Editorial

Antiphospholipid syndrome

The relation between the presence of antibodies apparently reactive with negatively charged phospholipids and thrombotic disease has been established. Current evidence also supports an association between these antibodies and recurrent miscarriage. Many questions remain, however, regarding the identification of the antigenic targets, the optimal laboratory techniques for diagnosis, the pathogenetic mechanisms of autoimmune thrombosis, and the most appropriate treatment in antiphospholipid syndrome (APS).

The laboratory hallmark of APS is positivity in tests for lupus anticoagulant, anticardiolipin antibody (ACA), or both. In secondary APS such "antiphospholipid" antibodies are present in a patient with thrombosis or recurrent miscarriage against a background of systemic lupus erythematosus or a related disorder. Diagnostically more challenging is primary APS where the thrombosis occurs in the apparent absence of other disease. While venous thromboembolism is most frequent, arterial thrombotic events, especially in the cerebral circulation, are prominent.

Disabling stroke in a young and previously apparently healthy individual is an all too familiar presenting feature of primary APS. The detection of antiphospholipid antibodies is not always of such potential clinical importance, however, as they arise in response to some infections and in these instances appear rarely, if ever, to be associated with thromboembolism. They may be persistent, as in syphilis and hepatitis C infection,[1] but are often transient.

It is now apparent that antiphospholipid antibodies are heterogeneous. Lipid binding plasma proteins are necessary for their immunological expression.[2–4] In APS, β_2-glycoprotein I (β_2-GP I) and prothrombin are involved. Protein C, kininogen, and annexin V (placental anticoagulant protein 1) are also implicated.

To establish the diagnosis of APS in a subject with relevant clinical manifestations a laboratory screen must include enzyme linked immunosorbent assays (ELISAs) for ACA, and coagulation based assays for lupus anticoagulant, as in many instances there is positivity in one type of assay only. There are significant problems; although attempts have been made to standardise ACA ELISAs there is considerable variability between assays.[5] Furthermore, the clinical significance of low titre positives and IgM only antibodies is debated. In relation to lupus anticoagulant tests, a range of phospholipid dependent assays is employed. They are, of necessity, indirect and therefore influenced by preanalytical and coagulation variables, and quality control data indicate ongoing, very significant problems in their application and interpretation.[6] To exclude transiently positive tests of doubtful clinical significance, it is necessary to repeat positive tests after a period of six weeks or more.

The identification of the antigenic targets of antiphospholipid antibodies has led to the development of more specific tests, in particular those that measure directly anti-β_2-GP I. ACA that are associated with infections appear not to react with β_2-GP I but bind to immobilised cardiolipin alone.[7] The anti-β_2-GP I assay thus offers the potential for improved specificity in the diagnosis of APS, although the positive predictive value of the assay for thrombosis remains low.[8] In relation to lupus anticoagulant, in over 50% of instances these represent antibody to phospholipid bound prothrombin, but in some cases of APS the in vitro anticoagulant activity is β_2-GP I dependent. These two types of coagulation inhibitor behave differently in coagulation assays and can be discriminated to some extent by their relative effects in the kaolin clotting time (KCT) and the dilute Russell's viper venom time (DRVVT).[9] UK guidelines on testing for lupus anticoagulant have been published[10] and are currently being updated. Despite rapid advances in the development of new immunoassays for antiphospholipid antibodies, at present a comprehensive laboratory screen must still include two coagulation based assays (usually the kaolin cephalin clotting time performed with sensitive reagents in combination with the KCT or DRVVT) as well as ELISAs for IgG, and probably IgM ACA. Although promising and conceptually attractive, an anti-β_2-GP I assay does not yet have an established role as a replacement or additional test.

The advances in our understanding of the immunology of APS have not been accompanied by clarification of the pathogenetic mechanisms that lead to arteriovenous and placental thrombosis. Although β_2-GP I has in vitro anticoagulant properties through inhibition of prothrombinase, contact activation, and ADP induced platelet activation, there is scant evidence that the association with thrombosis relates to this. Indeed, deficiency of β_2-GP I appears not to be a prothrombotic condition.[11] Other potential mechanisms have been explored. For example, there is in vitro evidence for interference in the protein C dependent anticoagulant pathway,[12] but this fails to explain the range of thrombotic manifestations in APS. Although platelet reactive antibodies are also often present there is little evidence to date that in vivo platelet activation is a direct result of autoantibody binding. Whether antiphospholipid antibodies are pathogenetically linked to thrombosis is therefore open to some doubt. The antibodies are clearly heterogeneous and frequently accompanied by other, clearly distinguishable autoantibodies including those that react with antigens expressed on vascular endothelium[13] and on platelets. It is the antimembrane glycoprotein antibodies that are responsible for the thrombocytopenia that is an occasional feature of APS.[14] Whether antiendothelial antibodies contribute to the thrombotic manifestations is the subject of current investigation. It can be reasonably hypothesised that pathogenic antiendothelial cell antibodies lead to cell damage or apoptosis[15 16] resulting in exposure of phosphatidyl serine at the cell surface. Proteins that bind avidly to negatively charged phospholipids, such as β_2-GPI and prothrombin, may then interact, revealing cryptic epitopes to which "antiphospholipid antibodies" then develop. In this model antiphospholipid antibodies are a secondary phenomenon in a disorder of vascular endothelial autoimmune damage. At present we should accept only that antiphospholipid antibodies represent a

useful laboratory marker of an incompletely understood prothrombotic condition.

There is an urgent need for a resolution to the outstanding questions regarding the identification and pathogenicity of antiphospholipid antibodies as it is becoming increasingly clear that details of the optimal clinical management may differ from those applied to other thrombotic disorders. Although the predictive value of antiphospholipid antibody positivity for thrombosis is low when there has been no prior event, the thrombosis recurrence rate in subjects with APS is high.[17] Furthermore, more intensive anticoagulant treatment with warfarin than that generally used may be indicated.[18] These observations require confirmation through the performance of prospective studies on unselected subjects with APS, but until such data become available it may be prudent to regard patients with APS as at high risk for recurrence when making clinical decisions regarding the intensity and duration of anticoagulant treatment. Other considerations should include the presence and management of additional thrombotic risk factors, the nature and severity of the presenting thrombosis, and the undoubted risks of haemorrhagic complications of warfarin treatment. In women with recurrent miscarriage, treatment with low dose heparin along with aspirin during pregnancy may improve the outcome,[19] whereas immunosuppression with corticosteroids results in significant iatrogenic morbidity and no benefit to mother or fetus.[20]

Future research in APS should focus on the furtherance of our understanding of the pathogenesis of the disorder, improvement in the laboratory assays for the provision of accurate diagnostic and prognostic information, and the performance of controlled clinical trials to determine optimal therapeutic strategies for sufferers from this still enigmatic condition.

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