis	**0.015**	0.134
≥2 bleeding sites	0.273	0.464
Non-pregnancy-associated cases	0.062	0.226
Idiopathic cases	0.183	0.226
APTT >100 seconds	0.273	0.577
Factor VIII >1 IU/dL	0.923	0.176
Inhibitor titer >20 BU/mL	0.17	0.295
Hemoglobin <10 g/dL	0.06	0.062
Use of bypassing agents	0.424	0.627
Use of aPCC	0.474	0.226
Use of recombinant factor VIIa	0.741	0.695
aPCC: activated prothrombin complex concentrate; APTT: activated partial thromboplastin time; BU: Bethesda unit; OS: overall survival; RFS: Relapse-free survival.		

Legends

Table 1. Demographic and clinical characteristics of patients. BU: Bethesda unit; FVIII: Factor VIII.

Table 2. Clinical features, treatments, and outcomes in acquired hemophilia A patients. aPCC: activated prothrombin complex concentrate; BU: Bethesda unit; CR: complete remission; CTX: cyclophosphamide; Dx: diagnosis; F: female; IST: immunosuppressive therapy; Inh: inhibitor; M: male; MP: methylprednisolone; rFVIIa: recombinant activated factor VII; RTX: rituximab. ¥ Patient deceased.

Table 3. Factors affecting relapse-free survival and overall survival in acquired hemophilia A. aPCC: activated prothrombin complex concentrate; APTT: activated partial thromboplastin time; BU: Bethesda unit; OS: overall survival; RFS: Relapse-free survival.