

Acquired haemophilia

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Abstract: Acquired haemophilia (AH) is a severe bleeding diathesis that affects both males and females. It is caused by suddenly appearing autoantibodies that interfere with coagulation factor VIII (FVIII) activity. Although some conditions such as autoimmune diseases, cancer and puerperium seem likely to induce AH, in more than half of the observed cases autoantibodies to FVIII are idiopathic. The clinical picture is characterized by spontaneous and post-traumatic subcutaneous bleeds as well as massive mucosal membrane hemorrhages (from the genitourinary and gastrointestinal tracts). Typical abnormalities in AH are prolonged activated partial thromboplastin time and normal results of the other haemostatic tests (platelet count, prothrombin and thrombin times, fibrinogen concentration). Acquired haemophilia is definitely confirmed by quantification of FVIII neutralizing antibodies. Bleeds are usually treated with activated prothrombin complex concentrates and activated recombinant factor VII. In most patients with AH, the use of immunosuppressive agents results in autoantibody elimination and restoration of normal FVIII plasma activity.

Key words: autoantibodies, bleeding, factor VIII, immunosuppression, inhibitor

INTRODUCTION

Acquired hemophilia (AH) is a severe hemorrhagic diathesis induced by autoantibodies impairing the function of coagulation factor VIII (FVIII) [1]. These autoantibodies are defined as the circulating anticoagulant or the FVIII inhibitor. Contrary to classical hemophilia A with its basis being the FVIII gene mutation located on the sex chromosome X, acquired hemophilia occurs both in women and in men. Although the reason for a tendency to bleeding in either classical or acquired hemophilia is the same – a diminished patient plasma FVIII activity, the clinical pictures of both diseases differ; in classical hemophilia spontaneous hemorrhages to articulations are typical, while in AH extensive blood subcutaneous extravasations and mucosal membrane bleeds are usually observed. The AH etiology remains unknown. Some diseases (autoimmune disorders, malignant neoplasms) and clinical conditions (puerperium) seem to induce the AH occurrence, but in more than fifty percent of the cases, FVIII autoantibodies are of an idiopathic origin [2].

The first manifestation of AH is often a fulminant hemorrhage. In such a situation only an instant diagnosis and immediate administration of appropriate treatment can save the patient's life. The main aim of this study is to discuss the

current recommendations concerning establishing a diagnosis and treatment of AH.

Antibodies characteristics and prevalence

Autoantibodies present in AH belong to the class IgG immunoglobins, usually subclasses IgG₁ and IgG₄, and they bind with FVIII by epitopes located on its A₂ and C₂ domains [3]. The autoantibodies anticoagulating action mechanism lies in the impairment of FVIII reaction with the phospholipids (antibodies anti-C₂), disruptions in the tenase complex formation (antibodies anti-A₂), and possibly also in blocking the FVIII binding with von Willebrand factor [4]. The kinetics of FVIII interactions with autoantibodies observed in AH is different from that observed in classical hemophilia complicated by alloantibodies [5]. If in classical hemophilia alloantibodies present in an appropriate concentration completely neutralize FVIII activity, in acquired hemophilia, even with a very high patient serum titer of autoantibodies, a residual FVIII activity can be found in serum. This several-percent FVIII activity usually does not protect patients from severe bleeds. Autoantibodies do not bind the complement and do not induce allergic reactions.

It is estimated that the annual AH incidence is 0.2–1 per 1 million individuals, however, due to frequent diagnostic errors it cannot be excluded that the statistics are underrated [6]. The disease occurs usually in the 6th–7th decade of life, and concerns men and women equally. Acquired hemophilia very rarely occurs in children. In more than half the cases, the FVIII autoantibodies occurrence is not related to any disease or clinical condition. Such a form of AH is called idiopathic. Quite a significant percentage of AH patients (20%) repre-

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sent individuals with a coexisting autoimmune disease, usually systemic lupus erythematosus, but also with rheumatoid arthritis, ulcerative colitis or a lymphoproliferative disease [7]. In 10% of AH cases a malignant neoplasm is detected, usually lung cancer and prostate cancer [8]. An especially interesting form of the disease, constituting also 10% of all cases, is AH occurring in pregnancy or more frequently, during three months after delivery. The pregnancy-related inhibitor occurs more often during the first pregnancy and does not show a relapse tendency in following pregnancies; interestingly, FVIII autoantibodies that occur in pregnancy and puerperium often disappear spontaneously within twelve to thirty months from the occurrence [9]. Case reports explaining the AH occurrence by a recent exposure to a surgical procedure or administration of medications (i.e. penicillin, chloramphenicol, phenytoin) can be found in the bibliography [7].

Clinical symptoms and diagnosis

In nearly 90% of cases AH manifests itself in a severe hemorrhagic diathesis causing death of 7.9–22 % of patients within a few days [10]. In contrast to classical hemophilia, spontaneous bleeds to joints are rarely observed in the course of AH. Extensive subcutaneous blood extravasations as well as mucosal hemorrhages (from the gastrointestinal tract, urinary tract and female generative tract), bleedings from postoperative surgical wounds and after tooth extraction procedures, and also extensive, painful intramuscular hematomas are most typical. Retroperitoneal space hemorrhages were also described. Cerebral hemorrhages which usually fail to be stopped on time have the most dramatic course.

AH should therefore be suspected in patients with no tendencies to hemorrhages for the major part of their lives who suddenly present with symptoms of severe hemorrhagic diathesis. Acquired hemophilia is definitely confirmed by detecting the FVIII inhibitor in laboratory tests. The tests are unfortunately only available in specialized hematological laboratories; therefore the time required for diagnosing often alarmingly extends, the consequence being a delay in the appropriate antihemorrhagic treatment administration, which determines the survival. What is more, quite often before being diagnosed, the patient undergoes invasive diagnostic or surgical procedures which can result in complications such as difficult to manage hemorrhages requiring massive blood transfusions. It is therefore necessary to consult a hemostasis specialist, as soon as possible, in all cases of the AH suspicion [11]. On the other hand, it should be stressed that if the clinical picture is typical of AH, then merely on the basis of screening hemostasis test results an initial AH diagnosis can be attempted and an appropriate antihemorrhagic treatment introduced.

In a patient with AH with normal prothrombin, thrombin and bleeding time values, and normal platelet count and fibrinogen concentration, a two-, threefold prolongation of the activated partial thromboplastin time – APTT can usually be seen. Such a constellation of test results can also occur only

in coagulation factors VIII, IX, XI and XII congenital deficiencies, and in the case of lupus anticoagulant presence in the examined serum, which, as it is well known, (*in vivo*) does not induce bleeding tendency, but predisposes to thrombosis. With the reason for a prolonged APTT being the presence of a nonfractionated heparin in the blood sample, the thrombin time is significantly prolonged or indeterminable.

The presence of the anticoagulant is definitely confirmed by the APTT prolongation in the mixture of equal volumes of examined serum and of normal serum (so called correction test). It is then necessary to determine the FVIII activity, which in healthy individuals ranges between 50–150 % of normal values, and in AH patients – 0–15 % of normal values. The last stage of FVIII inhibitor laboratory diagnosis is to measure its concentration, that is its titer, expressed in Bethesda units (B.U./ml). One B.U. is defined as the titer of antibodies inactivating 50 percent of the FVIII activity in the mixture of equal volumes of examined plasma and normal plasma, after a two-hour incubation in a temperature of 37°C [12].

Management

The management strategy with the AH patient includes two main aims: the immediate one, which is the bleeding treatment and prophylaxis, and the long-term goal consisting in the inhibitor elimination (fig.). In pregnancy related or drug administration related acquired hemophilia stopping the bleeding is of the greatest importance, because in a considerable percent of cases the antibodies disappear spontaneously in several or up to twenty months from delivery, or from the discontinuation of drug administration. In a small number of AH cases without a coexisting hemorrhagic diathesis the management can be limited to the inhibitor elimination. It is always necessary to remember that there is a possibility of the coexistence of different diseases favoring the occurrence of acquired hemophilia. Detecting and appropriate treatment of these diseases may have an important impact on the outcome.

Bleeding prophylaxis and treatment

Table 1 shows medications used in stopping bleeding in AH patients [10,11,13,14]. It has to be stressed that fresh frozen plasma and cryoprecipitate transfusions are usually ineffective; the concentration of FVIII contained in them is low and quickly inactivated by antibodies. Only in a limited number of patients with a low inhibitor titer the administration of large doses of human FVIII concentrate may prove efficient. Greater hopes are placed in porcine FVIII, which in a significant number of patients does not show cross reactivity with human FVIII [15]. Research with the use of genetic engineering methods is being carried out in order to produce the porcine FVIII. Descriptions of stopping less serious bleedings after the synthetic vasopressin analogues transfusion – desmopressin (Minirin, Ferring, Sweden) in patients with a low FVIII antibodies titer can be found in the literature. Desmopressin

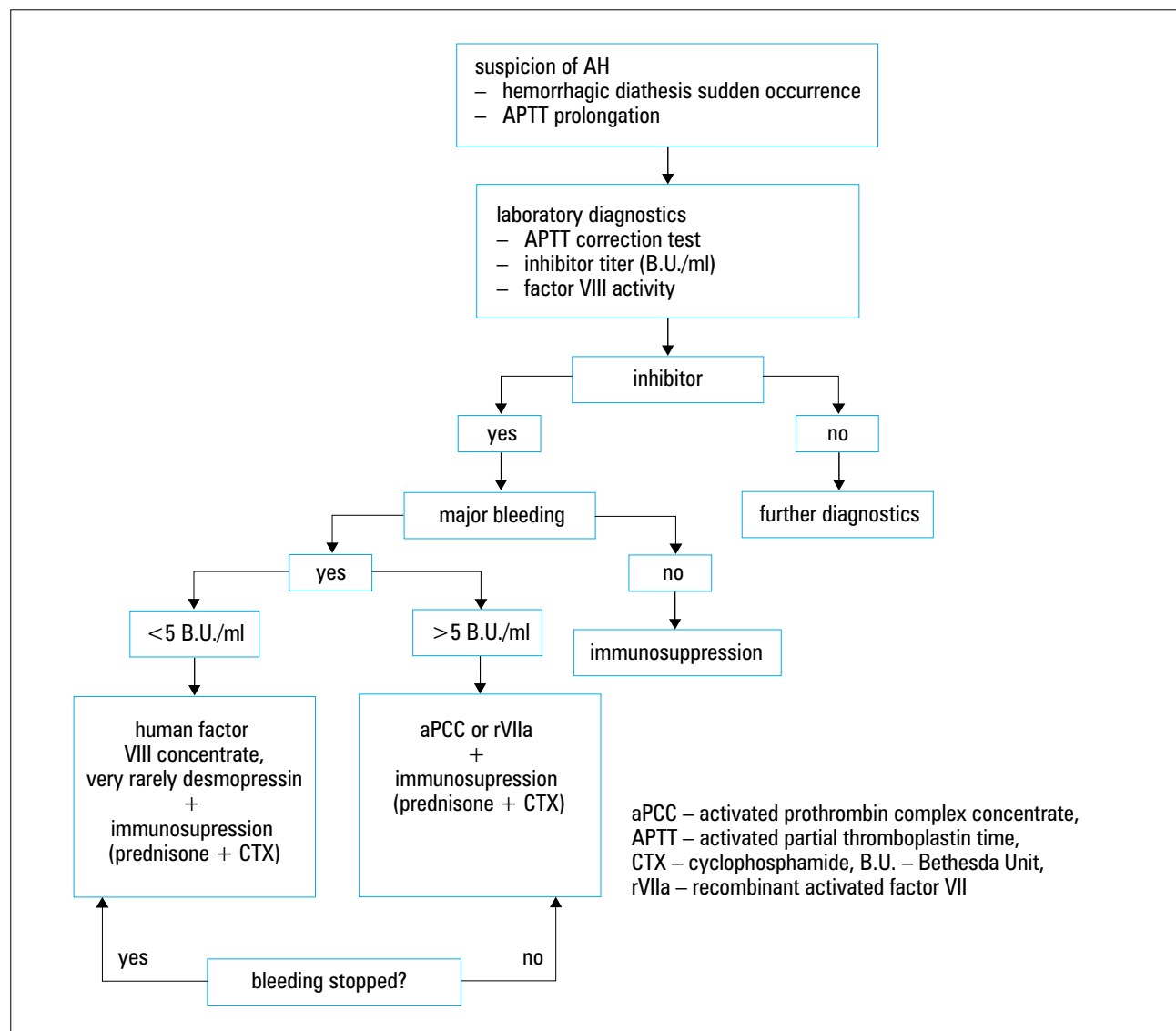


Fig. Algorithm of acquired hemophilia (AH) patient management [23]

releases FVIII from the vascular endothelium to the circulatory system. While administering FVIII concentrates and desmopressin, FVIII activity in plasma should be monitored. Evidence of an efficient treatment is a rise of FVIII activity by at least 30% of normal values.

According to the majority of authors, medications of choice in bleedings inhibition in AH patients are activated prothrombin complex concentrates – aPCC and recombinant activated factor VII (rVIIa) [16]. These concentrates activate blood clotting with the omission of the FVIII presence dependent stage. Their efficacy in the treatment of acquired hemophilia-associated bleedings has been proven in clinical studies. These medications have two serious drawbacks. Firstly, there are no laboratory methods to show their efficacy. Secondly, the administration of aPCC and rVIIa is costly. It is enough to say

that the price of 1 unit of aPCC (FEIBA, Baxter-Immuno, Austria) is about 4.5 zlotys, and the price of 1 mg of rVIIa (NovoSeven, Novo Nordisk, Denmark) is around 3500 zlotys. The administration of aPCC and rVIIa is related to the risk of thrombotic complications occurrence. The risk seems to be greater with aPCC [17,18]. Some authors therefore advise against the simultaneous administration of aPCC and anti-fibrinolytic drugs, such as tranexamic acid which efficiently inhibits mucosal membrane bleeds, but is contraindicated in the case of hematuria, renal insufficiency and thrombosis.

The inhibitor elimination

Factor VIII antibodies can be relatively quickly eliminated from the circulatory system with the use of extracorporeal ad-

Table 1. Treatment of bleeding in acquired hemophilia

Medication	Dosage
human FVIII concentrate	50–100 u./kg body weight, <i>i.v.</i> every 8–12 h or in continuous intravenous infusion.*
porcine FVIII concentrate	50–100 u./kg body weight <i>i.v.</i> every 8–12 h*
desmopressin (Minirin, Ferring)	0.3–0.4 µg/kg body weight. (in 100 ml 0.9% NaCl) in intravenous infusion of a minimal duration of 30 min. every 24 h*
aPCC (Feiba, Baxter-Immuno)	50–100 u./kg body weight <i>i.v.</i> every 8–12 h**
rVIIa (NovoSeven, Novo Nordisk)	70–90 µg/kg body weight <i>i.v.</i> every 2–4 h
adjuvant treatment: tranexamic acid# (Exacyl, Polfa Warszawa)	15 mg/kg body weight <i>p.o.</i> or <i>i.v.</i> every 8 h (daily dose is usually 3 × 1.0 g)

* factor VIII plasma activity monitoring recommended

** maximal daily dose 200 u./kg body weight

contraindication in urinary tract bleeds

aPCC – activated prothrombin complex concentrate, FVIII – factor VIII., *i.v.* – intravenously, *p.o.* – orally, rVIIa – recombinant activated factor VII

sorption on columns using staphylococcal protein A (Therasorb®), which selectively binds the Fc fragment of human IgG, or through plasmapheresis [19,20]. The first method is not available in Poland. Regarding plasmapheresis, the exchange of 40 ml plasma/kg (about 3 l in an adult subject) allows the elimination of about 50% of the total number of antibodies. The effect of plasmapheresis (as of extracorporeal adsorption) is however of short duration, the procedure itself technically difficult and possible to perform only in highly specialized centers. Therefore, immunosuppressive medications play the most important role in the inhibitor elimination. It is believed that the immunosuppressive therapy should be administered as soon as possible after AH has been diagnosed; yet, possible contraindications to this therapy should always be taken into account. It should not be forgotten that there is a risk of many adverse effects occurrence, i.e. bone marrow suppression or severe infections, especially dangerous in elderly patients with accompanying chronic diseases, associated with the immunosuppressive treatment.

Table 2 shows immunosuppressive medications used in the inhibitor elimination in AH patients. In view of there being no randomized clinical studies data, it is believed that the first line treatment consists in oral prednisone in a daily dose of 1 mg/kg body weight, in monotherapy or in combination with cyclophosphamide (CTX) [21,22]. The latter is usually administered in a daily dose of 100–150 mg. A positive response expressed in the inhibitor elimination and the normalization of the FVIII plasma activity is observed in sixty-seventy percent of patients receiving time prednisone and CTX

Table 2. Most frequently administered drugs eliminating factor VIII (FVIII) autoantibodies

Medication*	Dosage
prednisone**	1 mg/kg body weight/d <i>p.o.</i> for max. 6–8 weeks
cyclophosphamide**	100–150 mg/d <i>p.o.</i> for max. 6–8 weeks
azathioprine	2 mg/kg body weight/d <i>p.o.</i> for max. 6–8 weeks
cyclosporine A	10–15 mg/kg body weight/d under serum concentration control, which should be 150–350 ng/ml
IVIg	0.3–0.4 g/kg body weight/d for 5 days or 1–2 g/kg body weight/d <i>i.v.</i> for 2–5 days
rituximab	375 mg/m ² once a week (for ≥4 consecutive weeks)
vincristine#	1 mg/ m ² <i>i.v.</i> (max. single dose 2 mg)
2-CDA	0.1 mg/kg body weight in a 24-h <i>i.v.</i> infusion for 7 days[25] or 0.12 mg/kg body weight in a 2-h <i>i.v.</i> infusion for 5 days

* Usually ≥2 medication combination used (see text).

** Prednisone and cyclophosphamide recommended for the first-line treatment in doses given in the table.

most frequently with cyclophosphamide or prednisone (see text)

d – daily, IVIg – intravenous immunoglobulins, 2-CDA – 2- Chlorodeoxyadenosine, other– see tab. 1

simultaneously. In patients in whom a six-eight-week-long administration of corticosteroids and CTX was unsuccessful in the inhibitor elimination, the second-line drugs such as rituximab, cyclosporine A and other immunosuppressive and immunomodulating medications shown in table 2, may be administered [10,11,13,23–25]. A combination of two or more medications is usually used, i.e. vincristine (usually in a dose of 2 mg *i.v.* in the first day of treatment) together with CTX (500 mg *i.v.* in the first day and then – in the second to fifth days – 200 mg *p.o.* every 24 h) and prednisone (100 mg orally every 24 h in the first to fifth days) in the four-week cycles [26]. The findings concerning the great efficacy of rituximab administered in monotherapy or in combination with corticosteroids or cyclophosphamide, seem to be very promising [27]. It is estimated that AH recurrence occurs in twenty percent of patients who obtained remission as a result of the first course of immunosuppressive therapy. In such cases the second attempt to eliminate the inhibitor should be made, and the same immunosuppressive drugs which induced the first remission may be used. In women of child-bearing age CTX and other alkylating agents administration must be avoided. In pregnant women with AH a corticosteroid alone or in combination with azathioprine is recommended [13].

Some authors think that the administration of immunosuppressive drugs and large doses of FVIII in intravenous injections at the same time can contribute to shortening the time

required for the inhibitor elimination. Hungarian authors achieved the inhibitor elimination in 90% of AH patients after a three-week administration of human FVIII concentrate (30 i.u./kg body weight every 24 h for the first week, 20 i.u./kg body weight every 24 h for the second and 15 i.u./kg body weight every 24 h for the third week) in combination with cyclophosphamide (200 mg *i.v.* every 24 h, to reach a cumulated total dose of 2–3 g) and methylprednisolone (100 mg *i.v.* every 24 h for the first week and in gradually diminishing doses for the following two weeks) [28].

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