The pathophysiology of Lupus Anticoagulant and the consequences for laboratory diagnostics

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Lupus anticoagulant is a prolongation of routine clotting assays caused by anti-phospholipid antibodies. Its presence correlates strongly with a history of thrombosis and pregnancy morbidity and it is one of the serological criteria to define the antiphospholipid syndrome (APS). The results of External Quality Assessment Programs showed that there was a significant discordance between the results obtained in the different participating labs and therefore strict guidelines for the performance of the assay have been formulated by both the International Society of Thrombosis and Haemostasis (ISTH) and the Clinical and Laboratory Standards Institute (CLSI). There are differences in the recommendations of both organizations but there is no difference in opinion that the crucial step in the assay is to show that the prolongation of the clotting assays is less when the amount of phospholipids in the assays is increased (the so-called confirmation step).
One of the important differences between the guidelines of the ISTH and the CLSI is the importance of the mixing assay. The ISTH stated that when a prolongation of a clotting assay is found, the first step to do is to repeat the assay with the sample mixed 1:1 with normal plasma to exclude a factor deficiency. The CLSI argued that confirmation is the important determinant to establish a lupus anticoagulant and should be performed first. This discussion has stimulated us to investigate the importance of the mixing step. We noticed that factor deficiency results only in a little bit stronger lupus anticoagulant activity and the only problem that can occur is that some negative samples can become weakly positive. The important consequence of this observation is that lupus anticoagulant can be measured in samples of patients on oral anticoagulant, the recommended treatment of these patient, which was not allowed in most of the guidelines.
It is very surprising that an assay result (prolongation of an aPTT) that is normally used to diagnose a risk of bleeding correlates with thrombosis when the cause of prolongation is the presence of antiphospholipid antibodies. Nevertheless, of the three assays we have to detect the presence of antiphospholipid antibodies, lupus anticoagulant correlates by far the best with the clinical manifestations that define APS. More importantly, there are now studies showing that the presence of lupus anticoagulant predicts an increased risk of recurrence. Lupus anticoagulant should somehow contain a clue that could lead us to the cause of the increased risk of thrombosis. Lupus anticoagulant is caused by auto-antibodies against β_2-Glycoprotein I or prothrombin. The general consensus is that these antibodies prolonged clotting assays by dimerizing these proteins which results in an increased affinity of the complexes for negatively charged phospholipids. The affinity is now strong enough to compete with clotting factors for these phospholipids and thereby inhibiting in vitro coagulation. The proof-of-concept for this hypothesis was twofold (i) F(ab)2 fragments of these autoantibodies can cause a prolongation of a clotting time while F(ab) fragments cannot and (ii) extra phospholipids can circumvent the prolongation of the clotting assays. In the literature there were a number of publications that suggested that this hypothesis can only be partly true. To understand the strong correlation between lupus anticoagulant and the risk of thrombosis and pregnancy morbidity, it is essential that we understand how antiphospholipid antibodies interfere with coagulation.