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REVIEW ARTICLE

Hughes syndrome (the antiphospholipid syndrome): 25 years old

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Abstract The antiphospholipid (Hughes) syndrome (APS) is a unique thrombotic disorder, causing both arterial and venous thrombosis, linked to the presence of antibodies directed against phospholipid–protein complexes. The first papers describing the syndrome were published in 1983 and, over the next two years, a series of publications described in detail the various clinical manifestations of the syndrome. Laboratory standardisation workshops were also set up and, in 1984, the first "world" symposium on APS was held. The international APS conferences have continued to grow in numbers and in stature. The APS has already had an impact in obstetrics, in medicine, in psychiatry, and in surgery. The approximate figure of 1 in 5 is a useful guide—1 in 5 of all young strokes, 1 in 5 recurrent miscarriages, 1 in 5 DVTs. More precise data will become available in the worlds of epilepsy, migraine, Alzheimer's, and MS. The advent of newer "biologic" immunosuppressives such as rituximab may offer help in selected cases. Intravenous immunoglobulin has proved successful, especially in the emergency setting.

Keywords Hughes syndrome · Antiphospholipid syndrome · Thrombosis · Miscarriage

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Introduction

The antiphospholipid (Hughes) syndrome (APS) is a unique thrombotic disorder, causing both arterial and venous thrombosis, linked to the presence of antibodies directed against phospholipid–protein complexes. Following the initial description of the clinical syndrome in 1983, the succeeding years have substantially added to the clinical dimensions of the syndrome.

To quote Miguel Villardell, dean of medicine in the University of Barcelona—"There are two 'new' diseases of the late twentieth century, AIDs and the antiphospholipid syndrome".

A history of APS

The clinical description of the syndrome was made over a decade from 1975 to 1985. The initial clinical observations were made in Jamaica in 1975, during studies into Jamaican neuropathy. Intriguingly, the serological profile of "false"-positive viral and rickettsial disease laboratory (VDRL) and antinuclear antibodies (ANA) was frequently seen. It was assumed (probably wrongly) that antiphospholipid antibodies (aPL) might cross-react with neuronal phospholipids, and there appeared to be a distinct subset of patients with what was initially called "the anticardiolipin syndrome".

The first papers describing the syndrome were published in 1983 [1] and, over the next two years a series of publications described in detail the various clinical manifestations of the syndrome. Laboratory standardisation workshops were also set up [2] and, in 1984, the first "world" symposium on APS was held. The international APS conferences have continued to grow in numbers and in stature.

Much is now known about the syndrome—the requirement for phospholipid-binding proteins such as beta-2 glycoprotein1 (β2GPI) and prothrombin [3], the worldwide distribution [4], the genetics, and the generally agreed guidelines on treatment.

Aetiology

Like other autoimmune disease, APS is genetically determined. Although family studies of APS are in their infancy, there is evidence that the "lupus" haplotype HLA B8, DR3, C4 null is over-represented in this group of patients—as are other autoimmune diseases, lupus and thyroid disease, for example, in APS families. The epidemiology is not yet worked out (interestingly, there has been a suggestion that APS is less frequent in Afro-Caribbeans and Chinese populations than in whites—unlike lupus) [5]. Thrombosis is a rare occurrence for predominantly Chinese patients with lupus hospitalised in Singapore [6]. Known thrombotic risk factors such as smoking and the oral contraceptive pill, not unexpectedly, increase the thrombotic risk.

Diagnosis

There are now internationally agreed criteria for classification of APS [7], updated in 2006 [8]. As with all classification criteria, these cannot, indeed, should not, be used for diagnosis. Clinical diagnosis depends on observation and on past experience. In this setting, even single case observations can contribute to the clinical picture. In diagnosis, the sky's the limit—this is a "new" disease, and it is the role of the enquiring physician to probe into the recesses of the syndrome.

Clinical features of APS

Strokes and transient ischaemic attacks

In a routine neurology clinic, aPL are found at an overall prevalence of 6.8% in stroke patients [9]. A later study, looking at younger stroke patients (under 45) found a prevalence of 20% [10]. A large American multi-centre stroke survey pushed this percentage up to 45% [11], though possible flaws in this study suggest that this is an over-estimate.

Magnetic resonance imaging (MRI) scans of the brain may show numerous high-intensity lesions. When present they can predict a poorer future prognosis [12].

Migraine and headache

Headache, often migrainous, is one of the commonest—and most significant—symptoms of APS. The history is often of headaches that are present in childhood, and then disappear before returning in the thirties and forties. Migraine appears to be one of the cornerstones of APS. The cause is uncertain, but it is highly significant that the headaches often vanish when full anticoagulation is started, e.g. for DVT.

Memory loss

Cognitive disturbance—however measured—is a common and sometimes severe manifestation of APS. Clear improvement can be achieved with anticoagulation, suggesting that the pathogenesis may be a stage less than infarction—"sludging" perhaps. The same might be said for the reversal of some other neurological features such as chorea.

Epilepsy

In 1985 it was reported that in lupus, seizures were associated with the APS [13]. Epilepsy, in all its forms, is a major manifestation of APS—indeed a recent study found that 15% of cases of "idiopathic" teenage epilepsy had aPL. The important contribution of the syndrome to the study of epilepsy has recently been reviewed [14].

Multiple sclerosis

Myelitis, balance, and sensory problems occurring in APS often lead to mistaken diagnosis of multiple sclerosis (MS). In an audit at St Thomas's hospital, patients were asked the question "Did your doctor(s) at any stage mention a possible diagnosis of MS?" Nearly one third (32%) of aPL-positive patients answered "yes" compared with 8% of controls.

Differential diagnosis is difficult, and compounded by a number of features, notably:

(a) Single-point-in-time MRIs may fail to differentiate.
(b) Borderline positive aPL levels may be dismissed as being of no significance.

Repeat MRIs may help to distinguish (the picture in M.S. changing) as may an E.E.G. (more commonly abnormal in APS [15]). The clinical findings of livedo and a dry Schirmers test point towards APS. So also may the history,

and we have suggested a "four-point questionnaire", which may help to distinguish the two conditions, positive answers being more common in APS.

1. History of headache, migraine, and stroke.
2. History of thrombosis.
3. History of recent pregnancy loss.
4. Family history of thrombosis or autoimmune disease.

Movement disorders

Chorea, described in initial papers on APS [1] is one of a variety of movement disorders seen. These disorders include tics, athetosis and even Parkinsonian features.

Why the brain?

The central nervous system is clearly particularly vulnerable in APS. There are a number of possible reasons for this. First, the brain and clotting are strongly linked. Second, brain endothelium differs in a number of crucial ways from other endothelia—for example, brain endothelium expresses little thrombo-modulin. Third, there is the intriguing possibility that some aPL may react directly with neuronal antigens. If true, this might re-open a role for immunosuppression in certain cases of APS, and there are now anecdotal reports of the successful use of rituximab in both cerebral lupus and cerebral APS.

Heart

One of the original features described in APS was pulmonary hypertension [16]. While there is no doubt that pulmonary hypertension is now a well-recognised complication of the pro-thrombotic APS, the extent of the association remains uncertain. For example, our own practice includes cases with "borderline" aPL readings and cases in whom previously positive aPL tests later became negative.

Myocardial infarction (MI) is a major association [17] and it is our recommendation that all patients developing MI under the age of 40 should be tested for aPL. We have recently described a case of MI in a young man with APS who ingested cocaine. A vasoconstrictive stimulus, and pro-coagulant state, combined to produce coronary artery occlusion [18]. An interesting observation has been the diagnosis of syndrome X in nine of our patients to date [19]. Significantly, when adequate anticoagulation is achieved the angina may disappear.

APS may play an important role in the increased tendency to accelerated arterial disease in SLE and of altered endothelial dysfunction. Studies in the use of markers of "early" atherosclerosis, for example, show abnormal results in APS patients who have had none of the other recognised risk factors for early arterial diseases [20, 21].

Kidney

A significant contribution to pathology and to treatment and prognosis has been achieved by re-assessment of the degree of microvascular thrombosis in lupus kidney biopsies, especially in aPL-positive individuals.

One of the most interesting clinical observations has been the demonstration of renal artery stenosis in a number or our APS patients, notably those with livedo and with hypertension. The localised and stenotic (thrombotic?) arterial lesions (also seen in the celiac story: see below) are totally different in appearance from the picture of renal artery disease seen in atheroma in older patients. The hypertension in APS patients with renal artery stenosis treated with careful anticoagulation is much better controlled [22].

Adrenal

Following an initial description of the case of a young man with APS and widespread arterial thrombosis who developed adrenal infarction and acute adrenal failure [23], we have come across a number of similar cases.

This clinical observation has important implications for very sick APS patients with "catastrophic" features. Failure of the adrenal glands could add vitally to the clinical picture.

Liver and the gastro-intestinal tract

We have recently reported a sizeable series of patients with celiac artery stenosis [17, 24]. Many of the patients had "classical" features of mesenteric ischaemia with abdominal pain after large meals, upper abdominal bruits, and so on. Others were relatively asymptomatic, presumably because of good collateral circulation.

Liver thrombosis, including Budd–Chiari syndrome, was a feature of our original clinical description of the syndrome [1]. Liver function abnormalities are, in fact, common in APS patients, possibly as a result either of vascular "sludging" or of small-vessel thrombosis. Interestingly, a number of cases of non-alcoholic cirrhosis have been reported in APS [25].

Eyes

Ocular features range from sudden (monocular) visual loss to field defects. One interesting clinical observation in some of these cases is that visual impairment can be totally reversed if anticoagulation is immediate.

Ear nose and throat

Meniere's disease, vertigo, and balance disorders are major features in some APS patients. Indeed, the frequency of these manifestations may be under-recognised [17, 26]. Some patients have prominent ENT manifestations of APS including tinnitus. Very notably, the tinnitus can improve when anticoagulation to an INR > 3 is attained.

Blood

Thrombocytopenia distinguishes APS from other thrombophilic disorders [27]. The platelet count can fall precipitously but, more often, a chronic "borderline" platelet count (e.g. 105,000) is seen. Possibly as a manifestation of the abnormal platelet membrane biology, altered by aPL, a "pseudo-thrombocytopenia" (lower platelet count in EDTA on automatic counting) is well described in APS [28]. Individuals with APS may also produce antibodies directed against platelet membrane glycoproteins [29].

Haemolytic anaemia, with or without positive Coombs' test, is a well-reported association [17, 30]. A small number of cases of marrow infarction have been described [31].

Orthopaedics

Avascular necrosis of bone—most commonly of the femoral head, but also of other bones such as the navicular, is a complication of APS, presumably as a result of ischaemia in vulnerable sites [32]. In addition, metatarsal fracture may occur [33] along with other spontaneous fractures of the spine, ribs and elsewhere.

Far outweighing these in importance is the contribution of aPL to the problem of post-orthopaedic surgery venous thrombosis. Routine pre-operative screening for known pro-thrombotic disorders such as APS is not yet the norm.

Catastrophic APS

Early in our clinical descriptions of APS, we saw a number of cases of widespread disease (multiple thrombosis, multiple organ failure), often ending in intensive care [34]. The name "catastrophic APS" caught on. Dr Ron Asherson has, together with Richard Cervera, collected the world literature of case reports of this rare syndrome [35]. The stimuli which convert a relatively healthy aPL-positive individual to a critically ill patient with widespread thrombosis are unknown.

Infections are a strong candidate but, equally, APS patients are seen daily with infections without the "catastrophic" consequences.

Pregnancy loss

It is tempting to attribute pregnancy loss in APS to placental ischaemia and infarction. However, the process may be more complex. For example, Salmon et al. [36] have put forward evidence to suggest complement-mediated inflammatory processes may play a part in the process.

Nevertheless, the recognition of APS as probably the leading treatable cause of recurrent miscarriage (and late pregnancy loss) has proved to be one of the major advances in obstetrics in the past 50 years. Anticoagulation (aspirin plus or minus heparin) has improved the pregnancy success rate from less than 20% to over 90% in most centres [36].

Treatment

There are four major treatments for APS—aspirin, heparin, warfarin, and immunosuppressives.

The mainstay of treatment is aspirin (or, in selected cases, clopidogrel). A multicentre trial is currently in progress comparing aspirin with low dose warfarin in aPL-positive individuals who have not previously thrombosed.

Heparin (low molecular weight heparin has largely replaced "old" heparin) is now used widely in APS pregnancies [36]. On starting heparin therapy many APS patients notice improvement in headaches and in "cerebral function". For this reason, we now use a therapeutic trial of four weeks' heparin in APS patients with severe headache/migraine.

Warfarin is used in more severe cases. In many patients, notably those with cerebral involvement, it is clinically obvious that a higher INR is needed. For example, in one patient with severe movement disorder, the abnormal movements returned every time the INR fell below 3.4. For such patients, it is our policy whenever possible, to teach self-testing of INR [37].

Immunosuppressives

In the early 1980s, we treated our lupus/APS patients with immunosuppressives such as azathioprine and cyclophosphamide. The results—as far as APS and thrombosis were concerned—were disappointing. The advent of newer "biologic" immunosuppressives such as rituximab may offer help in selected cases [38, 39]. More proven is intravenous immunoglobulin, which has certainly proved successful, especially in the emergency setting [40]. However, care is needed as immunoglobulins can increase plasma viscosity and, perhaps, increase the risk of thrombosis in the short-term.

The future

The APS has made an impact in obstetrics, in medicine, in psychiatry, and in surgery. The approximate figure of 1 in 5 is a useful guide—1 in 5 of all young strokes, 1 in 5 recurrent miscarriages, 1 in 5 DVTs. More precise data will become available in the worlds of epilepsy, migraine, Alzheimer's, and MS.

But it is in lupus where, perhaps, the most noticeable impact has been made. Many, many patients previously treated with high-dose steroids are now successfully on more appropriate therapy.

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