Review Article

Anticardiolipin antibodies—clinical associations

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Attention was first drawn to the presence of an anticoagulant in patients with systemic lupus erythematosus (SLE) by Conley & Hartmann (1952) who described two patients with haemorrhagic disorders and prolonged prothrombin and whole blood clotting times. This anticoagulant appeared to act at the level of the prothrombin converter complex of the clotting cascade and prolonged all phospholipid dependent coagulation tests – activated partial thromboplastin time (APTT), the Russell viper venom test (RVVT) and, less often, the prothrombin time. The thrombin time is usually normal. It became evident over the years that this 'lupus anticoagulant' was not particularly associated with bleeding but, paradoxically, with thrombosis (Mueh *et al.*, 1982).

A more sensitive and reliable technique of solid phase radioimmunoassay for the detection of antibodies to cardiolipin (a-CL) was devised by Harris *et al.* (1983a). Subsequent studies have shown a close relationship between these antibodies and the 'lupus anticoagulant', both members of a 'family' of antibodies to phospholipid, an integral part of the clotting cascade. However, phospholipids are also present in cell walls of endothelial cells, platelets and even neuronal cells and the actions of the antibodies against these phospholipids have been thought to be important in the pathogenesis of some of their clinical effects.

Approximately 30% of patients with the 'lupus anticoagulant' or antibodies to cardiolipin will have a false positive test for syphilis. The VDRL test is usually of low titre (1:4–1:8) in these patients (Harris *et al.*, 1985a).

The mechanism of action of these antibodies remains obscure. Carreras *et al.* (1982) postulated that they may facilitate coagulation by preventing the release of arachidonic acid from blood vessel endothelium. Prostacyclin production is thereby reduced and platelet aggregation may occur. Inhibition of prekallikrein (Fletcher Factor) and the resulting impairment of fibrin clearance as a mechanism was suggested

by Angles-Cano *et al.* (1979) and this mechanism has been demonstrated in several patients by Sanfelliop & Drayna (1983) and Elias & Eldor (1984). Comp *et al.* (1983) have described IgG from two patients with the lupus anticoagulant that inhibited the function of human thrombomodulin, the endothelial co-factor in the activation of protein C by thrombin. Thus the feedback inhibition of coagulation by activated protein C is prevented. This has recently been verified by other workers (Cario *et al.*, 1986).

There is also a clear association with thrombocytopenia and Harris *et al.* (1985a) suggest that anticardiolipin antibodies may play a direct role in mediating platelet destruction. It has been postulated that lupus anticoagulants damage platelets and increase their adhesiveness initiating thrombosis (Editorial, 1984).

It has been shown that a-CL antibodies may be of the IgG, IgM or IgA subclass. Harris *et al.* (1986) have recently demonstrated the importance of the actual levels of a-CL antibodies in predicting thrombosis, recurrent fetal loss or thrombocytopenia and this seems to hold true particularly for the IgG subclass, while a group of patients with drug-induced 'lupus anticoagulant' activity recently analysed were found to have predominantly IgM elevations which appeared to be unassociated with any of the thrombotic clinical complications (Gharavi *et al.*, 1986).

Investigations by Dr G.R.V. Hughes and his associates from 1983 onwards at the Hammersmith Hospital and the Rayne Institute of St. Thomas' Hospital, have led the way to further detecting and delineating the character of the antiphospholipid antibodies, their clinical associations and the efficacy of various therapies in the prevention of the associated clinical complications. Since then, two International Conferences have been held in London with investigators from many countries participating and it has become clear that not only has the original finding of an association with thrombosis been confirmed but that the clinical associations of antiphospholipid antibodies now extend far beyond the original concept and that there is significant 'spill-over' to non-lupus patients and indeed to the general population.

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It is the purpose of this review article to summarize briefly the important advances being made in this rapidly developing field and in particular in relation to the more recently recognized clinical syndromes.

Venous thrombosis and pulmonary embolism

Recurrent venous thrombosis, in association with the lupus anticoagulant and more recently with anticardiolipin antibodies has been documented by most authors (Mueh *et al.*, 1982; Harris *et al.*, 1983a; Elias & Eldor, 1984; Boey *et al.*, 1983). Thrombosis of leg veins has been most frequently reported (DVT) and is often accompanied by pulmonary embolism. Other sites affected have been the renal veins (Asherson *et al.*, 1984a), extending to/from the inferior vena cava, hepatic veins, associated with veno-occlusive disease or a Budd-Chiari syndrome (Hughes *et al.*, 1984a; Vermynen *et al.*, 1986), retinal veins (Hall *et al.*, 1984), the axillary veins (Boey *et al.*, 1983) and superficial thrombophlebitis (Peck *et al.*, 1978).

Arterial occlusions

Arterial occlusions particularly involving large cerebral arteries causing stroke or transient ischaemic attacks (TIAs) are common.

Recently, the association of myocardial infarction, particularly in the young, has been documented (Asherson *et al.*, 1986a) and cases have also been reported by Vermynen *et al.* (1986) and Bingley & Hoffbrand (1986). Of great interest was the finding by Hamsten *et al.* (1986) of a 21% incidence of raised anticardiolipin antibody levels in survivors of myocardial infarction under the age of 45 years. Additional vascular occlusions were experienced in 8/13 patients and these included cerebral infarction, lower limb-arterial occlusions, new myocardial infarctions, pulmonary embolus and DVT.

Involvement of the axillary artery giving rise to an aortic arch syndrome was reported by Asherson *et al.* (1985a) who also documented the occurrence of large vessel arterial occlusions involving the lower limbs particularly, resulting in gangrene and amputation of the extremities (Asherson *et al.*, 1985b, 1986b), and mesenteric artery occlusions with resultant bowel infarction (Asherson *et al.*, 1986c).

Retinal artery occlusions have been described by Hall *et al.* (1984) and are usually associated with 'cotton-wool' spots – infarcts of the nerve fibre layer of the retina.

Renal infarction occurred in a patient in the series of patients with chorea reported by Asherson *et al.* (1986a) and was also seen in the patient described by Bingley & Hoffbrand (1986) in their review.

Recurrent fetal loss

Recurrent fetal loss is particularly common in SLE and its association with antiphospholipid antibodies and placental vessel thrombosis has attracted much attention (Derue *et al.*, 1985; Nilsson *et al.*, 1975; Soulier & Boffa, 1980; Lubbe *et al.*, 1983).

A number of patients with this complication have been reported who do not in fact have SLE, but only a positive antinuclear factor. Even more intriguing is the documentation of other patients in whom the presence of antiphospholipid antibodies appeared to be the sole immunological abnormality detected and this has important implications in the screening and treatment of such patients (Ware-Branch *et al.*, 1985).

Lockshin *et al.* (1985) found that the measurement of antibodies to cardiolipin was the most sensitive assay in predicting fetal distress (as judged by the fetal heart rate) or death in patients with SLE. The therapy of such patients with steroids and salicylates has resulted in a marked increase in the number of live children in patients with this condition.

A decidual vasculopathy and, often, extensive placental infarction is found in many patients who demonstrate recurrent fetal loss (Ware-Branch *et al.*, 1985; De Wolf *et al.*, 1982), but in others, placental infarction has been quantitatively insufficient to account for abnormal fetal heart rates or death of the fetus (Lockshin *et al.*, 1985) and other mechanisms such as prostacyclin/thromboxane imbalance may be implicated in these.

Thus all pregnant patients, even those without SLE, who have a history of recurrent fetal loss without obvious cause should be screened for a-CL antibodies.

Post-partum syndrome

Ware Branch and his co-workers at the University of Utah (1986) have recently identified a unique post-partum syndrome in several of their patients with antiphospholipid antibodies, consisting of spiking fevers, pleuritic chest pain and dyspnoea, and had chest X-rays showing pleural effusions and patchy infiltrates. All tests to demonstrate an infectious aetiology were negative but venous thromboses were present in two. Multifocal ventricular ectopy occurred in one, while another developed a cardiomyopathy.

Pulmonary hypertension

The occurrence of pulmonary hypertension (PHT) in association with the 'lupus anticoagulant' in SLE was first noted by Asherson *et al.* (1983) and this association has also been reported in a patient with discoid LE (Asherson *et al.*, 1985c) and with mixed connective

tissue disease (MCTD) (Hainaut *et al.*, 1986). The 'lupus anticoagulant' has also been found in several patients who presented with pulmonary embolism (Jaffe *et al.*, 1985) and fatal PHT (Anderson & Ali, 1984) even in the absence of SLE. This association of pulmonary hypertension and SLE has recently been reviewed by Asherson & Oakley (1986) who concluded that the association probably applied *only* to those patients with thromboembolic PHT which, in some, might be unrecognized clinically. Preliminary studies on a small number of patients with 'primary PHT' have not demonstrated the presence of a-CL antibodies, tending to confirm this hypothesis (Asherson *et al.*, 1984b).

Labile and accelerated hypertension

The occurrence of 'labile hypertension' in patients with high levels of circulating anticardiolipin antibodies has been commented on by Hughes (1985b), and several contributors to the recent 2nd World Symposium on Anti-Phospholipid Antibodies alluded to the high frequency of hypertension in their pregnant patients.

A recent case reported by Joaquin *et al.* (1986) from France draws attention to accelerated hypertension in a young patient with SLE. Renal biopsy revealed ischaemic changes from intravascular microthromboses. This syndrome of striking glomerular and arteriolar thrombosis was first documented by Kant *et al.* (1981) in six of their patients and Bingley & Hoffbrand (1986) have also encountered a similar patient.

The hypertension encountered in the patients with livedo reticularis documented by Sneddon (1965) and Thomas *et al.* (1982) seems to confirm its association with this often-encountered dermatological accompaniment of the syndrome.

Pre-eclamptic toxæmia

Pre-eclamptic toxæmia (PET) develops in 5–10% of pregnancies and is a major cause of prenatal and maternal mortality. Its aetiology remains obscure. However, pathologically there is a remarkable similarity between the placental changes in this condition and those found in patients with antiphospholipid antibodies and recurrent fetal loss. A decidual vasculopathy with necrosis and extensive infarction is seen, consistent with a thrombotic state.

A variety of coagulation abnormalities have been associated with PET and these include intravascular coagulation, thrombocytopenia, anti-thrombin III deficiency, and Factor VIII consumption (Vaziri *et al.*, 1986). The presence of antiphospholipid antibodies

may represent yet another disturbance resulting in a coagulopathy.

In addition, there may be disturbance of the normal prostacyclin (PG12)/thromboxane (TXA2) ratio. Decreased PG12 production in umbilical, placental and uterine vasculature has been demonstrated in the condition (Stuart, 1981) as well as decreased PG12/TXA2 ratio (Walsh, 1985).

Abnormal vascular function and morphology has also been demonstrated in PET (Asikjacr *et al.*, 1982) and this condition may provide a 'study model' which may explain the 'labile' hypertension mentioned above.

Central nervous system syndromes

Central nervous system (CNS) syndromes are being encountered with increasing frequency in patients with antiphospholipid antibodies and have been the subject of recent reviews (Hughes, 1983; Harris & Hughes, 1985). Thus increasing numbers of patients with cerebral thrombosis and TIAs (amaurosis fugax most frequently) are being documented. Many of these do not in fact conform to the strict diagnostic criteria for SLE as laid down by the American Rheumatism Association (ARA) (Tan *et al.*, 1982) and are referred to as 'lupus-like' or 'variant lupus'.

Migraine, which appears not to differ from the 'classical' variety, often heralds the onset of a major cerebral catastrophe and is a prominent prodrome. Epilepsy also appears to be more frequently encountered and the occurrence of chorea in association with the 'lupus anticoagulant' and a-CL antibodies has recently been documented. Bouchez *et al.* (1985) documented three patients with lupus anticoagulants, while Asherson *et al.* (1986d) have collected a total of 12 patients with chorea and SLE of whom 9 demonstrated elevations of anticardiolipin antibodies as well as other features of the 'syndrome'.

Behavioural abnormalities leading to dementia associated with multiple cortical infarcts, demonstrable on computed tomographic (CT) scanning, has occurred in several patients, either initially as an isolated phenomenon or as part of a generalized CNS symptomatology usually with recurrent strokes (Asherson *et al.*, 1986e).

A patient with Guillain-Barré syndrome (GBS) in association with a-CL antibodies and recurrent thrombocytopenia was reported recently (Harris *et al.*, 1983b) and this association has also been stressed by Frampton *et al.* (1986) who found elevations of IgG, IgM but particularly IgA a-CL antibodies in their patients with acute GBS. They correlated the high levels of IgA a-CL antibodies with severe disease requiring ventilation or of those who died, suggesting a pathogenetic role for these antibodies in this condi-

tion. The association of optic neuritis with antiphospholipid antibodies in SLE (in many cases associated with a transverse myelopathy) was reviewed by Oppenheimer & Hoffbrand (1986) in a recent publication. They also commented on the useful value of the a-CL antibody test in the differentiation of this combination of symptoms between patients with SLE and those suffering from multiple sclerosis.

The pathogenesis of large vessel cerebral occlusions and those involving smaller vessels and causing cortical dysfunction and dementia is clearly thrombotic in nature. However the occurrence of migraines, epilepsy, chorea and GBS may be related to neurological interactions between the antiphospholipid antibodies and phospholipid in brain or myelin. This hypothesis still requires much study.

Valvular lesions

A group of patients with valvular heart disease, lupus anticoagulant and stroke was recently identified by Chartash *et al.*, in New York (1986). These patients had 'atypical' presentations of SLE and all had clinically significant valvular disease (predominantly aortic insufficiency, occasionally mitral insufficiency) as demonstrated echocardiographically.

Lubbe & Walker in New Zealand (1979) have also encountered this association, while Asherson *et al.* (1986d) in their series of patients with chorea and antiphospholipid antibodies documented two who had mitral insufficiency. The association of chorea and mitral insufficiency in young patients in the past has led to the diagnosis of acute rheumatic fever. However, as this illness is no longer seen except in Third World countries, a similar presentation may perhaps herald the onset of disease such as SLE.

Apart from aortic and mitral insufficiency, the demonstration of obstruction of a prosthetic mitral valve by clot in one patient with the 'lupus anticoagulant' and endocarditis in another (Lubbe, W.F., 1986—personal observation) raises the possibility that recurrent TIAs occurring in a small number of these patients are embolic phenomena.

Livedo

Livedo reticularis, a cyanotic discoloration of the skin with a characteristic network pattern caused by stasis of blood in the superficial skin drainage was first described in SLE by Golden (1963).

Its relationship to cerebro-vascular disease was first highlighted by Sneddon in 1965 who described six patients, all of whom had had cerebrovascular accidents (in some cases multiple), and who also had essential hypertension. This association was later also

documented by Quimby & Perry (1980) and Thomas *et al.* (1982).

All patients investigated had CT scan evidence of cerebral infarctions, but, although most were female, they did not appear to have any features suggestive of SLE or related 'auto-immune' disorders.

The occurrence of livedo, labile hypertension and cerebrovascular disease in SLE patients with antiphospholipid antibodies was emphasized by Hughes in his Prosser-White oration (1984). A recent case report has documented central retinal artery occlusion in association with antiphospholipid antibodies and "Sneddon's syndrome" (Jonas *et al.*, 1986) and further investigation of the relationship of this unusual vascular phenomenon to the other features associated with antiphospholipid antibodies is required.

Peripheral vascular syndrome

Johansson *et al.* (1977) described five patients with circulating anticoagulants who demonstrated a vascular syndrome consisting of recurrent deep venous thrombosis and necrotizing purpura with painful superficial ulcers around the ankles. Skin biopsies revealed a massive proliferation of haemorrhagic dermal capillaries without any significant inflammatory reaction. Large or medium-sized vessels had thickened or hyalinized walls and cases showing thrombosis of dermal vessels demonstrated complete absence of inflammatory cells.

A similar condition appears to have been described by Bard & Winkelmann (1967) ten years earlier under the title of 'livedo vasculitis' who documented nine patients with a livedo-like pattern of purpura and scars. They pointed out that an overlap with livedo reticularis occurred and highlighted the earlier observations of Feldaker *et al.* (1955) who also described endothelial cell proliferation and thrombosis occurring in that condition. Circulating anticoagulants were not looked for in this group of patients, but interestingly enough, one of the Bard & Winkelmann cases (1967) had a false-positive serological test for syphilis.

Haematological abnormalities

Thrombocytopenia is a common finding in patients with antiphospholipid antibodies but it is not usually associated with haemorrhage (Shapiro & Thiagarajan, 1982) unless severe or accompanied by another clotting defect. One theory as to its aetiology is that antiphospholipid antibodies may bind phospholipid in platelet membranes resulting in enhanced uptake and destruction by the reticulo-endothelial system. Studies by Harris and co-workers (1985a) have de-

monstrated a high frequency of these antibodies not only in SLE and auto-immune disorders but also in approximately 30% of patients with auto-immune thrombocytopenic purpura (Harris *et al.*, 1985b). An association with haemolytic anaemia has also been suggested, presumably based on a similar mechanism, but this has not yet been substantiated.

Asherson *et al.* (1985d) have found that a large group of patients with elevations of a-CL antibody and one or more of the associated clinical complications did not conform to the American Rheumatism Association diagnostic criteria for SLE. Although they were all ANA positive, they were usually negative for dsDNA antibodies and tended to have fewer of the typical manifestations of SLE such as fevers, malaise and polyserositis. On the other hand, they seemed to have more CNS features.

Treatment

This is still largely experimental and many large scale prospective studies are needed in order to determine the most effective and least harmful therapy. Rather than attempting to reduce the antibody levels, it seems to be far easier to prevent their effects. The use of steroids and salicylates in order to achieve increased fetal salvage has been most encouraging in patients with recurrent fetal loss.

Anticoagulation (e.g. with warfarin) is advised for patients with a tendency to develop vascular occlusions and who have high titres of these antibodies. Antiplatelet compounds, particularly salicylates, have also been shown to be useful anec-

dotally. Because of the high risk of 'recurrent' thrombosis in these patients after warfarin withdrawal (Asherson *et al.*, 1985e) it is advised that long-term anticoagulation be continued in these patients pending reduction (either spontaneous or induced) of high a-CL antibody levels.

The use of long-term immunosuppression, high dosage steroids or other heroic methods such as plasmapheresis is not justified.

The associations of the antiphospholipid antibodies have expanded broadly over the past two to three years. Many disciplines in medicine are involved. Recurrent fetal loss, an acute post-partum syndrome and possible associations with pre-eclamptic toxemia are of great obstetric interest with the diversity of CNS manifestations varying from Guillain-Barré syndrome and chorea to multi-infarct dementia involving the neurologist. The dermatologist's interest has been sparked by the associations with livedo reticularis and peripheral vascular syndromes and the cardiologist too is involved in the links documented with pulmonary hypertension, systemic hypertension and valvular lesions. The finding of glomerular thrombi associated with 'accelerated' hypertension will also involve the nephrologist.

Of more than passing interest is the realization that there is 'spill-over' of these antibodies to sections of the population not suffering from overt 'autoimmune' disease. Their prevalence in young patients with stroke, myocardial infarction and other hitherto unexplained vasculopathies will provide great interest over the next few years.

Developments in this field make this one of the exciting new discoveries in medicine today.

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