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Acquired haemophilia: overview and case report

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Abstract

Background. Acquired haemophilia (AH) is a rare autoimmune disease with an annual incidence of approximately 1-4 cases per million population. It is characterised by autoantibodies against circulating factor (F) VIII. AH usually affects middle aged or elderly population, yet a distinctive subgroup of AH patients are young females who develop AH as a complication of pregnancy. This specific category is referred to as postpartum AH. The trigger for AH remains unknown in more than 50% of cases. AH may be asociated with autoimmune diseases, solid cancers, inflammatory bowel disease, infections and use of some drugs. ***Case report***. The pattern of bleeding in AH is quite distinct from that seen in classical congenital form of haemophilia A or B. The principal manifestations are extensive bleedings into the skin and soft tissues that may have life-threatening consequences. Prolonged activated partial thromboplastin time (aPTT) is a specific laboratory finding in these patients. Other key haemostasis parameters are within normal range. Mixing studies demonstrate the presence of time-dependent factor FVIII inhibitor. The treatment consists of haemostatic arm with aPCC (activated prothrombin complex concentrate) or rFVIIa (recombinant activated FVII), and an immunosupressive arm. If AH is recognised early and haemostatic treated effectively, the disease is likely to go into remission. *Anestezjologia i Ratownictwo 2011; 5: 45-50.*

Keywords: acquired haemophilia, prolonged activated partial thromboplastin time, recombinant activated FVII, activated prothrombin complex concentrate

Introduction

Acquired haemophilia (AH) is a rare acquired autoimmune disease that manifests as a blood clotting disorder. The annual incidence is 1 to 4 cases per million population [1]. In our experience, the annual incidence of 1 case per million population appears to be closer to reality. Despite its low incidence, the disease must always be considered in patients presenting with suspicious clinical and laboratory features. If left untreated, severe bleedings are likely to be fatal, the mortality rate of AH attaining 22% [2]. The disease is characterised by acquired inhibitors against coagulation factor (F) VIII. As a rule there are no inhibitors against coagulation factor IX (FIX). It is very likely that FVIII, which is a much larger molecule than FIX, constitutes a greater antigenic stimulus for the body's immune system. Inhibitors are polyclonal antibodies of IgG subtype [3]. The disease incidence has two peaks. The first one occurs at the age of 20-30 years due to postpartum AH, and constitutes a rare postnatal complication that usually occurs after the first childbirth. The most common manifestation of the disease is continuous vaginal bleeding that usually starts two months after childbirth. Even if left untreated, the disease has a favourable prognosis, and a nearly 100% long-term complete remission is achieved [4]. The second peak of incidence occurs at the age of 68-80 years. According to the literature data, the annual incidence of the disease in the over-85 age group is as high as 14.7 cases per million population [1]. The cause of disease remains unknown in approximately 50% of cases. In addition to pregnancy in females, the triggering factors include autoimmune

diseases (systemic lupus erythemathosus, rheumatoid arthritis, Sjoegren syndrome, scleroderma, multiple sclerosis, Graves disease, autoimmune haemolytic anemia), cancers (prostate, colon, stomach, gallbladder, breast , lymphoproliferative malignancies, myelodysplastic syndromes), inflammatory bowel diseases, some drugs (penicillins, sulphonamides, phenytoin, methyldopa, clopidogrel, interferon-alpha) infections (acute hepatitis B and C) and some other conditions [5,6].

Clinical picture

Unlike classical haemophilia A and haemophilia B, which affect only males – females being disease carriers – AH affects both sexes equally. The bleeding pattern in AH, however, is completely different from that seen in classical congenital haemophilia. In the latter, the hallmark is bleeding into joints (haemarthrosis). AH is characterised by bleeding into the skin, mucous membranes and soft tissues. Bleeding episodes are often very extensive and involve large areas of the body surface (Figure 1.). The physician attending the AH patient is usually surprised by the extent of bleeding. Haemorrhage results in a decrease in haemoglobin (Hb) levels, and a haemorrhagic shock may ensue. Bleeding into soft tissues may deteriorate rapidly and may lead to compartment syndrome. Less frequently, the disease manifests itself as haematuria or gastrointestinal bleeding [7].

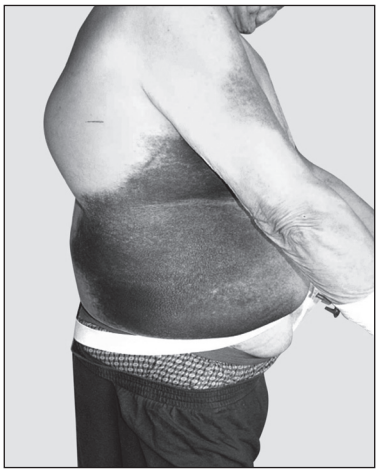

Figure 1. Massive haemorrhagic skin suffusion in a patient with acquired haemophilia (published with permission of NovoNordisk®)

Laboratory tests

The next step is haemostasis screening, which reveals prolonged activated partial thromboplastin time (aPTT) in the presence of normal other haemostasis parameters, including prothrombin time, thrombin time and platelet count. Isolated aPTT prolongation may be a result of one or more coagulation FVIII, FIX, FXI and FXII factors deficiencies, therefore tests are done for all of them. In patients with acquired haemophilia, testing will reveal low plasma FVIII levels, but always with some measurable residual FVIII activity (even after incubation at high antibody concentrations). Also in the clinical context of extensive bleeding, residual FVIII levels are measurable in the presence of high-titre inhibitory antibodies.

Mixing tests are customarily performed to distinguish between true FVIII deficiency and the presence of inhibitory substance. Equal volumes of patient plasma and normal plasma pool as a control are incubated. Tests are performed and compared immediately following the mixture of normal and patient test plasma and after two hours of incubation. aPTT that remains prolonged even after two hours of incubation is suggestive of an inhibitor to FVIII. Reduced FVIII levels, artificial aPTT prolongation which does not correct on mixing with normal plasma may sometimes be associated with lupus anticoagulant. Lupus anticoagulants are not time dependent, and specific tests should be done in the context of differential diagnosis.

Finally, titres of inhibitory antibodies to FVIII, expressed in Bethesda units (BU) are measured. High-titre inhibitory antibodies may translate into increased risk of bleeding and poorer response to immunosuppressive therapy.

The differential diagnosis must always consider the possibility of several other causes of aPTT prolongation, such as the presence of conventional heparin in infusion mixtures prepared for the patient, milder forms of haemophilia A, B or C and vonWillebrandt's disease.

Treatment

In contrast to classical haemophilia A and B, for which treatment recommendations has been well-established, there are no such clear and uniform treatment algorithms available for AH. The potential for major bleeding problems is high and therefore these patients require specialist management in, or at least

close cooperation with, a haemostasis units. Treatment recommendations are based on clinical data of patients suffering from AH. No randomised clinical trials have been conducted to date.

There are always two main goals of treatment: urgent control of bleeding episodes and elimination of inhibitors using an immunosupressive treatment modality. The incidence rate of fatal bleeding in AH patients who receive no haemostatic treatment may range between 22% and 31% [3,6,8]. The principal drugs available for the treatment of bleeding episodes include: activated prothrombin complex concentrate (aPCC; FEIBA®, which contains activated factors VII, IX and X) and recombinant activated factor VII (rFVIIa; NovoSeven®). FEIBA® is given by IV infusion at doses ranging from 50 to 100 IU/kgBW/8-12 hours (maximum 200 IU/kgBW/daily). The treatment is effective in 76%-100% of bleeding episodes, and approximately ten consecutive doses are required to control severe bleeding [8,9]. We do not use FEIBA® in combination with antifibrinolytics because the thrombogenicity issue has not yet been fully clarified. Special caution should be exercised in elderly patients and in individuals with underlying cardiovascular disease.

Recombinant activated FVII (rFVIIa; NovoSeven®) is an alternative agent, which has the advantage of carrying no risk of transfer of blood-borne viruses and other pathogens. The drug can also be used together with antifibrinolytics. The same standard dosage regimen as for other rFVIIa approved clinical indications is used, i.e. 90-120 μg/kgBW/2-3 hours until the bleeding stops [10]. The response is effective in 100% of cases if the medication is used as a primary therapeutic modality, and in 75% of cases (plus 17% partial response) when it is used in the context of salvage treatment [11]. Clearly, there is a risk of thromboembolic complications, the recently reported rate being approximately 7.2% in the AH setting [12]. The complications are mainly attributed to old age of AH patients and to the presence of risks factors, such as smoking, hypertension, previous cardiovascular events, type 2 diabetes and obesity. Particular caution is required in patients with tissue factor expression (non-stable atherosclerotic disease, disseminated intravascular coagulation, sepsis). There are some other treatment options described in the literature, such as FVIII concentrates, desmopressin and porcine VIII [13-15]. These treatment strategies should not be considered in countries where rFVIIa and aPCC are available, except in patients in whom previous first-line treatments have failed. In Slovenia, rFVIIa is considered the therapy of choice because of the reported favourable clinical experience, and because of the above mentioned efficacy and safety of the drug and its viral safety. Another advantage of rFVIIa is that it can be used in combination with antifibrinolytic treatment - usualy we choose tranexamic acid - especially in the presence of mucosal bleeding. As stated recently, anti-fibrinolytic agents are contraindicated in conjunction with aPCC administration [16].

Immunosuppresive tratment starts hand in hand with haemostatic measures. First-line treatment consists of prednisone 1 mg/kg BW in combination with cyclophosphamide 50-100 mg/day orally for up to six weeks. In females of child-bearing age azathioprine may be used instead of cyclophosphamide. As reported, 70%-80% of patients respond to a combination of corticosteroids and cyclophosphamide [17]. Alternative treatment modalities include rituximab, cyclosporine A, mycophenolate mophetil and chloro-deoxyadenosine [18-20].

After a complete and sustained response has been achieved, aPTT and FVIII plasma levels should be regularly monitored. Poor prognostic features in AH include old age (over 65 years), failure to achieve complete disease remission and underlying malignant disease.

During the past five years, seven patients with AH were treated in Slovenia. In two patients, haemostatic treatment was started with aPCC (in one case it was ineffective and was later replaced by rFVIIa), and in five patients with rFVIIa. Haemostatic therapy proved effective in all patients receiving rFVIIa. All rFVIIa treated patients were given also tranexamic acid.

Conclusion and an illustrative case report

Even if AH is a rare disease, it must always be considered as an important option in the differential diagnosis of unexplained bleeding, especially when associated with prolonged aPTT. The disease may be fatal if unrecognised, as illustrated in the following case report.

We report a 70-year-old patient with a newly diagnosed acquired haemophilia A and concomitant acute coronary syndrome with ischaemia, who received rFVIIa to control intractable life-threatening bleeding. The patient was referred to the Department of Rheumatology where he was diagnosed with idiopathic

arthritis. Despite the presence of skin haemorrhages the patient was started on symptomatic therapy for arthralgias with diclofenac injected intramuscularly into the right gluteal region. Immediately after the first injection, the patient developed an extensive haematoma, measuring 15x15 cm . There was a significant drop of haemoglobin (Hb), from 113 g/L to 85 g/L. Haemostasis tests gave the following results: aPTT 101.8 s, prothrombin time (PT) 0.98, international normalised ratio (INR) 1.07, thrombin time (TT) 16.8, fibrinogen 4.8 g/L, and subsequently FVIII:C 0.10 IU/ml. Acquired haemophilia A was diagnosed. The patient required transfusion of two packed red blood cell units and 500 ml of fresh frozen plasma (FFP). Just prior to being transferred to the Department of Haematology he reported anginal chest pain, which was not completely relieved by sublingual nitrate.

On admission to the Department of Haematology the patient was free of anginal pain ; control laboratory tests showed: Hb 92 g/L, platelets (Plt) 259 10^9/L, PT 1.0, INR 1.0, aPTT 77.3 s, fibrinogen 5.6 g/L and initial troponin I (TnI) three hours after the onset of anginal pain 0.020 μg/L. Considering the patient's history of stable angina and ischaemic heart disease, his chest pain was attributed to progressive angina, which appeared to be due to posthaemorrhagic anaemia rather than acute coronary thrombosis. A large haematoma, persisting in the right gluteal region, and absence of increase in Hb levels suggested that the haemorrhage had not been arrested. rFVIIa at a dose of 90 μg/kg/3h was initiated (Figure 2.). Control laboratory findings after the first dose of rFVIIa revealed aPTT 60.3 s, TnI 0.273 μg/L and anti-FVIII:C inhibitor titre of 92 Bethesda units (BU). At the same time the patient suffered repeated episodes of typical anginal pain. The ECG revealed reversible ST segment depressions in precordial leads V_1-V_6 during sinus tachycardia, obviously due to posthaemorrhagic anaemia. ST changes in precordial leads disappeared after blood transfusion and correction of blood haemoglobin levels. However, control TnI increased to 0.850 μg/L and non-ST elevation myocardial infarction (NSTEMI) was diagnosed. The patient was transferred to the Coronary Unit, where he stayed for 48 hours. While in ICU he was treated with rFVIIa at a dose of 90 μg/kg/6h (Figure 3). During that time he was haemodynamically stable and we decided to prolong the time interval between rFVIIa doses to lower the risk of possible coronary thrombosis [21]. Throughout the treatment with rFVIIa he was free of anginal pain, and no further ECG changes were noted. Angiotensine-converting enzyme inhibitor and intravenous nitrate were initiated. The patient received no acetylsalicylic acid or heparin. Beta-blocker therapy was continued. Haemoglobin levels remained constant at 100 g/L, and anginal pain did not recur despite continued therapy with rFVIIa.

On return to the Department of Haematology the patient's laboratory findings were as follows: Hb

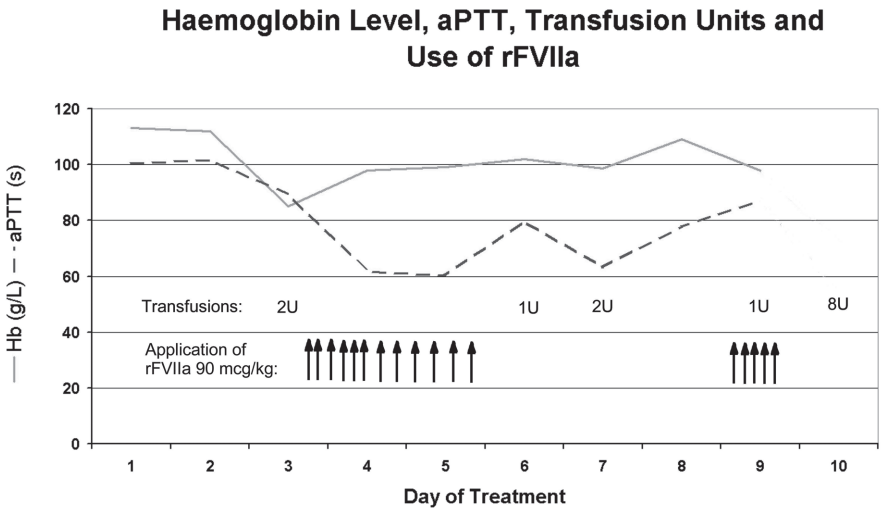

Figure 2. Haemoglobin, aPTT, timing of rFVIIa administration and transfusion requirements during the course of treatment (reference hemoglobin values for male 133-167 g/L; reference aPTT value 24-35,5 seconds)

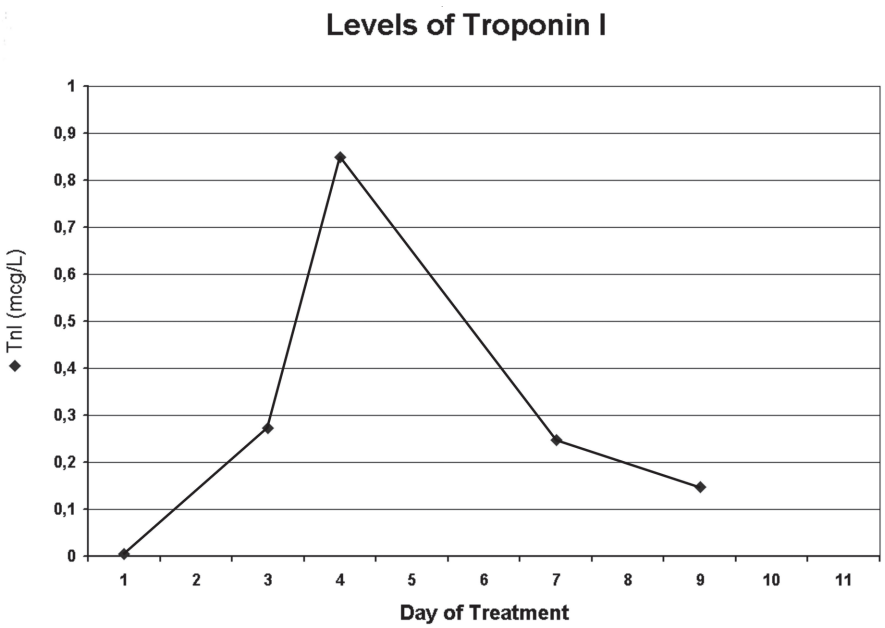

Figure 3. Dynamics of troponin I levels (nornal reference TnI level < 0,1 mcg/L)

99 g/L, Plt 237 10^9/L, aPTT 34.0 s, PT 0.80, INR 1.22, fibrinogen 10.99 g/L, repeated FVIII:C of 0.09 IU/ml and Bethesda inhibitor titre 90 BU. His TnI fell to 0.087 μg/L (Figure 3). Treatment with rFVIIa was discontinued and the patient was started on cyclophosphamide 1.0 g/m^2 and rituximab 375 mg/m^2 once weekly. The same day the patient had another episode of anginal pain. His ECG tracings were unchanged from the previous ones, and he developed a clinical picture of pulmonary oedema resulting in cardiac arrest. Complete cardiopulmonary resuscitation and transfer to the Intensive Care Unit were required. Urgent coronary angiography revealed three-vessel disease with 60-70% stenosis of the left main coronary artery, 99% stenosis of the left circumflex artery and an old occlusion of the right coronary artery with left-to-right collaterals. There were no acute thrombotic coronary lesions. Percutaneous intervention was not performed because of severe chronic coronary disease and because endothelial damage, very likely caused by coronary intervention, would preclude further rFVIIa treatment. No neurological sequelae were observed after resuscitation. During the following 48 hours progressive hypotension and the clinical picture of cardiogenic shock developed. Bleeding into the thoracic and abdominal space, caused by cardiopulmonary resuscitation, was ruled out by chest CT scan and abdominal ultrasound. Because of bleeding at the site of the arterial puncture, performed at the time of coronary intervention, rFVIIa at a dose of 90 μg/kg/2h was reinitiated and the patient received additional transfusions of packed red blood cell units and FFP. The patient died of refractory hypotension caused by cardiogenic shock.

Acute thrombosis leading to myocardial infarction is assumed to be due to disruption of an atherosclerotic plaque resulting in exposure of TF to blood with circulating FVII/FVIIa [22]. Consequently, the process leads to clot formation. This was obviously not the case in our patient, in whom coronary angiography excluded acute thrombotic coronary lesions. Elevated TnI levels were attributed to myocardial ischaemia due to a rapid drop in Hb levels after uncontrolled haemorrhage as a consequence of unrecognised AH. Increased TnI levels were presumably due to the so-called troponin leak [23,24]. We therefore decided to proceed with rFVIIa treatment in spite of elevated TnI levels, being aware that the risk of acute thrombotic coronary event in progress could not be entirely excluded. There are no published data of the use of rFVIIa in this setting or in the setting of percutaneous coronary intervention [25]. Pulmonary oedema, hypotension and progressive cardiogenic shock were attributed to heart failure caused by severe ischaemic heart disease and triggered by massive blood loss.

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Konflikt interesów / Conflict of interest

Samo Zver: Occasional consultancy on haematology area in Slovenija for Cellgene, Johnson and Johnson, NovoNordisk

References

1. Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the UK hemophilia centre doctors organisation. Blood 2007;109:1870-7.
2. Yee TT, Pasi KJ, Lilley PA, Lee CA. Factor VIII inhibitors in hemophiliacs: a single center experience over 34 years 1964-97. Br J Haematol 1999;104:909-14.
3. Giangrande P. Acquired hemophilia. World Federation of Hemophilia 2005;38:1-7.
4. Baudo F, deCataldo F for the italian association of hemophilia centres (AICE). Acquired factor VIII inhibitors in pregnancy: data from the italian hemophilia register relevant to clinical practice. Br J Obs Gyn AECOL 2003;110:311-4.
5. Francini M, Capra M, Nicolini N, Veneri D, Manzato F, Baudo F, et al. Drug-induced anti FVIII antibodies: a systematic review. Med Sci Monit 2007;12:RA55-RA61.
6. Francini M, Lippi G. Acquired factor VIII inhibitors. Blood 2008;112:250-5.
7. Yee TT, Taher A, Pasi KJ, Lee CA. A survey of patients with acquired hemophilia in a hemophilia centre over a 28-year period. Clin Lab Haematol 2000;275-8.
8. Holme PA, Brosstad F, Tjonnfjord GE. Acquired hemophilia: management of bleeds and immune therapy to eradicate autoantibodies. Haemophilia 2005;11:510-5.
9. Sallah S. Treatment of acquired hemophilia with factor inhibitor bypassing activity. Haemophilia 2004;10:169-73.
10. Roberts HR, Monroe DM, White CG. The use of rFVIIa in the treatment of bleeding disorders. Blood 2044;104:3858-64.
11. Hay CR, Negrier C, Ludlam CA. The treatment of bleeding in acquired hemophilia with rFVIIa: a multicentre study. Thromb Haemost 1997;78:1463-7.
12. Sumner MJ, Geldziler BD, Pedersen M. Treatment of acquired hemophilia with rFVIIa: a critical appraisal. Haemophilia 2007;13:451-61.
13. Kasper CK. Human FVIII for bleeding in patients with inhibitors. Vox Sang 1999;778(Suppl 1):47-8.
14. Mudad R, Kane WH. DDAVP in acquired hemophilia A: a case report and review of the literature. Am J Hematol 1993;43:295-9.
15. Abshire T, Hoots K, Kessler C, Macfarlane D, Bergman G. Preclinical and clinical experiences with recombinant porcine FVIII product. Haemophilia 2006;12(Suppl 2):644.
16. Baxter Corp. Product monograph: FEIBA VH Immuno; 2005.
17. Huth-Kuehne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Lévesque H, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica 2009;94:566-75.
18. Söhngen D, Specker C, Bach D, Kuntz BM, Burk M, Aul C, et al. Acquired factor VIII inhibitors in nonhemophilic patients. Ann Hematol 1997;74:89-93.
19. Stasi R, Brunetti M, Stipa E, Amadori S. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. Blood 2004;103:4424-8.
20. Shaffer LG, Phillips MD. Successful treatment of acquired hemophilia with oral immunosuppressive therapy. Ann Intern Med 1997;127:206-9.
21. NovoSeven product monograph (2000), NovoNordisk A7S, Bagsvaerd, Denmark.
22. Gerotziafas GT, Chakroun T, Depasse F, Arzaglou P, Samama MM, Elalamy I. The role of platelets and recombinant factor VIIa on thrombin generation, platelet activation and clot formation. Thromb Haemost 2004;91:977-85.
23. Missov E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive heart failure. Circulation 1997;96:2953-8.
24. Mazer CD, Leong-Poi H, Mahoney J, Latter D, Strauss BH, Teitel JM. Vascular injury and thrombotic potential: a note of caution about recombinant factor VIIa. Semin Cardiothorac Vasc Anesth 2007;11:261-4.
25. Review and Recommendations for the Off Label Use of Recombinant Activated Human Coagulation Factor VII (NovoSeven®), VA MedSafe, Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, February 2007.