Antiphospholipid antibody syndrome: a review

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The antiphospholipid antibodies include those responsible for the biological false-positive tests for syphilis, lupus anticoagulant activity and anticardiolipin antibodies (ACA) measured by specific radioimmunoassays. Clinical manifestations that have been associated with antiphospholipid antibodies include arterial and venous thrombosis, thrombocytopenia, recurrent abortion and neurological disease. Although often found in patients who fulfil the usual criteria for systemic lupus erythematosus (SLE), the antibodies and various clinical features may occur at least as frequently, if not more so, in patients who do not have SLE[1]. Two such patients have been seen over the last year and illustrate the wide clinical spectrum of disorders associated with antiphospholipid antibodies. In this paper current understanding of the antiphospholipid antibody syndrome is reviewed and the aetiological significance of the antibodies and the mechanism of action are discussed.

Case reports

Case 1: A Caucasian female first presented in 1972, aged 26, with a four-week history of intermittent claudication of the left calf. Arteriography showed a left common femoral artery and profunda block, and at operation organized clot was removed. Subsequently occlusion of the common iliac artery and thrombosis of successive bypass grafts occurred, leading to a left below-knee amputation in April 1974.

In 1975 she developed left-sided hemichorea, which resolved in three months but recurred two years later on the right side. She had two spontaneous first trimester abortions in 1976 and 1978. In 1978 hypertension and proteinuria were found and a renal biopsy revealed diffuse proliferative glomerulonephritis.

In 1983 she suddenly developed dysphasia. CT scan showed a left cerebral infarction. No abnormality of neck or intracranial vessels was seen on digital subtraction angiography.

At the time of her cerebral infarction her kaolin partial thromboplastin time (KPTT) was noted to be prolonged, with mixing studies confirming the presence of lupus anticoagulant activity. Anticardiolipin antibodies were detected. She was anticoagulated with warfarin and has remained well since that time. Further details of this case have been published elsewhere[2].

Case 2: An Egyptian-born surgeon suffered a myocardial infarction at the age of 32. Nine years later he developed painless haematuria and transient hypertension. This was followed by vertigo and unsteadiness. The following month he presented in England for the first time with a right hemiparesis. A CT scan showed diffuse cortical infarcts. He was noted to be thrombocytopenic. His KPTT was prolonged, not corrected by mixing with normal plasma. Anticardiolipin antibodies of both IgM and IgG class were markedly elevated but there was no serological evidence of SLE. He has since had an episode of renal colic, haematuria and proteinuria which was attributed to renal infarction. He has also experienced episodes of transient monocular field defects and a new mitral regurgitant murmur has been detected.

Initially he was treated with prednisolone and azathioprine with some reduction in his ACA levels but no change in lupus anticoagulant activity. Because of the haematuria anticoagulation was not initially undertaken. He has recently suffered a cerebellar infarction and has started warfarin treatment.

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Antiphospholipid antibodies

Lupus anticoagulant activity was first described in 1952 by Conley and Hartmann[3] who reported a clotting defect in the plasma of two patients with SLE. The abnormality was a prolongation of KPTT that was not corrected by mixing with normal plasma, thus differentiating it from clotting factor deficiencies. The activity has been shown to be due to immunoglobulins of IgG and IgM classes by plasma fractionation[4] and it appears to act as a prothrombin complex inhibitor[5]. There is evidence from several routes that the anticoagulant activity is due to an antiphospholipid antibody. This includes correlation with biological false-positives for standard tests for syphilis[6] and the absorption of the activity out of plasma by cardiolipin[7]. Harris and others[6] in 1983 were able to detect ACA by solid phase radioimmunoassay and have found that these have the same, or closely related, specificities as lupus anticoagulant. The clinical associations between the two antibodies have been confirmed in many studies.

The relationship between antiphospholipid antibodies and anti-DNA antibodies is a matter of some debate. Monoclonal antibody studies have shown some cross-reaction between anti-DNA antibodies and cardiolipin and ACA and DNA *in vitro*[8,9]; however, others have found no correlation between ACA, anti-DNA or lupus anticoagulant in patients and no inhibition of the cardiolipin binding activity of ACA by DNA or vice versa[6]. Many patients have raised ACA without raised anti-DNA antibodies. This debate is covered more fully by Harris in his review of the immunological aspects of the subject[1].

Venous and arterial thrombosis

Paradoxically, lupus anticoagulant appears to have no relation to abnormal bleeding but is associated with a thrombotic tendency. In 1980 Mueh and others[10] carried out a retrospective study of patients with lupus anticoagulant activity, finding one or more thrombotic events in 11 of the 35 studied. Boey and others[11], in a study relating clinical and serological findings in patients to the presence or absence of lupus anticoagulant, studied 60 patients – 49 with SLE and 11 with other connective tissue disorders. Of 31 with lupus anticoagulant activity, 18 had had thrombotic disorders ($P<0.01$) which included deep venous thrombosis, pulmonary embolism, renal vein,

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axillary vein and central retinal vein thrombosis and cerebral infarction. Associations have also been reported with peripheral arterial occlusion[2], as in our first case, and pulmonary hypertension, both idiopathic and in SLE[12]. Hamsten and others[13] have studied ACA in 62 survivors of acute myocardial infarction less than 45 years of age. Patients with immunological diseases were excluded from the study. ACA levels were raised in 21% on at least two sampling occasions and these patients appeared to be at particularly high risk (8 out of 13 patients) of suffering recurrent thrombotic episodes, including myocardial and cerebral infarction, during a 36–64 month follow-up period. Valvular heart disease, in particular mitral regurgitation as in our second case, may be a further cardiac manifestation of the antiphospholipid antibody syndrome[14].

Harris *et al.*[15] studied patients with clinical and/or computed tomography or magnetic resonance imaging evidence of cerebral infarction; 13 patients had SLE and 2 'lupus-like illness'. The 11 tested showed lupus anticoagulant activity and all 15 had ACA. A clear association was demonstrated in the SLE stroke patients, and some of the patients with stroke but no evidence of SLE, who served as one of their control groups, also had raised ACA. Hart and others[16] carried out a retrospective study of lupus anticoagulant activity in 145 young patients with cerebral infarction and found 4 patients with lupus anticoagulant but no evidence of SLE. In 2 of these no other conditions associated with stroke were discovered after thorough evaluation.

Various mechanisms have been suggested whereby antiphospholipid antibodies might cause a thrombotic tendency. Plasma from a patient with anticoagulant activity has been shown to block the production of prostacyclin from the endothelium of rat aorta rings. This can be overcome by adding arachidonic acid. Carreras and Vermylen[17] have therefore suggested that the antibodies might cross-react with the phospholipids in the endothelial cell membrane, blocking arachidonic acid release and reducing prostacyclin production, thereby increasing platelet aggregation and thrombosis. An alternative mechanism by which thrombosis may occur is by reduction in fibrinolytic activity. Reduced plasminogen activator release has been demonstrated and it has been suggested that this is the result of immune-complex mediated endothelial cell damage[18]. Patient's plasma has also been shown to inhibit pre-kallikrein activity which would also reduce fibrinolysis[19]. A further possibility is that the antiphospholipid antibodies may activate platelets by binding to phospholipid in platelet membranes causing aggregation and thrombosis.

Neurological disease

The neurological associations of antiphospholipid antibodies are not confined to thrombotic problems. There are also associations with psychiatric problems and transient abnormalities that are probably the result of some other pathological process.

Chorea is a particular neurological manifestation of the antiphospholipid antibody syndrome suffered by one of our patients. It is a well recognized but rare feature of SLE with a reported incidence of 1–4% and has been reported both in pregnancy and in isolation. Bouchez[20] described 3 cases of chorea and circulating anticoagulant and found a total of 9 cases on review of the literature. More recently Asherson and others[21] have described 12 cases of chorea in SLE and 'lupus-like' disease associated with antiphospholipid antibodies. Chorea generally appeared early in the course of the disease and they noted that, in most patients, there was progression to other neurological disorders, particularly in the 7 out of 9 studied who had positive ACA. The pathogenesis of the chorea is uncertain; CT scans, including 5 taken during an episode of chorea, and one MRI scan taken at the time of chorea were normal. It has also been noted that chorea may disappear spontaneously and that it can occur on different sides in a single patient. These observations suggest that the chorea is due to reversible ischaemia rather than cerebral infarction.

ACAs have been found in severe Guillain-Barré syndrome with a statistically significant association of IgA ACA with severe disease[22]. The authors felt that this suggested a pathogenetic role in Guillain-Barré syndrome, though they acknowledged that the antibodies might represent a secondary phenomenon resulting from the destruction of myelin. It is possible that certain antiphospholipid antibodies may cross-react with epitopes on cerebral phospholipids such as sphingomyelin[8]. Optic neuritis and myelopathy in association with ACA in SLE have also recently been reported[23].

Recurrent abortion

Recurrent spontaneous abortion, as in our first case, has been associated with antiphospholipid antibodies. In a study of 43 women with SLE and other autoimmune disorders, 23 had a history of recurrent fetal loss; 16 of these had raised ACA and/or lupus anticoagulant activity. The association between antiphospholipid antibodies and fetal loss was statistically significant[24]. Lockshin and others[25] have found an association between mid-pregnancy fetal distress and raised ACA. The affected patients included 2 without SLE. A retrospective study has also been performed looking at the outcome of pregnancies in women with biologically false-positive tests for syphilis. A high rate of stillbirth, neonatal and infant death was found in those pregnancies reaching maturity (28 weeks)[26].

Examination of placentas of aborted fetuses shows multiple areas of infarction, though the degree of infarction has sometimes been felt to appear inadequate to account for fetal death[27], and it has been suggested that a deficiency of prostacyclin production by placental vessels may cause increased platelet aggregation, reduced blood flow, placental infarction and fetal distress[17].

Renal disease and thrombocytopenia

Renal disease in patients with SLE and circulating anticoagulant has been investigated by Glueck and others in Cincinatti[28]. They looked at the renal biopsies of 18 patients and described striking glomerular and arteriolar thrombosis in patients with circulating anticoagulant. A group of patients with SLE but no circulating anticoagulant served as controls.

Thrombocytopenia is another feature of the antiphospholipid antibody syndrome. In Boey's study[11] the platelet count was less than $100 \times 10^9/l$ in 9 out 31 patients with lupus anticoagulant activity but only 1 out of 29 without. Harris and others[29] have confirmed this in a larger series of 116 patients with SLE and

other autoimmune disease, of whom 43 were thrombocytopenic, 70% with raised ACA. There was a correlation between platelet and ACA levels. Of those patients with antibody levels more than 7 standard deviations above the mean, 75% had a history of thrombocytopenia. An association between idiopathic thrombocytopenia and raised ACA has also been found[30]. It is possible that the antibodies bind with platelet membrane phospholipids and cause enhanced uptake and destruction of platelets by the reticulo-endothelial system.

Another recently described association with antiphospholipid antibodies is livedo reticularis, which Hughes[31] and others have noted to occur with a high incidence of hypertension and stroke.

Treatment

The optimal treatment of patients who have antiphospholipid antibodies is the least well studied aspect of the syndrome. Patients with recurrent thrombosis should be treated with long-term oral anticoagulants. There have been several reports of patients having recurrent thrombotic episodes after stopping anticoagulants[32,33]. Antiplatelet drugs seem a theoretically logical adjunct to anticoagulants but, although they have been used as part of the treatment of patients with various features of the syndrome in many studies and reported cases, there does not seem to have been any controlled trial of their use. Steroid therapy has been found to be of value in recurrent abortion and where oral anticoagulants are contraindicated. Using prednisolone in conjunction with low-dose aspirin, Lubbe and others[34] reported a successful outcome of pregnancy in 5 out of 6 women with SLE, lupus anticoagulant activity and a history of recurrent intrauterine death. However, this regimen does not completely rectify the underlying pathophysiology of the disorder; Branch and others[35] have reported fetal death in spite of correction of the KPTT. They also noted that pre-eclampsia developed in all patients who gave birth to live infants, there being fetal growth retardation in 3 out of 5 cases. They emphasized the need for meticulous antenatal care.

Severe steroid side effects have been described in almost all patients treated, even by those advocating that 'it is no longer justified to withhold treatment' where there is a history of recurrent fetal loss in association with lupus anticoagulant[27]. Immunosuppressive therapy, including steroids, has been shown to decrease lupus anticoagulant activity and ACA levels in many studies, but the clinical benefit of lowering these levels seems uncertain since patients have sometimes been noted to deteriorate in spite of this reduction. Plasmapheresis combined with steroids and/or azathioprine lowers the ACA levels in the majority of patients studied; however, since the antibodies appear to remain elevated for many years in the absence of therapy, it is suggested that any immunosuppressive therapy is likely to need to be prolonged to maintain low levels[1].

Conclusion

The bulk of the literature on the antiphospholipid antibody syndrome comprises descriptions of clinical associations of the antibodies. A cause and effect relationship has not been proven. The possibility remains that the antibodies represent epiphenomena, having no direct role in the development of the conditions reported. However, there does appear to be a strong association between the antibodies and a wide diversity of diseases, some of which – particularly the thrombotic disorders – are amenable to preventive therapy. The population involved includes many young adults in whom the consequences of repeated thrombotic episodes may be particularly catastrophic.

A widely available investigation, namely the KPTT, can be used as a screening procedure even in the absence of local facilities for specific assay of antiphospholipid antibodies. Knowledge of the presence of the antibodies should modify treatment, particularly its duration. We therefore suggest that antiphospholipid antibodies should be sought in otherwise unexplained occlusive thrombotic disease, including myocardial infarction and stroke, in recurrent fetal loss and thrombocytopenia, in a much wider range of patients than those with SLE in whom they were first recognized.

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