



# Elevated APTT? How best to follow up

This step-by-step guide will help you refine your approach to an abnormal activated partial thromboplastin time.

**CASE ►** During an office visit, 23-year-old John K tells you that he recently experienced excessive bleeding after a dental extraction. He says that he has no personal or family history of a bleeding disorder and is not taking any medication that might have contributed to the problem.

His lab work shows a normal complete blood count and international normalized ratio (INR). His activated partial thromboplastin time (APTT), however, is 67 seconds (normal=24-37 seconds).

How would you manage his care?

**C**orrect interpretation of abnormal APTT readings requires an understanding of the clinical context in which the test is ordered and the test's limitations. In cases like Mr. K's, the top priorities are taking a careful history and performing a thorough physical examination.

Specifically, you need to ask about any personal or family history of spontaneous mucosal bleeding, menorrhagia, hemostatic difficulties with previous surgeries or dental extractions, medication use (including anticoagulants), and alcohol use. Find out whether there is a history of liver disease or malnutrition/malabsorption. Does the patient bruise easily?

As you would expect, such signposts warrant further investigations. And if the personal or family history does suggest a bleeding disorder, the patient should be referred to a hematologist.

**CASE ►** Mr. K's physical examination is unremarkable and his renal and liver panel—including serum albumin—are within the normal range. As noted earlier, he had no history of bleeding before the tooth extraction; his family history is negative for excessive bleeding, as well.

## Consider an artifactual cause

It's important to rule out artifactual causes of an abnormal APTT before undertaking a more detailed investigation. Although not applicable in this case, unfractionated heparin in a central venous or arterial catheter can prolong APTT.

■ **A high hematocrit value** will give falsely prolonged APTT. This is due to the increased concentration of citrate relative to the small volume of plasma.<sup>1</sup> The lab should be alerted if the hematocrit is high so that the volume of anticoagulant in the collection tube may be adjusted for more reliable results.

■ **Lipemic, hemolyzed, or icteric plasma specimens** interfere with the optical system of the instruments and may also give false results.<sup>2</sup>

■ **Delays and extreme temperatures can also alter results.** The specimen should not be delayed for more than 4 hours as factor VIII is labile and longer time will result in an artifactually prolonged APTT.<sup>3</sup> (See "APTT: Understanding the test" on page E2.) In addition, prolonged exposure to high tempera-

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**Ask patients with an elevated APTT about a personal or family history of spontaneous mucosal bleeding, menorrhagia, or hemostatic difficulties with previous surgeries or dental extractions.**

## APTT: Understanding the test

Activated partial thromboplastin time (APTT) measures the integrity of the intrinsic and common pathways of the coagulation cascade. Any deficiency or inhibitor of the clotting factors within the intrinsic or common pathways will result in a prolonged APTT. The factors involved in the intrinsic and common pathways are II (prothrombin), V, VIII, IX, X, XI, XII, and fibrinogen (factor I).

tures may enhance degradation of factors V and VIII, whereas prolonged exposure to cold temperatures may activate factor VII.<sup>4</sup>

**CASE ►** Because there is no physical evidence of liver, renal, or connective tissue disease in Mr. K's case and artifactual causes are not at work, the next logical step is a mixing study.

### Does the mixing study correct the prolonged APTT?

A mixing study with normal plasma will differentiate between a coagulation factor deficiency and the presence of an inhibitor. Correction of the prolonged APTT to the reference range after mixing a sample of the patient's blood with normal plasma in a 1:1 ratio implies a deficiency of a clotting factor in the intrinsic or common final pathway of the coagulation cascade. The deficiency may involve one or more of the following: factors VIII, IX, XI, or XII; high-molecular-weight kininogen (HMWK); and prekallikrein (PK). A clotting factor assay will identify the deficient factor.

**■ Congenital or acquired?** Assuming that a clotting factor deficiency exists, the next step is to determine the nature of the deficiency in terms of congenital or acquired defects. Congenital causes of factor VIII, IX, and XI deficiency are hemophilia A, B, and C, respectively. Hemophilia affects one in 5000 males born in the United States;<sup>5</sup> about 9 out of 10 have hemophilia A.<sup>6</sup>

Acquired causes of factor deficiencies are liver disease, warfarin use, disseminated intra-

vascular coagulation, and vitamin K deficiency due to malabsorption or malnutrition.

**■ Is an inhibitor at work?** The presence of an inhibitor is suggested if the mixing studies do not result in correction of the prolonged APTT to normal range.

If factitious use of heparin or thrombin inhibitors is suspected, thrombin time (TT) and reptilase time help determine if heparin or direct thrombin inhibitor is present. TT is prolonged by both heparin and thrombin inhibitors, but reptilase time is not affected by either of the drugs.

Lupus anticoagulant should be tested if there is no history of treatment with unfractionated heparin or direct thrombin inhibitors such as lepirudin and argatroban. However, antiphospholipid antibodies are estimated to have a prevalence of 1.0% to 5.6% in healthy populations.<sup>7</sup> Moreover, lupus anticoagulant is transient in most cases and is most often of no clinical significance. It is therefore important to interpret the lupus anticoagulant in the context of the illness.

**■ If the inhibitor is still a mystery,** you will need to test for specific factor inhibitors like factor VIII inhibitor (acquired hemophilia). Inhibitors are alloantibodies, which develop, for example, in patients with hemophilia who are treated with blood products such as fresh frozen plasma (FFP), cryoprecipitate, or factor VIII concentrate.

### When an elevated number doesn't mean what you think

There are certain limitations of APTT in identifying the deficient factors because the sensitivity of APTT to identify deficient common pathway factors is low.<sup>8</sup> (There may be deficiency of a common pathway factor but a normal APTT). Composition of the partial thromboplastin reagent can result in marked differences in the sensitivity of the test to coagulation factor deficiencies.

In addition, factor VIII levels may give false-negative results in pregnancy and in response to physical stress and trauma, as factor VIII rises markedly in both cases. Thus, it may mask a mild deficiency.

Deficiencies of factor XII, HMWK, or PK do not result in a bleeding disorder despite

prolonging the APTT markedly. This is important since factor XII deficiency has been found to be among the most common causes of unexpected prolongation of APTT.<sup>9</sup>

**CASE ►** You exclude an acquired bleeding disorder based on Mr. K's history, physical exam, and normal results on his liver panel and a complete blood count. However, a repeat APTT is prolonged and a mixing study with normal plasma corrects the APTT. Further testing demonstrates normal factors IX and XI, but his level of factor VIII is only 10% of the reference range, confirming a diagnosis of hemophilia A.

You advise Mr. K to get vaccinated against hepatitis A and B. You also discuss available treatment options and their indications. Recombinant factor VIII is the treatment

of choice for bleeding episodes. Prophylactic treatment is given before surgical procedures or activities that carry a high risk of provoking a bleed.

Factor VIII infusion 3 times a week to prevent hemarthrosis in severely affected patients is gaining acceptance. Desmopressin acetate (DDAVP) is the drug of choice for treatment of patients with mild hemophilia (factor VIII activity >5%).<sup>10</sup> Antifibrinolytic agents like ε-aminocaproic acid and tranexamic acid can be used for mucosal oral or dental bleeds. You also make sure Mr. K obtains a medical alert bracelet. **JFP**

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