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Management of acquired haemophilia A

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Keywords

Factor VIII : C, inhibitor, bleeding, recombinant factor VIIa, activated prothrombin complex concentrate, immunosuppression

Summary

Acquired haemophilia A (AHA) is caused by autoantibody inhibitors of coagulation factor VIII (FVIII : C). Recent onset of bleeds and isolated prolongation of the activated partial thromboplastin time (aPTT) are characteristic features of the disorder. Reduced FVIII : C activity and a detectable FVIII : C inhibitor in the Bethesda assay confirm the diagnosis. Patients should be referred to expert centres, whenever possible, and invasive procedures with a high risk of bleeding must be avoided, until haemostasis has been secured by adequate therapy.

Bypassing agents capable of inducing sufficient thrombin formation in the presence of FVIII : C inhibitors are treatment of choice, including currently available recombinant factor VIIa (NovoSeven™) and activated prothrombin complex concentrate (FEIBA™). These agents represent first line therapy to control acute or severe bleeds. To eradicate inhibitors, immunosuppressive treatment (IST) is indicated in patients with AHA. Glucocorticoids, cytotoxic agents and rituximab are most widely used. However, an ideal IST regimen has not been established so far. Adverse events of IST, including infections as the foremost cause death, are frequent complications in AHA.

Schlüsselwörter

Faktor VIII : C, Hemmkörper, Blutungsneigung, rekombinanter Faktor VIIa, aktiviertes Prothrombinkomplex-Konzentrat, Immunsuppression

Zusammenfassung

Die erworbene Hämophilie A wird durch Autoantikörper gegen den Gerinnungsfaktor VIII (FVIII : C) verursacht. Eine neu aufgetretene Blutungsneigung und isolierte Verlängerung der aktivierten partiellen Thromboplastinzeit (aPTT) sind Hinweise auf die Erkrankung. Die Diagnose wird durch reduzierte FVIII : C-Aktivität und im Bethesda-Test nachweisbaren FVIII : C-Inhibitor bestätigt. Die Patienten sollten in erfahrenen Zentren behandelt werden. Invasive Prozeduren mit hohem Blutungsrisiko sind unbedingt aufzuschieben, bis die Hämostase durch adäquate Behandlung wieder gewährleistet ist.

Therapie der Wahl ist der Einsatz so genannter Bypass-Produkte, die auch in Anwesenheit von FVIII:C-Inhibitoren eine ausreichende Thrombinbildung bewirken. Zur Verfügung stehen gegenwärtig rekombinanter Faktor VIIa (NovoSeven®) und aktiviertes Prothrombinkomplex-Konzentrat (FEIBA®). Bei akuten oder schweren Blutungen haben sich diese Medikamente als Erstlinientherapie bewährt. Zur Eradikation des Inhibitors sollten Patienten mit erworbener Hämophilie eine immunsuppressive Therapie (IST) erhalten. Glucokortikoide, Zytostatika und Rituximab sind die am häufigsten eingesetzten Substanzen. Allerdings existiert bislang kein optimales IST-Regime. Unerwünschte Arzneimittelwirkungen der IST, vor allem Infektionen als häufigster Todesursache, sind oftmals auftretende Komplikationen bei Patienten mit erworbener Hämophilie.

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Acquired haemophilia A (AHA) is an autoimmune bleeding disorder resulting from the formation of neutralising autoantibodies to factor VIII coagulant protein (FVIII : C) (1, 2). These autoantibodies, also designated inhibitors, can lead to a serious coagulation defect. Early recognition, appropriate diagnosis and prompt treatment are important elements to optimise the clinical outcome.

This article reviews several key aspects of AHA and sheds light on recent advances that may help to improve the management in patients with AHA.

Definition

There has been no formal consensus about definition of relevant items (such as partial or complete remission and relapse) in AHA, and the use of different criteria has created some difficulty in comparing data from studies and registries. Definitions as used in the GTH-AH 01/2010 are provided (▶Tab. 1).

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Tab. 1 Definitions according to GTH-AH 01/2010

item	criteria
acquired haemophilia A	• FVIII:C activity reduced to <50% (<50 IU/dl), • FVIII:C inhibitor detectable by Bethesda assay (≥0.6 BU*/ml), and • congenital haemophilia A excluded
partial remission	• no active bleeding, and • FVIII:C activity restored to >50% after stopping any haemostatic treatment for >24 h
complete remission	• PR, plus • FVIII inhibitor undetectable (<0.6 BU*/ml) • prednisolone reduced to <15 mg/d (or equivalent glucocorticoid dose), and • any other immunosuppressive drug discontinued
relapse	• FVIII:C activity declined to <50% after achieving PR or CR, and • FVIII:C inhibitor detectable

*BU: Bethesda units

Epidemiology

The European Acquired Haemophilia Registry (EACH2) is the largest cohort of patients with AHA available (3). The registry included 501 patients (53% male, 47% female), diagnosed between 2003 and 2008 by 117 centres in 13 European countries. The median age at diagnosis was 74 years. In about half of the patients, an underlying disorder was identified, including

- malignancy (12%),
- autoimmune diseases (12%),
- pregnancy (8%),
- infections (4%),
- drugs (3%), and
- other disorders (15%).

A similar pattern of co-morbidities has been reported in a smaller monocentric study encompassing a comparable recruitment time (4). As these conditions are common in an elderly population, the causal relationship remains unclear.

95% of the EACH2 patients had bleeding episodes reported at diagnosis, most often spontaneous haemorrhages (77%), but also bleeding caused by trauma (8%), surgery (8%), or delivery (4%).

- Frequent bleeding sites were
  - skin (53% of patients),
  - muscles (50%), and
  - mucosa (32%),
- less frequently
  - joints (5%) or
  - central nervous system (1%).

This pattern is remarkably different from patients with congenital haemophilia A with or without inhibitors, in whom joint bleeds are the most frequent and characteristic haemorrhagic phenotype. In EACH2, bleeding in AHA was severe in 70% of patients (in this registry defined as haemoglobin level below 8 g/dl, or dropping by more than 2 g/dl, or life- or limb-threatening, intracranial, deep muscle, or retroperitoneal bleeding) (3). The median time from bleeding event to diagnosis was 3 days (interquartile range 0 to 12 days). In about 10% of AHA patients, however, the time from bleeding event to diagnosis was more than a month.

The median FVIII:C activity at the time of diagnosis was 2% (IU/dl) (3). Most patients (75%) had a FVIII:C activity of <5%. The median inhibitor concentration was 12.8 Bethesda units (BU) /ml. FVIII:C activity or inhibitor concentration were similar in bleeding and non-bleeding patients (5).

Diagnosis

AHA is usually diagnosed upon assessment of abnormal bleeding. However, 5–10% of patients do not bleed at the time of diagnosis. A prolongation of the activated partial thromboplastin time (aPTT) is invariably found as a first laboratory clue to the disorder. Therefore, any unexplained, isolated APTT prolongation should always raise the suspicion of AHA. Invasive procedures with a risk of bleeding should be withheld until diagnostic workup has been completed.

A typical diagnostic pathway along with relevant differential diagnoses is illustrated (▶Fig. 1). Usually, the workup is straightforward. Unexplained, isolated aPTT prolongation should prompt assessment of FVIII:C activity. At this stage, differential diagnoses include other coagulation factor

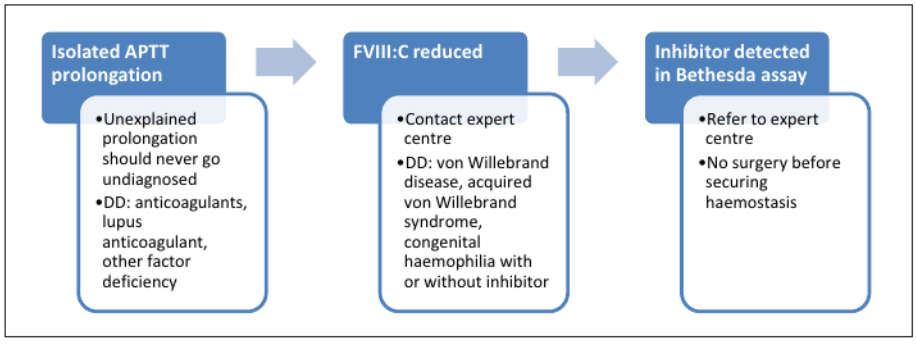

Fig. 1 Simplified diagnostic pathway for AHA

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deficiencies (of which, factor IX and XI deficiency cause isolated aPTT prolongation and bleeding), lupus anticoagulant (usually associated with increased risk of thromboembolism), and pharmacological anticoagulants (to be excluded by medical history and/or appropriate laboratory assays). Once a reduced FVIII:C activity has been confirmed, the differential diagnoses include congenital or acquired von Willebrand disease and congenital haemophilia A with or without inhibitor. The Bethesda assay will then be used to detect and quantify inhibitory antibodies against FVIII:C.

Sometimes, lupus anticoagulant and pharmacological anticoagulants can result in a false-positive Bethesda assay (6). Lupus anticoagulant can be excluded by diluted Russel viper venom time (dRVVT)-based assays. As coagulation is activated downstream of FVIII:C, dRVVT-based assays are less sensitive to FVIII:C deficiency than aPTT-based lupus assays. The dRVVT assays are used in integrated systems comprising mixing tests (with normal plasma) and confirmation tests (with higher phospholipid concentrations) (7).

Despite the lower sensitivity to FVIII:C inhibitors, Tripodi et al. found borderline or positive results in 22% of congenital haemophilia patients with inhibitors using a commercial dRVVT reagent (8). It is important to keep in mind that inhibitory autoantibodies against FVIII:C and lupus anticoagulant can coexist in some patients with AHA or may interfere with one another. Since a clear discrimination is not always possible, clinical history and symptoms need to be considered along with laboratory findings to diagnose difficult cases.

Once a diagnosis has been made, patients with AHA should be examined for underlying disorders. For further diagnostic workup, a staged protocol has been proposed, including imaging procedures (4).

Haemostatic management

Prevention of bleeding

Prevention of bleeds is of utmost importance in patients with AHA. Surgery and other invasive procedures must be avoided until haemostasis has been secured by adequate treatment. Placement of central venous catheters can result in severe haemorrhages and may require haemostatic treatment. Deep muscle bleeds, even those at risk of a compartment syndrome that would otherwise need surgical removal, should first and almost entirely be treated with haemostatic agents. In the majority of such cases, haemotherapy with high-dose administration of bypassing agents in short dosing intervals (2 to 4 h) can be sufficient to attenuate symptoms.

Strategy for treating bleeds

AHA preferentially occurs in elderly, fragile patients. In those patients, the risks and benefits of treatments need to be weighed carefully on an individual basis. In general, major and active bleeds should be treated as soon as possible with effective haemotherapeutics, whereby bypassing agents being the first choice (9). Delayed or insufficient treatment will often result in worsening of bleeding symptoms and the patient's general condition.

Muscle haematomas, gastrointestinal, urogenital, intracranial, and postoperative bleeding usually require effective haemostatic treatment. In contrast, ecchymosis and subcutaneous bleeds should be followed by close observation, and require treatment only, when additional symptoms occur (9).

Laboratory monitoring has not been established for the bypassing agents. Treatment needs to be guided by close clinical observation, combined with serial evaluation of blood counts and imaging procedures if appropriate. Structured assessments should be made every 8 to 24 h. The frequency of follow-up will depend on the severity of the bleeding event, the patient's general condition, and the intensity of treatment. Haemostatic therapy should be tailored accordingly by adjusting the dose and dosing intervals, or switching products, whenever necessary.

Patients with cardiovascular risk factors, who need bypassing treatment, may require even closer monitoring because of the thromboembolic potency of bypassing agents. Therapy should be reduced or stopped as early as possible after haemostasis has been achieved. However, treatment with bypassing agents should not be withheld in these patients, because the benefit clearly outweighs the risk.

Haemostatic agents

An overview on haemostatic treatments used in AHA is provided (▶Tab. 2).

> Bypassing agents are first choice for severe bleeds.

Recombinant human factor VIIa (rhFVIIa) used in doses of 46–150 µg/kg body weight at 2 to 24 h intervals was effective in 90% of non-surgical and 86% of surgical bleeds according to registries (10). Delayed treatment appeared to reduce efficacy (11). Thromboembolic complications were the most relevant type of adverse events, reported in up to 8% of treated patients (10). Thromboembolic manifestations were more often arterial than venous. Risk factors included advanced age, diabetes mellitus type 2, arterial hypertension, heart failure, and advanced arteriosclerotic disease.

Activated prothrombin complex concentrate (APCC) used at a dose of 75 U/kg every 8 to 12 h achieved complete response in 76% of severe and in 100% of mild to moderate bleeds according to a retrospective collection of 12 patients from 3 centres over a period of 10 years (12). Of note, inhibitor titres were higher in patients with severe bleeds. Those with high titres (>50 BU/ml) required more doses of APCC and had a longer time to bleeds resolution.

There are no reports on direct comparisons of rFVIIa and APCC in acquired haemophilia. However, a propensity score analysis of matched cases from the EACH2 registry indicated similar efficacy, with 93% of bleeds being controlled with either agent as first line treatment (5).

Tranexamic acid can be a valuable adjunct treatment according to the authors' experience. There is no contraindication for combined use of tranexamic acid and rFVIIa. By contrast, some reservation exists to combine tranexamic acid with APCC, although this may not be justified by data. For either combination, experience is very limited and mostly confined to case reports (13, 14). Thromboembolic complications have also been reported (15). Of note, tran-

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agent		dosing	note
bypassing agents	recombinant human factor VIIa (eptacog alfa [activated], NovoSeven™)	90 µg/kg every 2–3 h	prolong dosing interval to 4, 6, 8, or 12 h after achieving haemostasis
	activated prothrombin complex concentrate (human plasma protein with FVIII:C inhibitor bypassing activity, FEIBA™)	50–100 U/kg every 6 to 12 h	maximum single dose 100 U/kg, maximum daily dose 200 U/kg
factor VIII concentrates	various brands	required dose difficult to predict, start with 50 IU/kg every 6 to 8 h	limited efficacy, not recommended for severe bleeds. Close monitoring of peak and trough levels required
	porcine recombinant FVIII:C	in development (29, 30)	licensed by FDA, but not yet by EMA
other agents	desmopressin	0.3 µg/kg every 12–24 h	very limited efficacy, usually only for mild bleeds and low inhibitor titres
	tranexamic acid	0.5–1.0 g every 6–12 h	adjunct treatment. Use caution when combining with bypassing agents.

Tab. 2 Haemostatic agents to treat bleeds in AHA

examic acid is contraindicated for urogenital bleeds because of the risk of urinary outflow obstruction. Overall, combining tranexamic acid with bypassing agents is possible, and often useful, but must be used with caution in patients with major cardiovascular risk factors.

Administration of FVIII:C concentrates and desmopressin should only be considered for mild bleeds in patients with low inhibitor titres (9). A porcine sequence recombinant FVIII:C concentrate has recently been licensed in North America but not yet in Europe.

Thromboprophylaxis and antithrombotic treatment in high risk patients

Anticoagulants should be avoided in actively bleeding patients and as long AHA has not yet achieved remission. Upon remission, FVIII:C activity often increases to >100% of normal, and thromboprophylaxis should be considered. Patients with coronary artery disease, a history of stroke, or atrial fibrillation may require antiplatelet therapy or full-dose anticoagulation after achieving remission.

Inhibitor eradication

All patients with AHA should receive immunosuppressive treatment (9). Spontaneous disappearance of inhibitory autoantibodies can occur in a certain proportion of cases, specifically in pregnancy-associated AHA, but may need > 30 months to occur (16, 17). Of note, patients remain at high risk of bleeding, including fatal haemorrhages, until remission is achieved (18).

Immunosuppressive treatment (IST)

Most frequently drugs for IST in AHA are steroids, cyclophosphamide, and rituximab (19). Azathioprine, vincristine, mycophenolate mofetil, and cyclosporine A have also been used. Many studies have reported on the efficacy of these agents and different combinations thereof, but data are difficult to interpret because of different or inconsistent endpoints, lack of control groups, and/or missing information on relapse, as reviewed earlier by Collins et al. (20).

Steroids versus combination of steroid and cytotoxic drugs have been compared in many studies, reviews and meta-analyses and shown conflicting results (17, 20). The non-interventional United Kingdom 2-year surveillance study found similar rates of CR, time to CR, and overall survival (OS) when comparing patients, who started on steroids versus steroids and cytotoxic agents (21). In contrast, the EACH2 registry documented that CR was more likely in patients receiving steroids and cyclophosphamide (80%), as compared to steroids alone (58%) or rituximab based regimens (61%) (22). OS was not different with regard to the corresponding immunosuppressive regimen.

International consensus recommendations suggest immunosuppression to be initiated with either prednisolone alone (1 mg/kg) or a combination of prednisolone and cyclophosphamide (1–2 mg/kg) for 6 weeks (9, 23). Rituximab was suggested as second line therapy, when steroid/cyclophosphamide failed or was contraindicated (ibidem).

The GTH-AH 01/2010 consensus protocol was based on these recommendations (▶Fig. 2). IST started with steroid alone (week 1–3), and was escalated to steroid/cyclophosphamide (week 4–6) and steroid/rituximab (week 7–10), unless PR was achieved. Alternatives were provided for patients with contraindications to any of the drugs and patients developing AHA while on prednisolone >15 mg per day or equivalent. In case of relapse after PR or CR, the protocol suggested to increase prednisolone to the last effective dose for at least 1 week before tapering again.

Immune tolerance and intravenous immunoglobulin (IVIgG)

High-dose FVIII:C replacement that has been established as "immune tolerance therapy" in congenital haemophilia A with inhibitors and also been reported in AHA in combination with IST (24, 25). Nemes et al. (25) reported that daily infusions of FVIII:C concentrates combined with in-

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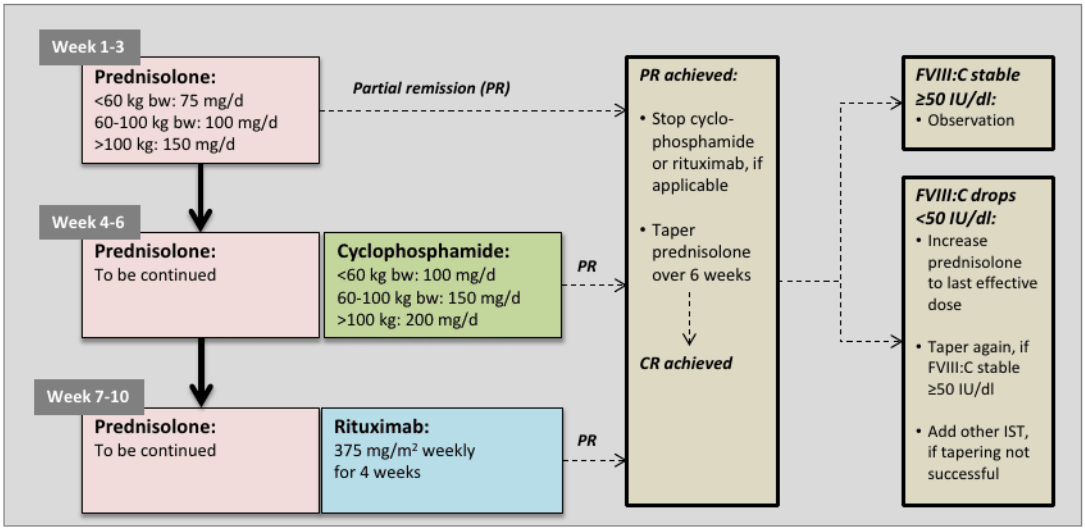

Fig. 2 GTH-AH 01/2010 consensus protocol

travenous cyclophosphamide and methylprednisolone resulted in 93% of CR (14 patients) after a median of 4.6 weeks; this appeared superior to six historic controls treated with steroids and cyclophosphamide (CR in 67% after a median of 28 weeks). However, time to CR in the active arm appeared similar to studies not using FVIII:C concentrates, and time to CR in the controls was very long. Therefore, these data are currently not considered to provide sufficient evidence for FVIII:C immune tolerance in AHA (20).

IVIgG has not been shown to be effective in AHA. Smaller studies as well as the EACH2 registry did not find an increase in the rate of CR or shorter time to remission.

Immunoadsorption

Immunoadsorption using sheep anti-human immunoglobulin affinity chromatography resins was reported to rapidly remove anti-FVIII:C antibodies in patients with AHA. The modified Bonn-Malmo protocol combined immunoadsorption (on day 1–5, weekly) with intravenous immunoglobulin replacement (0.3 g/kg on day 6 and 7, weekly), FVIII:C replacement (100–200 IU/kg, targeted to 80–100% FVIII:C activity), and IST (cyclophosphamide 1–2 mg/kg per day, prednisolone 1 mg/kg per day). A cohort treated with this protocol achieved control of bleeding and disappearance of the inhibitor within a median of 3 days, and CR in 88% at a median of 14 days (26).

Survival and causes of death

In the historic survey by Green and Lechner, published in 1987: "*22% of patients died either directly or indirectly as a consequence of having the inhibitor*" (27). In more recent cohorts, mortality ranged between 26% for EACH2 (3) and 42% in the UK surveillance study (21). The most frequent cause of death was consistently reported to be infection. Sepsis was reported in 33% and contributed to death in 11% of patients in the UK study (21). The choice of IST did not affect OS in either EACH2 or the UK surveillance study. However, survival was related to underlying disorder. In pregnancy-related AHA the proportion of patients alive at final follow-up was 100 %, in autoimmune disorders 71%, idiopathic AHA 58%, and malignancy 32% (22).

Prognostic factors: GTH AH 01/2010 study

Given the variable prognosis of AHA and the hazards of IST, prognostic parameters are urgently needed for appropriate treatment stratification. For instance, patients

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with baseline characteristics that might be expected a very long time needed to achieve remission could be treated more intensely up front, e.g. with a combination immunosuppressive therapy instead of steroid alone. This could reduce the overall duration of IST and, in particular, the duration of steroid exposure.

Baseline laboratory results such inhibitor titre or residual FVIII:C activity are of potential value to guide IST intensity. The largest registry of AHA reported so far, EACH2, documented that patients with higher baseline FVIII:C and lower inhibitor concentrations achieved remission faster, but this analysis was not adjusted for treatment choice (22).

The GTH-AH 01/2010 registry was designed to study baseline parameters as prognostic factors in patients treated according to a uniform IST protocol. The registry included 102 patients over a period of three years. Interim results recently reported indicate that baseline FVIII:C activity is indeed a predictor of the time needed to achieve remission, and also of overall survival (28).

Conclusions

AHA is a severe bleeding disorder that occurs in an elderly and vulnerable patient population.

- Early and precise diagnosis is vital to patients with AHA.
- Prevention of bleeds is important, as well as early and adequate haemostatic treatment once bleeds occur.
- Patient should be referred to expert centres, and IST should be started in all AHA patients as soon as possible.

Adverse events of IST, including infections as the foremost cause of death, need to be addressed by future clinical studies in this field. The GTH-AH 01/2010 contributed prognostic factors that may allow tailoring IST according to patients' baseline characteristics.

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Conflict of interest

A.T. and S.W. received research funding, honoraria for lectures, and fees for consultancy from Novo Nordisk and Baxter.
R.E.S. is a consultant to Bayer HealthCare, Biotest, CSL Behring and Pfizer and received unrestricted grants from Baxter Deutschland and CSL Behring and honoraria for lectures by these companies.
C.D. has nothing to disclose.

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