EDUCATIONAL COMMENTARY - DIAGNOSIS OF AN ABNORMAL PROTHROMBIN TIME AND ACTIVATED PARTIAL THROMBOPLASTIN TIME

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Learning Objectives
Upon completion of this exercise, participants will be able to

- explain why a prothrombin time (PT) or an activated partial thromboplastin time (APTT) may be prolonged.
- identify preanalytical and analytical variables that may contribute to a prolonged result.
- discuss clinical conditions and reasons for abnormal results.

The prothrombin time (PT) and the activated partial thromboplastin time (APTT) are common screening tests that can provide the clinician with a tremendous amount of information. The PT uses citrated plasma, which is added to a thromboplastin-calcium mix, and the length of time required to form fibrin is measured. The APTT consists of recalcifying plasma which is added to a standardized amount of platelet-like phospholipid reagents in the presence of activators, which may be kaolin, silica, or elagic acid. The time taken for a clot to form is then measured.¹

Abnormal PT or APTT Result: Preanalytical Causes
Preanalytical variables are important when diagnosing any patient. Results can only be as good as the quality of the samples. The ratio of blood to anticoagulant should be 9:1. When a sample is underdrawn there will be an increased amount of anticoagulant in the sample, which may falsely prolong results.² This will also happen in patients with a high hematocrit (>55%) due to the small plasma volume. When performing testing on patients with a high hematocrit, the amount of citrate added to the tube can be adjusted to account for the decreased plasma volume, correcting the coagulation result. The formula to adjust citrate concentration is provided below:

\[
C = (1.85 \times 10^{-3}) (100 - \text{HCT}) \times V_{\text{blood}}
\]

C = Volume of citrate required in the tube

1.85 \times 10^{-3} = a constant which takes into account the citrate volume, blood volume, and citrate concentration

HCT = the hematocrit of the patient

V blood = Volume of blood added to the tube
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AND ACTIVATED PARTIAL THROMBOPLASTIN TIME (cont.)

Time is also important. The PT sample is stable unspun and capped for 24 hours, while the APTT sample is only stable for 4 hours. Performing a test after a longer time period can cause an abnormal result. Additionally, if a patient is on heparin and the spun plasma sits on the red blood cells for >4 hours, the platelet factor IV (PF4) can neutralize heparin and shorten the APTT making an abnormal result appear normal. This “normal” APTT could result in the clinician giving a patient additional heparin and putting the patient at risk for bleeding.3

Abnormal PT or APTT Result: Analytical Causes
A normal PT and/or APTT indicate that a patient has normal levels of factor activity, i.e., >50%. A normal PT indicates a normal level of the factors in the extrinsic pathway (factor VII). A normal APTT indicates normal levels of factors found in the intrinsic pathway (factors VIII, IX, XI, and XII). When both the PT and APTT are normal, the factors of the common pathway (factors I, II, V, and X) are >50%.

It is important to understand how reagents perform based on their sensitivity. Some reagents are insensitive to factor deficiencies. A good reagent will prolong a screening test when a factor level approaches 40%. Many reagents have poor sensitivity and may not reflect a low level of a factor, giving a normal result. Conversely, a reagent may be too sensitive, and give a prolonged screening assay, when in reality the patient has a normal level of factor activity.4 An understanding of the sensitivity of your reagent can help determine if a normal result may not reflect an abnormal factor level.

Abnormal PT or APTT Result: Clinical Conditions
An abnormal PT or APTT result can be caused by:

- Medication: warfarin, heparin, antithrombins
- Factor deficiencies (hereditary or acquired)
- Nonspecific inhibitors (lupus anticoagulants)
- Specific factor inhibitors5

Medication
Warfarin affects the glutamyle residues of the vitamin K-dependent factors (II, VII, IX, X and protein C and S), rendering them nonfunctional and impairing fibrin formation. This oral anticoagulant is monitored by the PT. It is affected by diet and how well the patient adheres to taking the medication.1
Heparin is a very effective anticoagulant that binds to antithrombin and enhances its effectiveness 1000-fold. Heparin is given to prevent venous thromboembolic events and will result in a prolonged APTT. If the level of heparin is high enough, the PT may also be prolonged. Many samples for coagulation testing are drawn through a line that may be flushed with heparin. To determine if a sample is contaminated with heparin, a thrombin time can be performed. This is the most sensitive test to detect the presence of heparin.1

A new family of anticoagulants, the direct thrombin inhibitors or DTIs, are very effective anticoagulants because they directly inhibit thrombin. They will prolong the PT and the APTT as well as all clot-based assays. These anticoagulants should not be monitored by the PT or APTT. They can be monitored by an Ecarin clotting time or an anti-IIa assay.

Factor Deficiencies
The most common reason a PT is prolonged is due to oral anticoagulation. An isolated prolonged PT usually means a factor VII deficiency. This is a rare autosomal recessive bleeding disorder. Because factor VII has the shortest half life (about 4 hours), the PT will be the first test to be prolonged in any acquired bleeding disorders such as liver disease, disseminated intravascular coagulation, or a vitamin K deficiency.6

An isolated APTT prolongation may be due to intrinsic pathway coagulation proteins of VIII, IX, XI, XII, prekallikrein, and high-molecular-weight kinninogen (HMWK). HMWK, factor XII, and prekallikrein are contact factors. A deficiency will prolong the APTT but will not be an excessive risk for a bleeding disorder. Most of these patients have a risk for thrombosis, possibly due to a defect in activation of the fibrinolytic system.

If both the PT and APTT are prolonged, there may be a deficiency in the common pathway (I, II, V, X).

Inhibitors
Circulating anticoagulants or acquired inhibitors can develop in patients and affect coagulation results. These are immunoglobulins and are either allo- or autoantibodies. Specific inhibitors are directed against a specific factor. The lupus anticoagulant is a nonspecific inhibitor.
These inhibitors will prolong the PT and/or the APTT. To distinguish between a factor deficiency and an inhibitor, a mixing study is performed. In this test, equal parts of pooled normal plasma and the patient’s plasma are mixed together and a PT or APTT are performed. If the test returns to normal, the pooled normal plasma replaces the missing factor, and a factor deficiency is present. If the mixing study does not correct, there is a substance in the patient’s plasma that is inhibiting a factor. An inhibitor to a specific factor will cause a patient to bleed. A patient who has a nonspecific inhibitor, such as a lupus anticoagulant, will not bleed and actually may be prone to clotting. It is believed that the lupus anticoagulant interferes with the phospholipid components of the reagents that cause a prolongation of the APTT.\(^7\)

**Summary**

A prolonged PT and/or APTT result can be due to many causes. The laboratory must minimize pre-analytical variables and understand what analytical variables may impact results. Many clinical conditions will cause a prolongation of these screening results, and it is important to be aware of what tests may be affected.

**References**


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