The antiphospholipid syndrome

ABSTRACT—Ten years ago we described a group of patients with a combination of clinical features associated with the presence of antiphospholipid antibodies. These features included a tendency to both arterial and venous thrombosis, livedo reticularis, recurrent abortions and occasional thrombocytopenia. This striking clinical constellation was originally named the anticardiolipin syndrome and is now more appropriately called the antiphospholipid syndrome (APS). Although our early studies were directed on systemic lupus erythematosus in which up to a third of patients demonstrated features of the syndrome, it was clear even a decade ago that the APS would increasingly become the domain of neurologists and cardiovascular physicians. The consensus is that antiphospholipid antibodies have a pathogenetic role in the vasculopathy of the APS, but the mechanisms are still unknown. The establishment of good animal models for the APS is the best opportunity to develop rational and more targeted therapies. In our experience, treatments directed against the secondary thrombotic event have proved more successful than those directed against the underlying immunological abnormality.

The antiphospholipid syndrome (APS) is a hypercoagulable disorder in which patients may develop both venous and arterial occlusion. Its serological marker is the presence of antiphospholipid antibodies (aPL). The clinical ramifications are extensive (Table 1). Although it is only 10 years since the syndrome was clinically defined [1], it has aroused the interest of clinicians and researchers alike for a number of reasons:

- The presence of high-titre aPL is one of the strongest associates with thrombosis known in man.
- The definition of a discrete group of patients at risk of thrombosis (eg stroke) has important therapeutic implications.
- Thrombosis in placental vessels in pregnancy in these patients is an important, potentially treatable, cause of spontaneous abortion. In the past five years many more women with this syndrome have successfully completed their pregnancies.
- The association between aPL and thrombosis comes as near to being a 'cause and effect' link as any in immunology. The reasons for this assertion will be given later.

Patients present with both acute and less obvious thrombotic sequelae. Venous thrombosis can take many forms, such as recurrent deep venous thrombosis (occasionally after the oral contraceptive pill), ocular thrombosis, acute renal vein thrombosis, Budd-Chiari syndrome etc, and is associated with pulmonary hypertension. Unlike other known clotting disorders, arterial thromboses are a major feature of the disease. Arterial thrombosis of internal organs may result in a variety of presentations, such as acute Addisonian crisis (from infarction of the adrenals), renovascular hypertension, acute myocardial infarction and retinal artery occlusion [2].

Clinically, however, the brain is the most strikingly involved organ in the body. Time and again patients give histories of headaches, migraine and amaurosis, sometimes for many years. For others the onset is disastrous, with a major arterial stroke. Antiphospholipid antibodies are now internationally recognised as an important aetiological factor and may be present in 7% of all patients who have suffered a stroke [3]. They should be sought especially in young patients with strokes where they may account for up to 18% [25].

The APS presents a wide variety of neurological features. Some patients who have had several strokes may present clinically as multi-infarct dementia [4] or, in less extreme situations, with epilepsy, chorea, personality disorders etc. One of the strongest clinical associations is with myelopathy [5]. Although in itself a rare clinical problem, it provides an interesting experiment of nature. While the pathogenesis of myelopathy might well be thrombotic ischaemia, there is the possibility that in certain circumstances antibodies directed against phospholipids might react in vivo with certain neuronal phospholipids. Our studies in 1975 of ‘Jamaican neuropathy’ and viral myelopathy associated with false positive syphilis serology first started our detailed clinical studies of the relevance of aPL in general [6].

History

Although most studies of antibodies have concentrated on those against proteins, carbohydrates and polynucleotides, the role of aPL in the Wassermann
Table 1. Clinical features of the APS

| Major features | Deep venous thrombosis, Budd-Chiari syndrome and pulmonary thromboembolism |
|----------------|--------------------------------------------------------------------------------|
| Venous thrombosis; | Strokes, transient ischaemic attacks and multi-infarct dementia |
| Arterial thrombosis; | |
| Recurrent fetal loss | |
| Thrombocytopenia | |

Associated clinical features

- Leg ulcers, livedo reticularis and Sneddon’s syndrome
- Heart valve lesions
- Transverse myelitis, chorea and epilepsy
- Haemolytic anaemia
- Pulmonary hypertension

Others (less common)

- Migraine headache
- Splinter haemorrhages
- Labile hypertension
- Ischaemic necrosis of bone
- Addison’s disease
- Guillain-Barré syndrome
- Amaurosis fugax

reaction has been noted for more than half a century and is responsible for the false positive test for syphilis seen in some patients with systemic lupus erythematosus (SLE). But in SLE another antibody which was directed against a phospholipid involved in the coagulation process became known (confusingly) as the ‘lupus anticoagulant’. We showed that it was closely associated with thrombosis [7] and presented the full clinical description of the APS [8]. Immunoassays for antiphospholipid were developed and standardised [9].

Clinical features

**Rheumatology.** Because of research bias, earlier studies concentrated on patients with SLE. It is now almost certain that the vast majority of patients with the APS do not have SLE—or at best not ‘classical’ lupus. The constellation of thrombosis, abortion and/or thrombocytopenia associated with aPL is now known as the primary APS (PAPS) [10-12].

**Neurology.** The major problems are ‘major’ and ‘minor’ cerebral thrombosis. The use of MRI brain scans has highlighted the often widespread nature of the cerebral infarcts [13].

**Cardiology.** In addition to myocardial thrombosis, patients may develop valvular disease; in some cases this is due to a combination of valvular thrombosis and degeneration. In our studies the valves were involved in more than 30% of patients with SLE or PAPS [14,15]. Clinically these patients may develop nail splitter haemorrhages and clubbing.

**Gastroenterology.** Thrombosis of liver veins is common and occurs early in the course of the disease. The APS is probably the second commonest cause of Budd-Chiari syndrome [16].

**Nephrology.** Renal vein thrombosis, sometimes bilateral, is fairly rare; it occurred after a miscarriage in one of our aPL-positive patients. The reported incidence of thrombosis in the glomerular vessels varies widely and is associated with labile [17] and later severe [18] hypertension.

**Dermatology.** One of the most striking physical signs in aPL patients is livedo reticularis, sometimes widespread, sometimes subtle, eg confined to a small area on the back of the wrist [19]. More dramatic skin manifestations include widespread skin ulceration associated with vascular thrombosis.

**Haematology.** Thrombocytopenia is common. The platelet count often remains stable for many years; then, for reasons that are often obscure, the count drops, sometimes catastrophically. In a small number of patients autoimmune haemolytic anaemia is an associated feature [20].

**Endocrinology.** Adrenal thrombosis leading to Addison’s disease has been reported in a number of patients [21].

**Orthopaedics.** Avascular necrosis (AVN) of the head of the femur, although clearly associated with high steroid dosage, appears to be an earlier problem in
some patients with SLE than in others. We have also noted an increased risk of AVN in aPL-positive individuals, possibly as a result of the propensity to arterial occlusion [22].

Acute medicine. Occasionally a patient with aPL develops a sudden widespread, usually fatal, disease with thrombocytopenia, extensive thromboses, DIC and systemic collapse. We have referred to this syndrome as the ‘catastrophic antiphospholipid syndrome’; its cause is unknown.

Obstetrics. High levels of aPL are a serious hazard to pregnancy; for example, in our series of 100 patients, previous history of recurrent fetal loss was 81% [23,24]. Treatment aimed at reducing placental thrombosis is logical and many now report better pregnancy success rates in these patients.

How widespread is the syndrome?

Epidemiological and genetic studies are in progress worldwide, not only to determine the relative risk of stroke, abortions, myocardial infarction etc in these patients, but to assess whether other factors such as smoking, oral contraceptive use, hypertension etc present additional risks. In pregnancy clinics aPL measurement is standard in women who have had two or more miscarriages, and it may even become a standard (and cheap) screening test in all pregnant patients.

In neurology it appears that a new major cause of stroke has been identified, aPL positivity being recorded in 7% of our series of ‘general’ stroke patients [3] and in 18% of a series of younger stroke patients [25].

Mechanisms for thrombosis

Despite the strong association between aPL and thrombosis, the mechanisms remain to be defined (Table 2).

Several animal models have been established to study the syndrome [26]. For example, injection of mouse monoclonal or human polyclonal aPL is associated with thrombocytopenia, impaired placental development and fetal loss [27,28]. A cofactor, $\beta_2$-glycoprotein I, is an absolute requirement for aPL binding, suggesting that the epitopes recognised by aPL are phospholipid-protein complexes [29,30]. Furthermore, it is possible that other systems, such as anti-endothelial cell antibodies and endothelial antigen interactions, may influence disease expression in the syndrome. These permutations are reviewed elsewhere [31].

Animal models are providing further insights into the syndrome [32]. One of the more dramatic results is the demonstration that mice with the APS induced by immunisation with monoclonal anticardiolipin antibody have an increased rate of fetal resorption. The live fetuses and their compatible placenta are smaller than those of non-relevant Ig immunised mice [33]—a possible direct result of an antibody on clinical outcome, in this case pregnancy success. More recently we obtained similar results using a human monoclonal anticycardiolipin antibody (unpublished data).

Treatment

One of the reasons for the widespread interest in the APS has been its effect on approaches to therapy. Before its recognition, most features of SLE were attributed to inflammatory phenomena, requiring anti-inflammatory measures such as corticosteroids. Now it is recognised that features as diverse as fits, thrombocytopenia, miscarriage, endocardial disease and hypertension may all be the result of a thrombotic process. This concept has spread beyond the confines of SLE, and pinpointing aPL-associated thrombosis and taking appropriate anticoagulation measures have become important considerations in specialties as diverse as neurology and obstetrics.

Current treatment for APS patients revolves around various anticoagulation or anti-platelet regimes. In pregnancy, low-dose aspirin (75 mg daily), in addition to subcutaneous heparin in those with a history of thrombosis, is a logical first line of prevention and treatment and has improved the success rate in pregnant women who are aPL-positive with a previous history of recurrent fetal loss [24,34]. Clinical experi-

### Table 2. Suggested mechanisms of thrombosis

- Decreased prostacyclin production/release from endothelial cells
- Impaired fibrinolytic activity
- Increased platelet activation and aggregation
- Enhancement of expression of tissue factor by endothelial cells
- Impairment of antithrombin III activity
- Interference with the protein C activation
- Complement activation
- Interference with plasma $\beta_2$-glycoprotein I activity
ence suggests that patients with high titres of aPL and previous major thromboses require long-term, possibly life-long, anticoagulation; in these patients international normalised ratios (INR) have to be kept around 3 [35–37]. Steroids and immunosuppressive drugs to reduce antibody titres have not provided long-term benefit.

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Address for correspondence: Dr G R V Hughes, Lupus Arthritis Research Unit, The Rayne Institute, St Thomas’ Hospital, London SE1 7EH.