A Unique Case of Acquired Hemophilia A Presenting with Transient Ischemic Attack

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Case report

A unique case of acquired haemophilia A presenting with transient ischemic attack.

Running title: Acquired haemophilia A with ischemic attack

Keywords: Acquired haemophilia A, coagulation, haemostasis, stroke

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Abstract

Acquired Haemophilia A (AHA) is a rare but serious condition usually associated with significant spontaneous or traumatic bleeding and a high mortality rate. In this report, we describe the case of an elderly patient presenting a transient ischemic attack concurrently with AHA. Thrombotic event in AHA is occasionally associated with use of bypassing agents for treatment, but spontaneous thrombotic event was never described.

Case presentation

A 94-year-old man was admitted in the emergency room with symptoms of transitory neurologic deficit reported as a speech disturbances and facial asymmetry of 15 minutes duration. Symptoms were consistent with a left carotid transient ischemic attack (TIA) in a right-handed patient. At admission, the patient denied any bleeding or bruising. The patient medical history included essential hypertension treated with perindopril and amlodipine, hypercholesterolemia on simvastatin, gastroesophageal reflux disease on esomeprazole, benign prostatic hyperplasia on finasteride and chronic kidney disease (stage 4). Other past medical history revealed an episode of transient global amnesia more than ten years ago that motivated the prescription of clopidogrel since then. A colorectal adenocarcinoma was treated by hemicolectomy 25 years ago without recurrence. He reported also acetylsalicylic acid (ASA) allergy with grade 3 anaphylaxis in the past. No new treatment was recently introduced. A full neurological work-up diagnosed a probable TIA of atherosclerotic origin. There was no bleeding on brain computed tomography (CT) scan and no recent or past ischemic or bleeding lesion on magnetic resonance imaging. Ultrasound examination of carotids demonstrated stenosis of 70% and 60% of the right and left internal carotid respectively, both with a high-risk component of the plaque (hypoechoic aspect) predictive of occurrence of stroke (1, 2). There was no atrial fibrillation on 24 hours Holter monitoring. Even though the patient was already treated with clopidogrel, he received a loading dose (300 mg) because non-compliance with drug treatment is widespread. On day (D) 3 after admission, the patient developed a diffuse haematoma of the right arm at the site of the cuff placed here for continuous blood pressure monitoring, without muscle or nerve compromising and without significant decrease in haemoglobin level. The haemostasis work-up revealed an isolated prolonged activated partial thromboplastin time (aPTT) (81.4 sec, normal range 26.0-37.0 sec). Prothrombin time (PT) was normal and there was no reduction in fibrinogen level (5.5 g/l) or thrombocytopenia (506 $x10^9$/L). Factor VIII (FVIII) level was severely decreased (<0.01 UI/mL) and the Bethesda assay demonstrated an inhibitor (8.2 Bethesda Unit) that confirmed the diagnosis of AHA. There was no factor IX, XI or XII deficiency and the functional assay for the lupus anticoagulant was negative. Clopidogrel was discontinued as soon as the diagnosis of AHA was established. Because of the absence of life threatening bleeding and the high risk of recurrent stroke based on carotid plaque characteristics, and in accordance with the most recent recommendations(2), it was decided not to prescribe haemostatic therapy (bypassing agents, even at lower doses (2), FVIII concentrate (3) or recombinant porcine FVIII (rpFVIII) (2)). After weighing the risk of bleeding against the risk of infection and other complications (4), the patient was started on high dose prednisone (1 mg/kg) only, which led to a rapid increase of FVIII level (FVIII level: 0.16 UI/mL at D9, 0.39 UI/mL at D17, 0.65 UI/mL at D20 and 1.23 UI/mL at D22). The patient presented a possible TIA recurrence with blurred vision during 15 minutes at D19 (FVIII level 0.39 UI/mL). Although the patient was considered at high risk of bleeding complication due to the AHA, he was also considered at very high risk of stroke. Indeed, the TIA episode motivating the current hospitalisation occurred on clopidogrel and the patient had a TIA

recurrence during hospitalisation. Moreover, high-risk internal carotids stenosis showed on ultrasound examination were considered as an additional risk factors of recurrence of TIA or stroke, especially when considering the progressive normalization of FVIII level while on high dose prednisone. Our patient combined two antagonistic positions: a high risk of recurrent stroke and bleeding. Antiplatelet therapy belong to the standard treatment after ischemic stroke or TIA. After a multidisciplinary discussion and based on the literature data describing safe ASA desensitization protocols (5), we estimated that the theoretical anaphylactic risk was less than the risk of recurrent TIA. Desensitisation protocol was carried out in intensive care unit at D19, without any complication, with a dose of 100 mg od reached at D22. Prednisone was slowly tapered over a 6 months' time and the patient did not experience reoccurrence of AHA, TIA or stroke. A large work-up did not found any specific aetiology for this AHA. No cancer was detected on chest and abdominal CT scan, no autoimmune disease was suspected on interview and on immunologic blood assay (antinuclear antibodies, anti-neutrophil cytoplasmic antibodies) and no monoclonal antibodies was demonstrated on serum immunofixation electrophoresis. No new medication was recently introduced. Clopidogrel was the only current medication occasionally associated with AHA (6) but the patient was treated with this drug for many years. After a follow-up of 36 months, the patient is uneventful.

Discussion

AHA, caused by the development of autoantibodies directed against FVIII, is a very rare condition with an incidence of 1.5 per million people per year (7). It usually develops in the seventh decade without sex preponderance or in the post-partum period. If some genetic factors seem to be related to an increased risk of developing such antibodies (eg. gene polymorphisms of HLA and CTLA4, alloreactive CD4+ lymphocytes), environmental factors are well-known triggers (e.g. pregnancy, autoimmune disease, malignancies, drugs). However, no cause is found in around two-third of patients presenting with AHA (7). FVIII autoantibodies inhibit the activity and increase the clearance of FVIII, leading to low levels of FVIII often associated with bleeding and an increased morbidity and mortality. The usual manifestations of AHA at diagnosis are subcutaneous bruising, mucosal bleeding (epistaxis, gastrointestinal bleeding), muscle and retroperitoneal haematoma, intracranial haemorrhage (7). In contrast with congenital haemophilia A, FVIII level at diagnosis is not predictive of bleeding and spontaneous joint bleeding is unusual (7). Nonetheless, AHA is a medical emergency and patients are at risk of fatal hemorrhage until the inhibitor has been eradicated. AHA occurs frequently in elderly patients at particularly high risk of thrombosis due to the likelihood of underlying malignancy, inflammatory disorders, infections or cardiovascular disease). Results from the European Acquired Haemophilia Registry showed that a thrombotic event occurred in in 3.6% of patients treated by a bypassing agent (8). In the prospective observational from the Acquired Hemophilia Working Group of the German, Austrian and Swiss Thrombosis and Hemostasis Society, 5% of patients under recombinant factor VIIa experienced a thromboembolic event (9). Based on this data, experts' consensus

recommends a particular caution is in older patients and patients with predisposing thrombotic conditions. As our patients had a critical high risk of thrombotic recurrence without significant active bleeding, we chose to avoid unnecessary hemostatic treatment in line with current recommendation (2). In case of significant bleeding, rpFVIII or bypassing agents are options for first-line treatment, and in absence of head to head comparison, choice is based on availability and economic considerations. However, in patients at high thromboembolic risk, rpFVIII should be preferred because of thrombotic risk associated with bypassing agents (8, 9)). Long-term remission can be only achieved by controlling inhibitor production and immunosuppressive therapy is the cornerstone of the treatment. However, because of absence of strong prospective data, treatment is based on registry data (4) and expert recommendations (2, 10). Patients should be initially treated with prednisone (1mg/kg/d, for 4-6 weeks) alone or in association with cyclophosphamide (1-2mg/kg/d for a maximum of 5 weeks) or rituximab (375 mg/m^2 weekly, 4 injections (2) . Data are very limited on thrombotic risk in AHA patients receiving an immunosuppressive therapy. Many experts, recommend starting antithrombotic treatment when endogenous FVIII exceeds 50 IU/dL (2).

As stressed out by this case of AHA diagnosed at the time of an ischemic TIA, the management of AHA patients with thrombotic risk requires a subtle evaluation of the hemostatic balance. Besides the multidisciplinary approach, the use of thrombin generation assay to monitoring the effect of hemostatic drugs could be of interest, as already demonstrated in patients with haemophilia and inhibitors (11).

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient has given written informed consent to publish this case.

Disclosure statement

PF received travel grant from Sobi©. Others authors have no conflict of interest to declare.

Author contribution

All authors made substantial contributions to the acquisition, analysis, and interpretation of data. All authors were involved in drafting and revising the manuscript and have approved the published version.

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