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EDITORIAL

Plasma Coagulation Tests for Detection of Antiphospholipid Antibodies: What's Good, and What Might Be Improved?

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DRVVT is a test to detect Lupus anticoagulant (LA) as part for investigation for Antiphospholipid syndrome (APS) along with Anticardiolipin (aCL) and Anti-β2-glycoprotein-I (aβ2GPI) antibodies.

According to the revised classification criteria, APS is diagnosed only if one clinical and one laboratory criteria are satisfied [1]. The clinical criteria could be either one or more clinical episodes of arterial, venous, or small vessel thrombosis or pregnancy morbidity/fetal losses. Laboratory criteria require detection of Antiphospholipid Antibody (APA) when all or either LA, aCL antibody or aβ2GPI antibody is positive on two occasions at least 12 weeks apart. Diagnosis of APS should be avoided if less than 12 weeks or more than 5 years separate positive APA test and the clinical manifestation. This is especially true for a positive LA test, considering the variables that affect this test [1, 2].

No single test is sensitive for all LA. The recommendation is to perform two different tests that represent different assay principles. The dilute Russell viper venom time (DRVVT) is the most robust and specific test in detecting LA and should be the first test considered. The second test should be a sensitive activated partial thromboplastin time (APTT) using low phospholipids. LA should be considered as positive if one of the two tests gives a positive result [3].

In this edition of the journal, Ramaraj et al. [4] and Ahuja et al. [5] have also found that sensitivity of DRVVT is superior as compared to other tests for LA. Ahuja et al. evaluated the performance of four LAC tests (APTT-LA, kaolin clotting time—KCT, dilute prothrombin time—DPT and DRVVT). They found that the sensitivity increased to 100% if the number of assays was increased to three by incorporating APTT-LA, DRVVT and KCT. However, the ISTH recommends only two screening tests since the risk of false-positive results is increased to an unacceptable level if more than two screening tests are performed. This is more so since the KCT and DPT both lack standardisation.

LA testing by DRVVT becomes significant as it helps identify triple positivity (positive LA, aCL and aβ2GPI antibodies) which carries a much higher risk of thrombosis and pregnancy loss than patients with double or single positivity. Only some aβ2GPI antibodies are pathogenic, namely those directed against Domain I of the β2GPI molecule [6]. Triple positivity identifies the pathogenic autoantibody (anti-Domain I of β2GPI) present in patients with definite APS. Studies have shown that sole positivity of LA with negative aCL and aβ2GPI antibodies is not associated with thromboembolic events [7].

A positive LA test can be caused by the presence of aβ2GPI antibodies, antiprothrombin antibodies or antibodies to other cofactors. β_2GPI-dependent LA highly correlates with thrombosis in APS [8]. A reduction in final calcium concentration, from 10 to 5 mM increases coagulation times of dRVVT in plasmas of patients with aβ2GPI antibodies, while it shortens coagulation times in patients with aβ2GPI-negative LA. This simple modification can thus be used to identify β_2GPI-dependent LA [9].

DRVVT is important for the diagnosis of APS to detect triple positivity, but its variables demand proper standardization. Easiest thing is to report LA with aβ2GPI. If there is discrepancy between both, repeat DRVVT with

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lower concentration of calcium to potentially bring agreement between LA and aβ2GPI. Though most of the DRVVT reagents contain Heparin Neutralisation reagent, it is recommended to do thrombin time on the samples before DRVVT testing to rule out presence and also gauge the amount of heparin that could be present.

Testing for LA should be limited to patients who have a significant probability of having the APS. Generalized searches as a part of investigation of accidentally prolonged APTT on asymptomatic individuals are highly discouraged to avoid the risk of obtaining false-positive results or detection of transient lupus. Transient Lupus can be present in inflammatory conditions like appendicitis, tonsillitis, adenoiditis, synovitis and usually disappears on repeat testing after 12 weeks [10].

Thus, tests for lupus should be performed only if there is at least one clinical criterion (history of thrombosis/recurrent pregnancy loss) for APS. The positive test should be repeated after at least 12 weeks to avoid transient lupus due to associated inflammation. This phenomenon can also be seen in patients with thrombosis, but 12 weeks later it will become clear if the cause for thrombosis was LA or other risk factor.

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