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MINIREVIEW

The Lupus Anticoagulant (41879)

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Lupus-like anticoagulant (LLAC) is the term used to identify an acquired inhibitor (1) of blood coagulation, first described by Conley and Hartmann in patients with systemic lupus erythematosus (SLE) (2). A circulating "lupus-like" anticoagulant has been detected in 5–10% of all SLE patients. A lupus anticoagulant is also found in other diseases including immunologic, oncologic, gynecologic, and neurologic disorders (3–12). In autoimmune diseases a lupus anticoagulant may occur in families, suggesting a genetic predisposition (13–15). Methods now available can distinguish between lupus anticoagulant and other inhibitors of coagulation (i.e., agonist factor VIII, IX, X, XI, and XII) occurring in SLE (16–19) and, more generally, in autoimmune diseases. In fact, in mixtures of LLAC plasma and normal plasma an immediate inhibition can be observed which is not increased by prolonging the incubation period, in contrast to the gradual time-dependent inhibition that occurs in patients with other types of coagulation inhibitors.

Phospholipid and Lupus Anticoagulant Interaction. Only in the last few years have significant advances been made in our understanding of the lupus anticoagulant mechanism of action. The thromboplastin generation test using diluted plasma or serum from a patient with a "lupus anticoagulant" is normal, suggesting that the lupus inhibitor does not interfere with the generation of intrinsic prothrombin (1, 20–22). However, the abnormality can be revealed when the patient's plasma is used, instead of normal plasma, as source of prothrombin and fibrinogen (1, 20, 22). These findings suggest that lupus anticoagulant interferes with the activation of prothrombin, acting at the junction between intrinsic and extrinsic coagulation pathways. In other words, the anticoagulant inhibits the "prothrombin activator complex" (factor Xa, factor V, calcium, and phospholipids) and, more particularly, seems to be directed against the phospholipid fraction of the complex (3, 4, 23). This possibility is suggested by the observation that the inhibitory effect is considerably potentiated by reducing the phospholipid content of clotting mixtures (23–25). Moreover, the abnormal "prothrombin consumption" of blood containing the lupus anticoagulant can be corrected by adding a phospholipid mixture as a source of platelet factor 3-like activity (26). Recently, Thiagarajan *et al.* (27), using a specific immunologic interaction with negatively charged phospholipids, reported that this inhibitor is able to block the calcium ion-dependent binding of prothrombin and factor X to phospholipid micelles. In patients with "systemic lupus" the incidence of false-positive tests for syphilis is considerably higher when the anticoagulant is present. This observation further supports the possibility of an interaction between phospholipids and the lupus anticoagulant (28–30).

The Nature of Lupus Anticoagulant. Whether a cofactor in normal plasma, either prothrombin (31) or a gamma globulin (32), potentiates the LLAC inhibitory activity under appropriate experimental conditions is uncertain. More recent work characterized the cofactor as heat labile and different from complement (10), poorly absorbed by $BaSO_4$ or $Al(OH)_3$, with an approximate molecular weight of 200,000 on gel filtration (33). Moreover, it is possible that an artifact, due to the presence of traces of thrombin or platelet fragments in the test plasma (34), could account for all the findings suggesting the existence of a cofactor. In the past 15 years, much work has been done to identify the nature of lupus anticoagulant which is either an IgG (4, 32, 35–37), an IgM (4, 8, 27, 38), or a mixture of both (4, 8, 36, 39, 40). Thiagarajan and co-

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workers (27) identified the Fab μ tryptic fragment in monoclonal IgM paraprotein as the component responsible for lupus-like anticoagulant activity in a patient affected by Waldenstrom's disease. They also demonstrated that IgM reacted with phosphatidylserine and, to a lesser extent, with phosphatidic acid, but not with phosphatidylcholine or phosphatidylethanolamine. Phosphatidylserine seems to be located exclusively on the inner aspect of the platelet membrane (41). This could explain why the patient's radiolabeled Fab μ fails to bind to platelets, unless they have been previously activated with thrombin. Furthermore, this interpretation fits with the observation that platelets, if used as a source of phospholipids in a test system, support normal coagulation even in the presence of lupus anticoagulant (27). More recently, Lafer and co-workers (42), using monoclonal autoantibodies, demonstrated that anti-DNA antibodies, including antibodies with the characteristics of LLAC, can be serologically polymorphic having the capacity to bind to different structures containing phosphate ester. They also found that the same monoclonal anti-DNA antibodies binding polynucleotides can both react with phospholipids and mimic the *in vitro* action of LLAC.

Diagnosis of Lupus Anticoagulant. The prothrombin time is usually normal or slightly prolonged in patient with the lupus anticoagulant (3, 23). In contrast, a prolonged activated partial thromboplastin time (APTT), which is not corrected by adding normal plasma in mixing experiments, allows one to diagnose the presence of a lupus anticoagulant rather than a factor deficiency and represents the most widely employed screening test (3, 10, 32, 36, 39, 43, 44).

Differences in APTT values obtained using different commercial reagents have been attributed to the concentration of the platelet substitute in the preparation (25). Since the anticoagulant interferes with negatively charged phospholipids, the most sensitive tests used to detect LLAC are those with a reduced phospholipid content, such as the prothrombin time performed with dilute thromboplastin (1, 3, 9, 10, 23, 25, 28, 44).

Another test believed to be sensitive enough to detect lupus anticoagulant is the kaolin clotting time (KCT). Using this test, Exner and associates (34) indicated that the presence of an anticoagulant can be predicted when aliquots of the test plasma prolonged the KCT of normal plasma more than would be expected on the basis of dilution alone. Moreover, the same authors suggest that the KCT allows distinguishing between the classical "lupus inhibitor" alone and the presence of an associated coagulation factor deficiency on the basis of different mixing patterns. In this context, it must be remembered that because of the PTT sensitivity to the effects of the anticoagulant, factors such as VIII, IX, XI, or XII may appear deficient although being present in normal amounts when assayed by a two-stage assay (5, 6, 8, 10, 25). Despite these abnormalities, patients with lupus anticoagulant are not affected by a bleeding tendency (3, 4, 10, 29, 37, 44, 45), nor do they bleed excessively when undergoing surgery (1, 3, 23, 29, 37, 44, 46) unless another abnormality of the hemostatic system, such as thrombocytopenia, is present (7, 20, 39, 47).

Thrombosis and Lupus Anticoagulant. Paradoxically, such patients suffer from a still poorly understood thrombotic tendency (8, 23, 26, 48–52). Mueh *et al.* (29) have recently reported the occurrence of thrombosis in 8 out of 35 patients having a "circulating lupus anticoagulant." An explanation for the fact that these patients do not bleed could be that the phospholipid moiety of platelet membrane is not accessible to the antiphospholipid gamma globulin which might express its activity only against the artificial source of phospholipids used during "*in vitro*" tests. The effect of anticoagulant "*in vivo*" can also be minimized by the high affinity factor Xa binding receptor present on the platelet surface which promotes thrombin formation even in the absence of added phospholipids (53). Given the fact that these patients do not bleed, why should they be at increased risk of developing thrombosis? Rather unconvincing explanations were advanced which involved an excessive generation of thromboplastin as a "compensatory phenomenon" to the presence of a circulating anticoagulant (26) or abnormalities of the fibrinolytic system (54, 55). More recently, a functional abnormality in antithrombin III was suggested as a possible explanation of recurrent thrombosis in patients with circulating LLAC (56).

A very interesting study by Carreras and co-workers (35) in a young woman with a lupus anticoagulant and a history of recurrent abortions with multiple arterial thrombosis demonstrated that the IgG plasma fraction from this patient reduced the release of PGI_2 in an "*in vitro*" system. This defect could be by-passed when the prostaglandin precursor, arachidonic acid, was exogenously added to the system. It seems reasonable, therefore, to postulate an interference of the "anticoagulant" gamma globulin with the mechanism involved in arachidonic acid release from endothelial cell membrane phospholipids. As PGI_2 is the most potent vascular inhibitor of platelet aggregation (57), its impaired release could contribute to the thrombotic tendency. This hypothesis is now the subject of numerous investigations (58, 59). Moreover, the repeatedly reported intrauterine deaths in these patients (5, 35, 60–65) appear to identify a new syndrome that might be explained by the inhibitory effect of the patients' IgG on PGI_2 production by tissues other than endothelium. A therapeutic approach to patient with lupus anticoagulant makes use of steroids and usually leads to amelioration of the primary disease and disappearance of the "anticoagulant" activity (37, 39, 66, 67).

Since bleeding is not a clinical problem in these patients, there is no need to treat a laboratory abnormality. When heparin or warfarin have been used to treat thrombotic complications in patients with lupus anticoagulant, the risk of bleeding related to these drugs has been comparable to the normal population (29, 48, 51, 61). Effective prevention of further thrombosis has been achieved by Mueh *et al.* (29) with continuous intravenous infusion of heparin at an average dose of 1000 IU/hr. None of the seven patients with lupus anticoagulant bled while being treated on this schedule. If a selective inhibitor of platelet aggregation becomes available, this should have a place in the future management of patients with reduced vascular PGI_2 associated with thrombi consisting almost entirely of platelets (58).

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