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Antiphospholipid Antibodies, Thrombosis and Vasculitis

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Organisers: Munther Khamashta and Graham R.V. Hughes.

The antiphospholipid syndrome – from theory to discovery

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For us, the story started some 20 years ago. False positive serological tests for syphilis had been a recognized finding in systemic lupus erythematosus (SLE) for many years – indeed this was perhaps historically the 'oldest' immunological abnormality in SLE. We had been working on central nervous system lupus for some years particularly on antibodies which might cross-react with lymphocyte membrane markers and neuronal antigens – 'anti-neuronal antibodies'. In 1975, whilst working in Jamaica we studied 'Jamaican neuropathy' – a meningo-myelitis, now thought to be secondary to HTLV I infection. A number of these patients had some of the serological features of lupus or lupus-like disease, including false positive VDRL tests. We explored the possibility that the antibody (antiphospholipid) responsible for the positive VDRL in these Jamaican patients might cross-react with neural phospholipids, such as sphingomyelin and cephalin.

At around the same time, David Stollar in Boston was proposing antibody cross-reactivity between epitopes on the backbone on DNA and certain phospholipids.

In the event neither our cross-reactive brain theory, nor (in man) the cross-reactive DNA story has proved entirely correct, but both theories led in their way to interesting developments.

In the late 70s, we studied VDRL and the related lupus anticoagulant phenomenon in our large SLE population. We found an extremely strong association between the presence of lupus anticoagulant and thrombosis in SLE. More important, however, we felt that confining ourselves to lupus alone (especially to 'classical' ARA criteria positive lupus) was blinkering our clinical observations. Many of our original patients, whilst having catastrophic thrombotic episodes, had little or no other clinical or serological features of SLE. The large clinics we handle do perhaps have the advantage of allowing clinical perspective. In a very short time, we were convinced that a distinct syndrome existed – recurrent thrombosis (especially cerebral), livedo reticularis, migraines, thrombocytopenia and possibly, (with a backward look towards Jamaica) more widespread neuronal disease such as myelopathy and movement disorders.[1,2]

The laboratory advance came with the development of a cleaner, more direct antiphospholipid test. This test – initially a radioimmunoassay developed by Drs Aziz Gharavi and Nigel Harris in our laboratory – chose cardiolipin as the antigen.[3] Cardiolipin was pure and available 'on the shelf'. Obviously, a number of other phospholipids could have been selected, but in cardiolipin we were fortuitous – the main pathogenic antibodies in this syndrome are directed against negatively charged phospholipids (such as cardiolipin). The development of this assay and, shortly after, of an ELISA allowed the rapid screening of the large number of sera.[4] A large database of blood bank donors, post-thrombosis sera, etc, was obtained and clinical observations got under way.

We showed that anticardiolipin antibodies were a strong risk factor for thrombosis in pregnancy – so much so that antiphospholipid antibody measurements are now an initial investigation in patients with recurrent abortion.[5]

The associations have been widespread – ocular thrombosis, Budd-Chiari syndrome, arterial gangrene and oral contraceptive-associated deep venous thromboses to mention a few.[6] More sinister has been the development, in some cases, of progressive thrombotic cerebral dementia, pulmonary hypertension and thrombotic endocardial valvular disease.[7]

The mechanism for the thrombotic tendency is uncertain. The treatment is anticoagulation, though the best forms of anticoagulant treatment are open to debate. Even anticoagulation can be difficult – we have seen a number of patients, for example, with unexplained wide fluctuations in anticoagulant requirements. With every month that goes by, the ramifications of the antiphospholipid antibody syndrome appear to spread. We feel that the syndrome should, first and foremost, come within the province of the

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neurologist – already the association has altered our thinking about the aetiology of a number of neurological syndromes.[8]

How far do the associations go? The Symposium covered in this issue of the *Journal* underscores the wide clinical potential. Some associations are not internationally agreed – strokes, deep venous thrombosis, livedo reticularis, recurrent abortions. Others are more speculative (but almost certainly real). These include cardiac valvular disease and pulmonary hypertension. Others await confirmation – avascular necrosis, migraine, Evans' syndrome. The inter-relationships of the primary antiphospholipid syndrome and systemic lupus remain undefined. They are certainly related – indeed our original descriptions came from the lupus clinic. Hints at links come from reports of C4 null alleles in the primary antiphospholipid syndrome, of relatives with one or other disease, of low C4 levels, or of other autoimmune phenomena such as antithyroid antibodies or Coombs' positivity.

The two main questions, perhaps, remain unanswered. What is the pathogenesis of the syndrome? What is the treatment? Whether by effects on platelet phospholipids, endothelial cell phospholipids, or by other clotting mechanisms, there is now no doubt that a major thrombotic mechanism has now been defined.[9] This must, in turn, lead to more precise control of treatment.

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