A 77-Year-Old Man with a Prolonged Activated Partial Thromboplastin Time

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CASE DESCRIPTION

A 77-year-old man was admitted to another hospital because of increasing dyspnea and edema of the lower limbs. The patient reported a loss of appetite and a flu-like illness 4 weeks previously. He was on various medications for heart failure, including metoprolol, ramipril, spironolactone, torasemide, metformin, and digoxin. For chronic atrial fibrillation, the patient had received dabigatran (75 mg twice per day) for 12 months; dabigatran is a direct thrombin inhibitor that has recently been cleared by the US Food and Drug Administration for the prevention of stroke in patients with atrial fibrillation.

Five days before admission, the patient discontinued dabigatran on his own after recognizing a fresh hematoma on the right hip, easy bruising, and a conjunctival hemorrhage of the right eye. Routine laboratory investigations on admission revealed a prolonged activated partial thromboplastin time (aPTT) of 69 s (reference interval, 25–35 s) and a slightly prolonged prothrombin time (PT). Initially, these laboratory findings and the ecchymosis were attributed to the previous anticoagulant intake.

The patient’s other symptoms were felt to be due to exacerbation of congestive heart failure, and these symptoms resolved with optimization of his diuretic therapy. He developed fresh hematomas, however. Because the aPTT remained prolonged 2 days after admission (a total of 7 days after the last dabigatran intake), clotting factor activities were quantified.

Clotting factor VIII activity was below the detection limit (0 IU/dL; reference interval, 50–175 IU/dL) and the activity of factor XII was slightly reduced (53 IU/dL; reference interval, 70–150 IU/dL). The values for other coagulation parameters, including PT, fibrinogen, von Willebrand factor, platelet count, and platelet function were within their respective reference intervals.

DISCUSSION

The first step in pursuing an aPTT prolongation is to rule out an artifact. Doubtful results should be confirmed with a new sample. Such preanalytical issues as careful venipuncture technique, correct filling of sample tubes (containing adequate anticoagulant, e.g., sodium citrate), and avoidance of contamination (e.g., heparin from central catheters) are of major importance. Lipemic, icteric, or hemolyzed samples, or a high hematocrit (which increases the plasma citrate concentration) may cause interference with the clotting test.

Additionally, the patient’s medical history is important. Unfractionated heparin, fondaparinux, or low molecular weight heparin in therapeutic doses can cause modest aPTT prolongation. After intake of excessive vitamin K antagonists like warfarin, aPTT prolongation occurs with a concomitant markedly prolonged PT. The aPTT-prolonging effect of newer anticoagulants (e.g., the direct thrombin inhibitor dabigatran) has been documented.

QUESTIONS TO CONSIDER

1. Which differential diagnoses should be considered when aPTT prolongation is detected?
2. To what extent do new anticoagulants, such as direct thrombin inhibitors, affect standard coagulation tests?
3. What techniques should be used to evaluate the cause of a prolonged aPTT?
dabigatran had been discontinued 5 days before admission and therefore was unlikely to have been causative because its half-life in plasma is only about 14 h (3).

If these initial considerations do not offer plausible explanations for the aPTT prolongation, further analytical workup is required. Basically, aPTT is affected by the activities of clotting factors XII, XI, X, IX, VIII, V, II, and I, as well as by high molecular weight kininogen and prekallikrein. Measuring the PT and the thrombin time (TT) can efficiently narrow the number of required analyses. When the PT and TT are normal, major deficiencies of factors X, V, II, and I are unlikely, as is heparin contamination. Increased activities of factor VIII (e.g., in an acute-phase response), however, can partially mask deficiencies of other clotting factors, giv-

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**Fig. 1.** Diagnostic approach to evaluate a prolonged aPTT.

See text for details. HMWK, high molecular weight kininogen; PK, prekallikrein.
ing an only slightly prolonged aPTT. Importantly, factor VIII and factor IX deficiencies or severe factor XI deficiencies are associated with an increased risk of bleeding, whereas even drastic reductions of factor XII or rarely occurring high molecular weight kininogen and prekallikrein deficiencies do not cause excessive bleeding \((4)\). Again, the patient’s clinical presentation and history taking are mandatory for target-directed laboratory analysis.

Genetic aberrations with impaired synthesis or functional defects are responsible for hereditary forms of reduced clotting factor activity, as seen in hemophiliias A (factor VIII), B (factor IX), and C (factor XI). Acquired factor deficiencies may be attributable to underlying diseases (e.g., cirrhosis) or bleeding with high turnover. In these cases, the PT is also regularly affected. Because factor VIII reductions can be associated with impaired protection by its carrier protein, von Willebrand factor, it is advisable to quantitatively measure the von Willebrand factor antigen and test for the functional von Willebrand factor ristocetin cofactor. von Willebrand disease can occur in congenital or acquired variants. The latter potentially can occur as a paraneoplastic syndrome or be due to degradation of high molecular weight multimers (detectable in a multimer analysis) in cases of mechanical destruction, e.g., shear stress at prosthetic heart valves \((5)\). In younger individuals with a bleeding history, slightly prolonged or borderline aPTTs can be associated with mild forms of hemophilia or von Willebrand disease.

aPTT prolongations may also arise in the presence of unspecific antiphospholipid antibodies interfering with clotting assays. Additionally, the presence of specific inhibitors, commonly targeting factor VIII, can cause clotting factor degradation.

An algorithm for the workup for a prolonged aPTT is shown in Fig. 1.

**CASE FOLLOW-UP**

In our patient, a normal TT excluded heparin contamination. Lupus anticoagulant was ruled out by the results of 2 different assays (lupus-sensitive aPTT and diluted Russell viper venom time), as suggested by current guidelines \((6)\). Because of the normal PT, only the activities of factors VIII, IX, XI, and XII were measured. The factor VIII activity was <1 IU/dL, and this low activity was most likely responsible for the patient’s bleeding. The slight reduction in clotting factor XII activity \((53 \text{ IU/dL}; \text{reference interval } 70–150 \text{ IU/dL})\) was considered secondary.

The patient’s history did not point to a congenital disorder such as severe hemophilia A. Tests for von Willebrand factor antigen and von Willebrand factor ristocetin cofactor showed normal values, thereby excluding von Willebrand disease. Therefore, the strikingly impaired factor VIII activity was most likely caused by an acquired factor VIII inhibitor. This supposition was confirmed by aPTT-based plasma-mixing studies. The addition of small amounts of the patient’s plasma to normal plasma (containing clotting factor activities of about 100 IU/dL, thereby balancing potential clotting factor deficiencies) produced severe and nonlinear aPTT prolongation (see Fig. 2). This phenomenon became apparent only after a 2-h incubation at 37 °C, a result indicating the presence of a progressive inhibitor in the patient’s plasma.

![Fig. 2. Plasma-mixing studies.](image)

The patient’s plasma was added to normal plasma in different proportions. The aPTT was measured either immediately or after a 2-h incubation at 37 °C. Failure to correct the aPTT at a 1:1 dilution is indicative of an inhibitor. In this case, the presence of a factor VIII inhibitor became apparent only after the 2-h incubation at 37 °C, a result indicating the presence of a progressive inhibitor in the patient’s plasma.

Commonly, in the case of serious bleeding events, factor VIII concentrates can be used if inhibitor titers are very low. For patients with higher inhibitor titers (>5 BU/mL), bypassing agents or recombinant activated factor VII is preferable \((9)\).

Acquired factor VIII inhibitors have a reported prevalence of approximately 1.5 cases per million per year, with a major peak in elderly patients of either sex.
Pathophysiologically, the binding of auto- or alloantibodies to factor VIII impedes its clotting activity, with potentially life-threatening complications. Of note is that quantification of acquired autoantibodies with the Bethesda assay tends to underestimate the potency of the inhibitor, because the assay is based on linear type I kinetics, whereas coagulation factor inhibitors often follow the nonlinear, nonsaturable complex pattern of type II kinetics (8).

About 50% of affected patients were previously healthy (9). In the other half, associations with autoimmune diseases, malignant disorders, or pregnancy have been reported. Rarely, medications such as antibiotics (penicillins, sulfonamides, and chloramphenicol) and anticonvulsants can be causative. Drug-induced factor VIII autoantibodies frequently arise after preceding hypersensitivity reactions and mostly remit after discontinuation of the drug (10).

Our patient received treatment with prednisolone (initial dose, 1.5 mg/kg body weight) and a single cyclophosphamide dose (500 mg/m² body surface area). Under this regimen, the inhibitor titer dropped gradually. Meanwhile, the patient achieved complete remission, and prednisolone was gradually tapered to a current dose of 5 mg/day. Investigations for associated diseases yielded unremarkable results.

In summary, this case illustrates the laborious laboratory workup for aPTT prolongations. In addition to the clinical implications, a thorough evaluation of aPTT prolongations can have an important influence on the interpretation of other aPTT-based coagulation assays (e.g., protein C and S activities, activated protein C resistance, lupus inhibitors).

**References**