REVIEW

Antiphospholipid antibodies and cardiovascular disease

H L C Beynon, M J Walport

Vascular inflammation is a common feature of autoimmune diseases including systemic lupus erythematosus and the primary vasculitides (for example, polyarteritis nodosa, Wegener's granulomatosis, and Takayasu's arteritis). This inflammation is characterised by destruction of the vessel wall; perivascular infiltration of neutrophils, monocytes, and lymphocytes; and deposition of immunoglobulins and complement proteins.^{1,2} A novel type of autoimmune vascular damage has been characterised during the past few years associated with the presence of antiphospholipid antibodies. The predominant manifestation is vascular thrombosis in the absence of other markers of tissue inflammation.

Three techniques are commonly used in clinical practice to identify antiphospholipid antibodies. In order of increasing sensitivity these are the VDRL (Venereal Diseases Reference Laboratory), lupus anticoagulant, and anticardiolipin antibody (ACA) assays. Cardiolipin is the most usual antigen used in antiphospholipid antibody assays and was chosen for historical reasons because it is a constituent of the VDRL reagent. However assays for antibodies to other negatively charged phospholipids, such as phosphatidylserine and phosphatidic acid seem to be equally sensitive and much work is needed to define the best method of identifying these antibodies in clinical practice.

Antiphospholipid antibodies are found in two main clinical settings: (a) after chronic infection—for example, syphilis, malaria, leprosy—and (b) associated with autoimmunity. Only in autoimmune diseases do these antibodies correlate with thrombosis. The VDRL and anticardiolipin antibody assays do not distinguish between antiphospholipid antibodies associated with infection or autoimmunity—therefore interpretation of the relevance of a positive result from these assays is dependent on the clinical circumstances. In contrast, the lupus anticoagulant is more specifically found in association with autoimmune disease including the “primary antiphospholipid syndrome”. However, it may also be found after treatment with certain drugs, such as chlorpromazine, and its clinical significance in

this context is not certain. The test for lupus anticoagulant is technically more difficult and less sensitive than the newly established methods for detecting anticardiolipin antibodies.

Four questions about the association of these autoantibodies with cardiovascular disease will be considered here: (a) what is the nature of their association with thrombosis, valve lesions, and pulmonary hypertension; (b) is there any true association with coronary artery disease; (c) are the antibodies causally related to disease; and (d) what is the best treatment? The other significant clinical and haematological associations with these autoantibodies (recurrent spontaneous abortions, haemolytic anaemia combined with thrombocytopenia, and chorea gravidarum) fall outside the scope of this review and have been reviewed elsewhere.^{3,4}

Thrombosis

Thrombosis of the veins and arteries is the commonest clinical feature associated with the presence of antiphospholipid antibodies. These thrombotic events are often repeated and almost every portion of the circulation can be affected. Indications for assay of anticardiolipin antibodies include recurrent deep venous thromboses, early onset cerebrovascular disease (which may be associated with cognitive impairment and progression to multi-infarct dementia), and unexplained thrombosis in other circulations. The table shows the list of thrombotic events anecdotally associated with the presence of anticardiolipin antibodies. The eponymous Sneddon's syndrome, comprising livedo reticularis and cerebrovascular disease, is often associated with these autoantibodies.⁵

Valve disease

Libman and Sachs reported in 1924 a “hitherto undescribed form of valvular and mural endocarditis” in patients with systemic lupus erythematosus.⁶ There is now good evidence for an association of this form of endocarditis with the presence of antiphospholipid antibodies. In patients with systemic lupus erythematosus Galve and colleagues in 1989

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Accepted for publication
4 October 1991

Vascular associations of antiphospholipid antibodies

Arterial disease

- thrombosis of large arteries leading to: stroke, splenic infarction, mesenteric infarction etc.
- multi-infarct dementia
- marrow necrosis
- retinal artery disease
- deafness and vestibular failure
- adrenal infarction
- skin necrosis
- coronary thrombosis (see text)
- pulmonary hypertension

Venous disease

- recurrent deep venous thromboses with or without emboli
- Budd-Chiari syndrome

Placenta

- thrombosis of placental vessels

found anticardiolipin antibodies in eight out of nine patients with valve lesions and seven out of 16 patients without.⁷ This finding has been confirmed in a recent prospective analysis in which high titres of antiphospholipid antibodies (>5 SDs above the normal mean) were detected in 50 of 93 patients with systemic lupus erythematosus.⁸ Thirty nine of the patients with raised titres of anticardiolipin antibody were found to have at least one cardiac abnormality. Valve lesions predominantly affecting the mitral valve were present in 20 (vegetations in eight and diffuse valve thickening in 12). Pericardial effusion was present in 15 patients and four patients had evidence of myocardial dysfunction. In this study the overall sensitivity and specificity of high titres of anticardiolipin antibodies in predicting cardiac abnormalities in systemic lupus erythematosus was 78% and 74% respectively. In the same study eight of 12 patients with high titres of antiphospholipid antibodies who did not fulfil the American Rheumatism Association criteria for systemic lupus erythematosus also had cardiac abnormalities: four had mitral valve vegetations, three had diffuse thickening of the mitral valve, and one had severe aortic regurgitation. Others have confirmed the association between antiphospholipid antibodies and valvar heart disease in similar groups of patients.⁹⁻¹² There is an appreciable chance of ascertainment artefact resulting in the collection of biased data in such studies—that is, obstetricians are more likely to see a high prevalence of recurrent abortions in patients with antiphospholipid antibodies and it is not surprising that cardiologists also report that cardiac disease is common.

Pulmonary hypertension

Primary pulmonary hypertension was found in up to 14% of patients with systemic lupus erythematosus.^{13 14} In an uncontrolled study of 24 patients with autoimmune disease and pulmonary hypertension (22 systemic lupus erythematosus, one primary antiphospholipid antibody syndrome, one lupus/systemic sclerosis overlap) 21 patients had primary pulmonary hypertension with no evidence of thromboembolism and antiphospholipid antibodies were detected in 68%, compared with a background frequency in systemic lupus erythematosus of 30–40%.^{13 14} Further work is needed to establish whether this association is genuine.

Is coronary artery disease significantly associated with antiphospholipid antibodies?

Given that coronary artery disease is so common it would be surprising if there was a marked association of this condition with antiphospholipid antibodies. It was therefore remarkable when a prevalence of anticardiolipin antibodies of 21% was reported among 62 young (<45 years) survivors of myocardial infarction without other evidence of autoimmune disease.¹⁵ During a five year follow up

cardiovascular events (including stroke, lower limb occlusion, new myocardial infarction, and pulmonary embolism) were more common in eight out of 13 patients with raised titres of anticardiolipin antibody. No clinical features separated the groups of patients with or without anticardiolipin antibodies at the time of initial presentation with myocardial infarction. This study raises two questions: (a) which came first—the coronary artery disease or the anticardiolipin antibodies and (b) what relation, if any, did the subsequent vascular disease have to the autoantibody? Two other groups have also reported raised titres of anticardiolipin antibodies in cohorts of patients with coronary artery disease: (a) anticardiolipin antibody titres were raised in patients with angina and/or infarction compared with groups of patients with tuberculosis or rheumatoid arthritis¹⁶ and (b) there was a significant correlation between anticardiolipin titres (measured at the time of coronary artery bypass surgery) and the incidence of late graft occlusions.¹⁷

It is important to appreciate that the cut off point for “positive” results in each of these studies was 2 SDs above the normal mean—that is, a value that includes 5% of a normal population. This cut off value is much lower than the value of 5 SDs usually chosen in analyses of patients with systemic autoimmunity.

Other surveys^{18 19} of consecutive patients with coronary artery disease have not confirmed an association with anticardiolipin antibodies and the pathogenic significance of the low titres of these antibodies measured by some workers in these patients remains doubtful.

What is the prevalence of coronary artery disease among patients with autoimmunity and antiphospholipid antibodies? Myocardial infarction was identified in 13 (six systemic lupus erythematosus, three lupus like disease, and four primary antiphospholipid syndrome) of 300 patients with high titres of antiphospholipid antibodies.²⁰ This low prevalence of 4% myocardial infarction among patients with very high titres of anticardiolipin antibodies casts further doubt on the pathogenic significance of low titres of antibodies in some series of patients with coronary artery disease in the absence of other evidence of autoimmunity.

Pathogenesis

The data reviewed above strongly support the existence of genuine epidemiological associations of a subset of antiphospholipid antibodies with thrombotic vascular disease and with endocarditis, though the strength of these associations requires further clarification. The target of these autoantibodies *in vivo* has not been identified. Negatively charged phospholipids are widely distributed in cell membranes, but they are mainly located on the inner lamella of the cell membrane and in this location are not accessible to autoantibodies.²¹ Recent work has suggested that antigenicity *in vitro* of antiphospholipid antibodies depends on the interaction of the phospholipid with a protein cofactor β_2 glycoprotein I (apo-

lipoprotein H).²² It is unknown whether a cofactor is involved in vivo.

The in vitro and in vivo effects of antiphospholipid antibodies are paradoxical. In vitro the lupus anticoagulant prolongs the partial thromboplastin time by inhibiting the binding of the factor X and prothrombinase complexes to anionic phospholipid substrate.²³ In contrast, these antibodies are associated with thrombosis in vivo and several hypotheses have been proposed to explain this: (a) activation of platelets; (b) endothelial activation rendering the antibody procoagulant (inhibition of prostacyclin generation, inhibition of thrombomodulin generation of active protein C); (c) inhibition of fibrinolysis by interference with protein C and S function; (d) impaired prekallikrein action; and (e) inhibition of antithrombin III (reviewed in²⁴). None of the mechanisms has been convincingly proven to operate in vivo. It is noteworthy that inherited deficiencies of proteins C, S, and antithrombin III are each associated with recurrent venous, but not arterial, thromboses.

Treatment

It is disappointing that the treatment of patients with antiphospholipid antibodies has not developed beyond the empirical stage and no formal clinical trials have been published. It is common practice to prescribe long-term anticoagulation with warfarin for patients with venous thrombosis and antiphospholipid antibodies, because there is some evidence that there is a high risk of recurrent thrombosis when such treatment is stopped.²⁵ Significant valve lesions should be sought so that patients can be advised about antibiotic prophylaxis.

All other management issues are uncertain. Arterial disease, especially cerebrovascular, poses particular difficulties because there is good evidence of insidious progression in some patients.²⁶ Warfarin combined with low dose aspirin is a reasonable empirical treatment but there are no data showing effectiveness or ineffectiveness. The role of immunosuppression is even more uncertain—removing the antibodies is fine in principle but in practice requires the administration of large doses of steroids and cytotoxic agents. Corticosteroids are widely prescribed to patients with antiphospholipid antibodies, but there are no controlled data and this practice is not based on logical premises. In other autoimmune diseases such as systemic lupus erythematosus steroids are potent anti-inflammatory agents. There is no evidence that classic inflammatory mechanisms are involved in the pathogenesis of the vascular associations of the antiphospholipid syndrome. For this reason we usually restrict steroids and cytotoxic drugs to patients with co-existing systemic lupus erythematosus or related diseases with other clinical manifestations of inflammation.

Conclusion

The delineation of the clinical syndrome associated with antiphospholipid antibodies

has defined new challenges for clinicians and scientists interested in vascular biology. During the first major rush of enthusiasm it is likely that most of the important clinical correlates of the importance of these antibodies have been discovered. The important questions that now remain to be answered are: (a) what is the relevant antibody specificity and how should it be measured, (b) if the pathogenesis of thrombosis is mediated by the antibody, what is the mechanism, (c) what is the prevalence of the different clinical features of the syndrome in unselected individuals with antiphospholipid antibodies and what is the scale of the problem overall (that is, to what extent do "pathogenic" antiphospholipid antibodies contribute to thrombosis in unselected cohorts of patients), and (d) what is the best treatment? There are still more questions than answers.

HLCB is an MRC training fellow. This work was supported by the Arthritis and Rheumatism Council.

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VIEWS FROM THE PAST *George Dock*

There is no new thing under the sun.

Ecclesiastes 1.9

In this era when angiography, angioscopy, and pathology have concentrated on the importance of plaque disruption in causing coronary thrombosis it is salutatory to discover astute observations made in the last century.

George Dock in 1896 made observations that have a remarkably modern ring. . .

Why then did pathologists subsequently deny the importance of thrombosis? Perhaps because they had become remote from the clinical aspects of disease. That cannot be said of George Dock who was successively Professor of Pathology in Galveston, Professor of the Theory and Practise of Medicine, University of Michigan, and Professor of Medicine in St Louis.

M J DAVIES

A negro drayman, of fifty, a man of unusually powerful physique, with a history of perfect health, was seized in the night with pain in the heart-region and a sense of suffocation. He was seen by Dr H A West, who found no special symptoms other than those mentioned. Morphine temporarily relieved the pain, but in about two hours after the onset the patient suddenly died. I made an autopsy six hours after death, and, finding no marked evidence of disease in any other organ, took the heart unopened to my laboratory for careful examination. This was made by cutting the organ in slices, parallel to the auriculo-ventricular septum, and examining the vessels in each slice separately. . . . The branches of the aorta were all free from atheroma except the coronaries. The latter were affected in various degrees in their whole extent, being calcified, partially occluded or dilated. In the descending branch of the left, just below its origin, was a ruptured atheromatous

abscess, eight mm long, extending two-thirds around the dilated artery. The edges were overhanging, the flow uneven and ragged, presenting all the appearances of a recent rupture. This proved to be the case. On opening up the sections of the branches below the rupture they were found to contain a little blood with characteristic atheromatous material, such as cholesterol plates, blood pigment in crystals and masses, larger cells with highly refracting granules and amorphous and granular debris. The left lateral branch of the artery just below the rupture was obstructed by an atheromatous nodule in its wall, but all the other branches contained debris as far as they could be traced.

George Dock. Notes on the coronary arteries. In: Mauer AK, Mauer EF. *George Dock, MD: a bibliography of his writings*. 2nd ed. Los Angeles: Barlow Society for the History of Medicine/Friends of the Library of the Los Angeles County Medical Association, 1991.