

Acquired haemophilia A: a case report

Nabyta hemofilia A – opis przypadku

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Słowa kluczowe: nabyta hemofilia A, zaburzenia krzepnięcia, wydłużenie czasu częściowej tromboplastyny po aktywacji, czynnik VIII.

Abstract

Acquired haemophilia A is rare, autoimmune bleeding disorder caused by the production of autoantibodies against coagulation factor VIII (FVIII). The disorder affects 1.5 people per 1 million population a year, particularly the elderly. Unlike congenital haemophilia, the disease occurs in a similar proportion of men and women. An 86-year-old patient was admitted to the Department of Internal Medicine and Pharmacology with anaemia, progressive weakness, bruising in the subcutaneous tissue, and generalised stiffness of joints. Routine blood tests revealed isolated prolongation of activated partial thromboplastin time (aPTT) above 100 s. Activated partial thromboplastin time mixing test also showed prolongation of aPTT equal to 104.2 s. Factor VIII activity was 2%. The patient was referred to the Haematology Department, where a positive titre of anticoagulant 11 (BU) was obtained. After diagnosing acquired haemophilia A, the patient was administered activated prothrombin complex concentrate and prednisone, which resulted in clinical improvement and shortening of aPTT.

Streszczenie

Nabyta hemofilia A jest rzadką, autoimmunologiczną skazą krwotoczną spowodowaną produkcją autoprzeciwciał przeciwko czynnikowi VIII krzepnięcia. Zaburzenie to pojawia się u 1,5 osoby na 1 000 000 rocznie, głównie u osób starszych. Inaczej niż w hemofilii wrodzonej choroba występuje w podobnym odsetku u kobiet i mężczyzn. Kobieta 86-letnia została przyjęta do Kliniki Chorób Wewnętrznych i Farmakologii Klinicznej z powodu niedokrwistości, postępującego osłabienia, podbiegnięć krwawych w tkance podskórnej oraz uogólnionej sztywności stawów. W rutynowych badaniach krwi odnotowano wydłużenie czasu częściowej tromboplastyny po aktywacji (aPTT) powyżej 100 s. Wykonano test korekcji i nie uzyskano normalizacji wyniku po dodaniu osocza prawidłowego (aPTT – 104,2 s). Aktywność czynnika VIII wyniosła 2%, a miano inhibitora – 11 BU. Po zdiagnozowaniu nabytej hemofilii A wdrożono leczenie przeciwkrwotoczne za pomocą koncentratu aktywowanych czynników zespołu protrombiny oraz leczenie immunosupresyjne prednizonem i uzyskano poprawę stanu klinicznego oraz skrócenie aPTT.

Introduction

Acquired haemophilia A (AHA) is an autoimmune disorder associated with the production of antibodies directed against epitopes C2 or A2 and A3 of factor VIII. It inhibits coagulation factor VIII (FVIII) by binding with von Willebrand factor or factor IX, and X [1–4]. It affects 1.5 people per 1 million population a year. In the past the incidence was 0.2–1.0 cases per 1 million population a year [5], so we can observe a significant increase in its morbidity. The average age at which the disease is diagnosed is 73.9 years, with a significant increase in the frequency of diagnosis in women of childbearing age and the elderly. Four-year

survival in young patients is 62%, while in older patients it can be up to 40% [2].

In 51.9% of cases the disease is idiopathic, in others it coexists with neoplasm (11.8%), autoimmune disease (11.6%) such as rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroid disease, Sjögren's syndrome, antiphospholipid syndrome, and other connective tissue diseases. Pregnancy and the postpartum period contribute to an increased risk of incidence of AHA (8.4%). Other reasons include: infections (3.8%), inductions by drugs (3.4%), monoclonal gammopathy of undetermined significance – MGUS (2.6%), polymyalgia rheumatica (2.2%), dermatologi-

cal diseases (1.4%), and reaction after transfusion of blood products (0.8%) [2].

Case report

An 86-year-old, female patient was admitted to the Department of Internal Medicine and Clinical Pharmacology of the Medical University in Lodz for further diagnosis of anaemia (haemoglobin 6.6 g/dl) with accompanying isolated prolongation of activated partial thromboplastin time (aPTT = 109 s). In family history, there were no coagulation disorders. On admission, the patient was in an average general condition, conscious, with impaired autopsychic and allopsychic orientation, of dementia type. The patient's family reported that her condition had been deteriorating for 1 month. She demonstrated significant weakness and limited mobility due to stiffness of knee and ankle joints. The skin was covered with numerous bruises. In the past, the patient had undergone agranulocytosis after therapy of thiamazole. Laboratory results are shown in Table 1.

Due to significantly prolonged aPTT above 100 s, an aPTT mixing test was carried out.

A positive result obtained in this test (aPTT = 104.2 s) was the grounds for measuring the activity of factor VIII – the most frequently bound clotting factor by the anticoagulant in acquired haemophilia. The activity was 2% (with laboratory norm of 60–150%).

Such a low factor VIII activity made us continue diagnostics and treatment in the Department of Haematology. Based on the audited inhibitor titre (11 BU),

and repeated measurements of the activity of factor VIII, acquired haemophilia A was diagnosed.

The patient was ordered an antihemorrhagic therapy, which included administration of concentrates of activated prothrombin complex (aPCC) at a dose of 2000 U every 12 h. The therapy allowed a reduction of aPTT to 88.4 s and significantly improved the clinical condition, i.e. it inhibited formation of bruises. In order to eliminate the anticoagulant from the patient's plasma, treatment with oral corticosteroids was introduced. Prednisone was administered at a daily dose of 60 mg. The patient's family were asked to continue the prednisone treatment after hospitalisation. Despite implemented education, the family of the patient discontinued therapy, which led to the patient's death.

Discussion

A reduced amount of factor VIII in the blood leads to coagulation disorders, which are most often characterised with a tendency of spontaneous subcutaneous bleeding or bleeding induced by trauma, surgery, or other procedures causing a break in the tissue integrity. Less frequent symptoms include bleeding into joints, muscles, or retroperitoneal, gastrointestinal, intracranial haemorrhage [6].

A laboratory parameter that may imply acquired plasma haemorrhagic diathesis is isolated prolongation of activated partial thromboplastin time. An abnormal result of such a test should make a doctor suspect plasma haemorrhagic diathesis, resulting from abnormal intrinsic coagulation pathway and differentiation with other causes of prolonged aPTT, for example: Hageman's anomaly, Von Willebrand disease, and antiphospholipid syndrome [5] (Table 2) [7–11].

It is necessary to note the difference between antibodies against factor VIII in AHA, which are autoantibodies, and alloantibodies produced in the mechanism of alloimmunisation in patients with congenital haemophilia A after repeated transfusions of factor VIII concentrate. Alloantibodies in congenital haemophilia A include immunoglobulins G (IgG): IgG1, IgG2, and IgG4, while in acquired haemophilia A they are mainly IgG4; rarely IgG1 and IgG2. The neutralising activity correlates with the presence of IgG4 class antibody. These antibodies also differ in the kinetics observed during incubation. In congenital haemophilia A there is a linear relationship between an increasing concentration of antibodies, and a decrease in the activity of factor VIII, which are able to completely neutralise factor VIII. The antibodies in acquired haemophilia A have a long initial phase of inactivation, followed by a slow equilibrium phase with residual activity of factor VIII. However, patients with residual factor VIII activity in AHA, clinically report more severe bleeding than patients with congenital haemophilia, demonstrating the same level of FVIII activity [5].

Table 1. Results of patient's important laboratory tests

Laboratory test	Result	Reference interval
RBC [$\times 10^6 \mu\text{l}$]	2.58	4.20–5.40
HGB [g/dl]	6.6	12.0–16.0
HCT (%)	22.3	37.0–50.0
WBC [$\times 10^3 \mu\text{l}$]	8.6	4.0–10.0
PLT [$\times 10^3 \mu\text{l}$]	532	150–400
APTT [s]	109.0	23.0–33.0
PT [s]	12.8	12.0–16.0
Fibrinogen [mg/dl]	499	200–470
D-dimer [$\mu\text{g FEU/l}$]	9521	< 500
CRP [mg/l]	20.15	0.00–5.00
Protein [g/dl]	5.24	6.40–8.30
ALB [g/dl]	3.18	3.80–5.00
TSH [$\mu\text{U/ml}$]	5.7	0.27–4.2

RBC – red blood cells, HGB – haemoglobin, HCT – haematocrit, PLT – platelets, APTT – activated partial thromboplastin time, INR – international normalized ratio, PT – prothrombin time, CRP – C-reactive protein, ALB – albumin, TSH – thyroid-stimulating hormone.

Table 2. Differential diagnosis of aPTT prolongation [7–11]

Hageman anomaly, Prekallikrein deficiency, Fitzgerald factor deficiency	Asymptomatic. No need for treatment
Antiphospholipid syndrome	Manifests with venous or arterial thrombosis or obstetric failures. Often accompanied by decreased PLT and haemolytic anaemia. Presence of antiphospholipid antibodies, lupus anticoagulant
Congenital deficiency of factor VIII or IX	Inheritance linked to chromosome X. Women are more prone to manifest symptoms in the event of inheriting the mutation from mother and father with Turner syndrome
Congenital deficiency of factor XI	Severe bleeding after surgery of organs rich in fibrinolytic enzymes, e.g. prostate. Often abundant menstrual bleeding. Rarely, bruises and bleeding into joints
Von Willebrand disease	Subtype 2N – disrupted binding of vWF to factor VIII, vWF normal, reduced activity of factor VIII, prolonged aPTT. Symptoms of haemophilia
Presence of coagulation factors inhibitors	Medicines: – Heparin (mainly unfractionated) – Direct inhibitors of coagulation Inhibitors of individual coagulation factors: – VIII, V, IX, X
Multifactorial disorders	Usually complex coagulation disorders. Most often associated with liver disease or vitamin K deficiency. Often in majority of cases of disseminated intravascular coagulation
Laboratory errors	Factors causing prolongation of aPTT: – Haematocrit > 55%, haemolysis, hyperbilirubinemia, hyperlipidaemia – Traumatic venipuncture – Storage conditions prior to testing, spin of samples – Type of reagent – Type of recording device coagulation – Pre-incubation time with the activator – Presence of air bubbles in the sample Multiple performance measurement to exclude laboratory error

PLT – platelets, vWF – von Willebrand factor, aPTT – activated partial thromboplastin time.

The general practitioner suspecting AHA should order measurement of aPTT in a mixture of two volumes of plasma (aPTT mixing test). This laboratory test involves mixing the plasma of the patient with normal serum containing no anticoagulant but the right amount of clotting factors that provide proper aPTT. If the patient's plasma does not have anticoagulant, the mixture will not produce prolonged aPTT. Otherwise, the patient's plasma with the anticoagulant will bind clotting factors, thereby impairing their function and leading to prolongation of aPTT [1].

Activated partial thromboplastin time elongation in a mixture of plasma is a reason to measure the activity of clotting factors that may be responsible for the resulting disorder. Common, acquired coagulation inhibitor is the inhibitor of antihemophilic factor A; thus the activity of factor VIII should be measured first [12]. The correct value of the activity of factor VIII ranges between 50% and 150%. In AHA it is below the lower limit. It does not usually fall to zero, but its level ranges from a few to a dozen percent [5].

Reduction of the activity of factor VIII is caused by the presence of a specific inhibitor in plasma. Its quantity is determined in the Bethesda test. Non-neutralising antibodies, directed against factor VIII, are not detected in this assay. In this test, a number of dilution procedures are performed in the patient's serum in buffer, and then it is mixed with an equal amount of standard plasma. In the control trial the standard plasma is mixed only with buffer. The samples are incubated for 2 h at 37°C. Then, the residual activity of clotting factor VIII is determined [12]. The activity of the inhibitor is expressed in Bethesda units per millilitre (BU/ml). One Bethesda unit equals the amount of inhibitor that reduces the activity of factor VIII by 50% in standard plasma [13].

The amount of inhibitor in the patient's plasma is clinically associated with an increased risk of bleeding. The difference in the kinetics of alloantibodies produced in congenital haemophilia A and autoantibodies in acquired haemophilia is also reflected in treatment. In the event of alloantibodies bleeding

tendency increases linearly with increasing amounts of anticoagulant. If the value of the Bethesda test is below 5 BU/ml, factor VIII concentrate is applied. In other cases, the aPCC or recombinant activated factor VII (rFVIIa) is a better treatment option. In acquired haemophilia there is no relationship between the amount of anticoagulant, the residual activity of factor VIII, and clinical manifestation. Accordingly, the therapy is based on signs of bleeding but not on lab results [11].

Treatment of patients diagnosed with AHA includes antihaemorrhagic treatment and elimination of factor VIII inhibitor. Since the antihaemorrhagic therapy with the application of factor VIII concentrate does not appear to be highly effective and the results of its application are difficult to foresee, it is desirable to use bypassing agents of impaired factor VIII coagulation pathway. It is recommended to administer aPCC at a dose of 50–100 IU/kg every 8–12 h or rFVIIa at a dose of 90 mg/kg every 2–3 h of the bleeding episode. If the therapeutic purpose is not achieved, it is recommended that one bypass factor concentrate be replaced with another. APCC or rFVIIa therapy is effective in about 90% of AHA cases. It is necessary to be careful while administering the drugs because an improper dose might cause cardiovascular complications due to their procoagulant action. This especially refers to older people with concomitant cardiovascular diseases. Other drugs, like desmopressin applied at a dose 0.3 µg/kg, may be effective in patients with benign symptoms of AHA. However, its application should be considered only if there is no access to concentrates of bypassing factors of factor VIII [1, 6].

Factor VIII inhibitor is eliminated with the application of immunosuppressive therapy. It should be introduced immediately after AHA has been diagnosed. Corticosteroids are first-line treatment drugs. Here prednisone is recommended. It should be applied at a dose of 1 mg/kg/day *p.o.* for 4–6 weeks in monotherapy or in combination with cyclophosphamide at a dose of 1.5–2 mg/kg/day for 6 weeks [1]. There is no evidence that cyclophosphamide therapy is more effective than prednisone monotherapy. In both cases, remission is observed in about 70–80% of patients. If the level of factor VIII in the plasma does not increase within 2–3 weeks of the therapy, it should be modified. Other therapeutic options include administration of rituximab or cyclosporine [6].

Total eradication of the inhibitor is defined as normalisation of the level of factor VIII in plasma and lack of anticoagulant in laboratory tests. A negative result is obtained with the inhibitor level below 0.5 BU/ml. It is recommended that the aPTT level and activity of factor VIII be monitored once a month for the first 6 months after completion of immunosuppressive therapy. Then, every 2–3 months for 6–12 months. If possible, it is recommended that check-ups are performed every 6 months after 12 months of monitoring [1].

Conclusions

Acquired haemophilia A is a rare plasma haemorrhagic diathesis, which may lead to serious bleeding complications. Particularly elderly patients with symptoms implying abnormal coagulation should be examined for potential AHA. Prolonged activated partial thromboplastin time is a characteristic abnormality that implies the occurrence of AHA. Because of the possibility of rapid prevention of severe bleeding, which directly threatens life, elderly patients should have aPTT routinely measured in order to exclude AHA. After excluding other causes of prolongation of aPTT, e.g. drugs affecting haemostasis, the physician should bear in mind that he/she can make a measurement of APTT in the mixing test, because its prolongation may suggest the presence of an anticoagulant in blood. Finally, reduced activity of factor VIII in the patient's plasma and the presence of factor VIII inhibitor in a Bethesda assay prove the fact the patient is affected by the disorder.

Conflict of interest

The authors declare no conflict of interest.

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