

Acquired Hemophilia: An Overview on Diagnosis and Treatment

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Abstract: Acquired hemophilia (AH) is a rare but severe bleeding diathesis characterized by autoantibodies against a clotting factor, in most cases Factor VIII (FVIII). This bleeding disorder occurs more frequently in the elderly and may be associated with several conditions, such as malignancies, autoimmune diseases, postpartum or drugs; however, about half of cases remain idiopathic. At variance with congenital hemophilia, in which hemarthroses are the most common bleeding manifestations, in patients with AH hemorrhages involving soft tissues (muscle, skin) are more frequently reported. AH is diagnosed in patients without previous personal or family bleeding history in which prolonged activated partial thromboplastin time is not corrected after mixing and incubating for 2-4 hours at 37°C equal volumes of patient and normal plasma, FVIII:C levels are reduced and a specific FVIII inhibiting activity is detected and measured by the Bethesda assay or its Nijmegen modification. A prompt recognition of this life-threatening bleeding disorder and an early and aggressive treatment are mandatory, as diagnostic delays or inadequate treatments are associated with high mortality rates (up to 44% in literature). Therapeutic approach of AH is devoted to stop acute bleeds and to eradicate the FVIII autoantibody. Bleeding episodes can be treated with FVIII concentrates or desmopressin in patients with low titer inhibitors, but FVIII bypassing agents (activated prothrombin complex concentrates and recombinant activated FVIIa) are required for those with high-titer inhibitors or more severe bleeds. Steroids alone or in combination with cyclophosphamide are effective for eradicating autoantibodies in most cases. More recently, increasing evidence suggests a role for rituximab in this setting, in particular as a second-line approach.

INTRODUCTION

The occurrence of bleeding symptoms in patients with negative previous personal or family history of bleeding and the detection of abnormal coagulation tests caused by circulating specific autoantibodies (inhibitors) are clinical features of acquired hemophilia (AH). Prolonged activated partial thromboplastin time (aPTT) due to anti-Factor VIII (FVIII) autoantibodies is the most commonly reported condition [1], therefore AH is in the majority of cases an acquired Factor VIII deficiency.

AH occurs in the general population with a reported incidence of 1-4 cases per million/year, which increases with age [1, 2]. These data are likely to be underestimated because of undiagnosed or unreported cases, especially in the elderly, in which a major peak of incidence is shown (16.6 per million/year in patients aged >85 years) [2]. The age distribution shows a smaller peak between 20 and 40 years due to pregnancy-related cases [1, 3, 4]. For the same reason, incidence is similar in men and women, with the exception of the excess of female cases in young adults [1-3]. Other clinical conditions associated with AH are hematologic or solid malignancies, autoimmune disorders, dermatological disease or drug reactions (Table 1). However, in about half of patients AH occurs apparently in the absence of other concomitant disease (idiopathic AH), although in some cases an underlying disorder may be diagnosed long after the onset

of the bleeding abnormality [1-7]. This article will focus on current diagnostic and therapeutic approach to this rare but severe bleeding disorder, which is still associated with a high morbidity (about 90% of patients experience severe bleeds) and mortality (up to 44% in literature data) [1, 2, 4, 8, 9], mainly because of diagnostic delays and/or inadequate treatment.

CLINICAL FEATURES AND DIAGNOSIS

At variance with congenital hemophilia, hemarthroses are rare in AH, whereas most patients show hemorrhages involving soft tissues (muscle, skin) or mucous membranes (epistaxis, hematemesis, melena, hematuria). Bleeding after surgery, delivery or other invasive procedures is often the first sign of the clotting abnormality. AH is rarely diagnosed in asymptomatic subjects in which a prolonged aPTT is discovered by chance [1, 2, 4]. As previously mentioned, severe or life-threatening bleeds, requiring hemostatic and transfusion treatment, occur in 80-90% of patients, being fatal in 10-20% of cases. Overall mortality in AH patients is also higher, in particular in elderly patients and over the first weeks after the onset of symptoms, because of the underlying associated diseases, diagnostic delays, inadequate treatment of acute bleeds, bleeding complications during invasive procedures for controlling hemorrhages, or adverse events of treatment (infections, sepsis on immunosuppressive therapy) [1, 2, 4, 8, 11]. Spontaneous resolution of AH is reported in about 25% of patients, especially in drug-induced and pregnancy-related cases [1, 4, 12].

AH should be suspected in the presence of bleeding symptoms in patients with negative personal and family bleeding history showing an isolated prolonged aPTT (nor-

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Table 1. Clinical Conditions Associated with Acquired Haemophilia*

Hematologic malignancies	Chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin lymphoma, myelodysplasia, myelofibrosis
Solid tumors	Lung, prostate, pancreas, colon, stomach, melanoma, head, neck
Autoimmune disorders	Systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis, Sjogren syndrome, multiple sclerosis, myasthenia gravis, autoimmune thyroid disorders, autoimmune hemolytic anemia
Pregnancy-related	Rarely during pregnancy, usually 1-4 months postpartum
Drug-induced	Antibiotics (penicillin and derivatives, chloramphenicol), sulfa drugs, phenytoin, methyldopa, interferon, fludarabine, clopidogrel
Dermatologic diseases	Psoriasis, pemphigus
Other diseases	Acute hepatitis B and C, chronic obstructive pulmonary disease, asthma

*In about 50% of cases no underlying disease is identified (idiopathic cases).

mal prothrombin time). The presence of circulating inhibitors is revealed by the mixing test: mixtures of equal volumes of normal and patient plasma tend to correct the prolonged aPTT when such an abnormality is due to the deficiency of an intrinsic-pathway factor (Factor XII, XI, IX, VIII or von Willebrand factor), whereas aPTT will remain prolonged when an inhibitor against one of these clotting factor is present in the patient plasma. As interaction of the antibodies and coagulation factors is time- and temperature-dependent, incubation should be performed at 37°C and for 2 hours or longer, in particular for increasing sensitivity for detection of low-titer inhibitors [13]. As FVIII inhibitors may also interfere non specifically with the activities of the other related clotting factors, Factor IX, XI and XII plasma levels may result falsely low; increasing dilutions of patient plasma with normal plasma lead to dilute the autoantibody and to normalize activities of factors other than FVIII, which remains inhibited even by the diluted specific autoantibody. Lupus anticoagulant or heparin inhibition should also be excluded by appropriate tests. Once diagnosed, the FVIII inhibitor should be quantitatively evaluated by the classic Bethesda assay, in which residual FVIII:C activity is measured after dilution of inhibitor plasma with pooled normal plasma. The inhibitor level is the reciprocal of the dilution yielding about 50% residual FVIII:C and is expressed in Bethesda Units per ml (B.U./ml). The introduced Nijmegen modification enabled to improve the specificity of the assay, with better discrimination between positive and negative samples at the lower range [14].

Interestingly, inhibitor titers or residual FVIII:C activity are not directly related to the severity of bleeding symptoms or mortality [2, 11], thus their evaluation is not useful for prognostic stratification but is taken into account in the patient follow-up during the inhibitor eradication treatment.

CLINICAL MANAGEMENT

Patients with AH should be managed by a Hemophilia Center with laboratory and clinical experience in this setting, because of the severity of bleeding manifestations and of the

complexity of treatment. An early and appropriate therapeutic approach is crucial for a favorable outcome, which also depends on the treatment and prognosis of any possible concomitant disease or triggering condition [15].

Therapeutic strategy in patients with AH should be devoted both to stop acute bleeds and to eradicate the FVIII autoantibody, the cause of coagulation abnormalities and of bleeding (Table 2). A series of treatment options are available in both directions. Bypassing agents are the most commonly used first-line treatment, in particular for severe bleeds in patients with high-titer inhibitors [10, 16]. Both activated prothrombin complex concentrate (APCC) and recombinant activated factor VII (rFVIIa) have been shown to be effective in these patients [10, 16-18]. APCC doses ranging between 50 and 100 IU/Kg every 8-12 hours provided an excellent or good hemostatic efficacy in 76-100% of treated bleeds [10, 16, 17], with higher efficacy reported in moderate bleeding episodes [17]. A recent review of treatment of bleeding episodes with rFVIIa showed a 88% overall efficacy rate, with better results when rFVIIa was used as first-line treatment (up to 100%) than as a salvage approach [18]. Average doses of 90 µg/Kg (range, 40-180) of rFVIIa every 2-6 hours for a largely variable duration of treatment (1-40 days) have been reported [10, 16, 18]. Similar results with bypassing agents were also shown by the European Acquired Hemophilia (EACH and EACH2) Registry [11]. Other strategies for controlling bleeds, in particular in patients with low-titer inhibitors, include administration of desmopressin or of human or porcine FVIII concentrates [10, 16]. The latter, successfully used in the last decades [19], are presently not available for routine clinical use. A recombinant porcine product recently used in a phase 2 study in congenital hemophiliacs with inhibitors will be probably tested even in patients with AH. If available, immunoadsorption techniques for achieving a fast but transient removal of high-titer inhibitors may be a further strategy in patients with severe, life-threatening bleeds [20].

Eradication of FVIII inhibitors may be achieved in about 75% of patients undergoing immunosuppressive treatment

Table 2. Therapeutic Approaches and Options in Acquired Hemophilia*

Treatment of Acute Bleeds	Inhibitor Eradication
<p>- Human FVIII concentrates, desmopressin: usually in patients with low-titer inhibitors and non-severe bleeds</p> <p>- Porcine FVIII concentrate: presently not available (recombinant product on development)</p> <p>- FVIII bypassing agents: in patients with high-titer inhibitors and severe bleeds.</p> <p>--- APCC (50-100 IU/Kg every 8-12 hrs)</p> <p>--- rFVIIa (90-120 µg/Kg every 2-4 hrs, higher doses seldom reported)</p> <p>- Immunoabsorption (staphylococcal Protein A or sepharose-bound sheep anti-human antibodies): fast but transient inhibitor removal in life-threatening bleeds and very high-titer inhibitors</p>	<p>- Prednisone (1-2 mg/Kg/d) alone or plus cyclophosphamide (2 mg/Kg/d), at least for 5 weeks</p> <p>- High-dose immunoglobulins (0.4 g/Kg/d for 5 days or 1 g/Kg/d for 2 days), often in association with other treatments</p> <p>- Cyclosporine (200-300 mg/d) alone or in association with steroids, usually as second-line treatment</p> <p>- Rituximab (375 mg/m² weekly for 4 weeks), usually as second line treatment, in association with steroids</p> <p>- Immune tolerance induction: FVIII concentrate administration in association with various immunosuppressive agents.</p>

APCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII.

*Therapeutic strategy includes the identification and treatment of any possible concomitant disease or triggering condition.

with steroids alone (prednisone 1-2 mg/Kg per day for at least 5 weeks) or in combination with cyclophosphamide (1-2 mg/Kg per day) [1, 2, 10, 11, 16, 21, 22]. The latter association is likely to provide advantages in terms of inhibitor remission [1, 11, 16, 21, 22], but not with respect to overall survival [1, 2], in particular because of infection-related mortality [1, 11]. Thus, cyclophosphamide and other cytotoxic agents should be used cautiously especially in elderly patients, tailoring the dose and the duration of treatment for reducing side effects [10]. High-dose intravenous immunoglobulins should not be used as a first-choice treatment [2, 23] but may be useful as adjunctive therapy to other inhibitor eradicating approaches [2, 10]. Cyclosporine, usually in combination with steroids, has been successfully used as a second line treatment [24]. In this respect, encouraging results are reported with the use of rituximab in patients refractory to first-line immunosuppressive treatment [25]. This positive experience led to propose the combination of rituximab with immunosuppressive agents as a first-line approach for patients with high-titer inhibitors [26]. However, available data come from case reports or small series and larger prospective studies are needed for assessing efficacy and safety of rituximab in this setting. Finally, immune tolerance protocols, similar to those used for eradicating alloantibodies in congenital hemophilia, have been also proposed for treating FVIII autoantibodies. Successful eradication is reported in about 90% of patients treated with combinations of FVIII concentrates (20-100 IU/Kg per day) and immunosuppressive agents [27, 28]. Small case series have been presently reported and these interesting results need to be validated by more rigorous studies.

CONCLUSIONS

Recent national and international efforts with AH Registries [2, 11] and meta-analyses of literature data [1, 16] provided significant increase of knowledge of natural history and prognosis of this rare but severe bleeding disorder. De-

spite the lack of definite conclusions on the best hemostatic and inhibitor eradicating approaches, a series of effective options are presently available, giving the opportunity of tailoring the treatment to the patient clinical features. A prompt recognition of this life-threatening condition and an early and aggressive treatment, preferably by specialized centers, are mandatory, as diagnostic delays or inadequate treatments are still associated with high mortality rates.

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