Heart and Stroke: The Impact of Hughes Syndrome (Antiphospholipid Syndrome)

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Abstract

Following the description of the antiphospholipid syndrome (APS/Hughes Syndrome) in 1983, the clinical spectrum has widened. However, while APS is well recognised as a cause of both thrombosis and recurrent miscarriage, the extent of its role in heart and stroke pathology is now becoming clearer.

APS is an important cause of angina and myocardial infarction, especially in females under 40.

In stroke medicine, antiphospholipid antibody testing is almost certainly to become more routine in efforts at stroke prevention.

Introduction

The Journal of Heart and Stroke seems a very appropriate place to review the subject of Hughes Syndrome/antiphospholipid syndrome (APS).

To give two examples: published studies have reported that up to 1 in 5 young strokes (under 45) are linked to APS [1] and that up to 40% of younger female heart attacks are similarly associated [2,3]. In both situations, the lesson is that diagnosis and prevention could have been achieved with the help of simple blood tests and relatively simple treatment.

What if Hughes Syndrome?

It is a syndrome characterised by an increased propensity to blood clotting (often known in the media as ‘sticky blood’). Any organ of the body may be affected. Crucially, the thrombosis can involve arteries (e.g. stroke, myocardial infarction) as well as veins – a critical difference from other coagulopathies such as Factor V Leiden.

The most well-known features involve the brain (migraine, TIA, memory loss, seizures, stroke) and, in pregnancy, the placenta, leading to fetal loss – some women suffering a dozen or more miscarriages [3].

History

In 1983, we reported from our lupus clinic, a clearly defined syndrome [4,5]. Although we initially studied lupus patients (in whom approximately 25%-30% have features of ‘sticky blood’), we realised that the condition could, and did exist outside of lupus. We found that the syndrome was strongly associated with the presence of antibodies directed against phospholipids, and we gave it the (inexact) name “antiphospholipid syndrome” (APS). Later, it was found that the antibodies in fact recognised a protein–phospholipid complex.

Colleagues at the 6th International Conference on antiphospholipid antibodies (a PL) suggested it should be called Hughes Syndrome. Detailed review and updates are published elsewhere [6,7].

Headaches, TIA and Stroke

One of the most common and striking features of Hughes Syndrome is headache – often migrainous. A common pattern is for the migraine history to start in the teens, to improve, say, in the 20’s and to return with a vengeance in the 40’s – progressing, in some, to TIA or stroke.

Although the topic of migraine in APS is controversial [7] my own view is that next to memory loss, migraine is arguably the commonest manifestation of Hughes Syndrome /APS. Interestingly, there is often a family history of migraine, and a number of large family cohorts embracing migraine, APS and stroke are now being reported. So common is the association that it is my belief that a PL...
is possibly the main “missing link” between migraine and stroke [8].

As expected, the published figures linking Hughes Syndrome to stroke vary widely [9,10]. As mentioned, an early study from Rome found that in a younger population (under 45) a striking 1 in 5 of all strokes were associated with a PL [1].

**Other Neurological Features**

Hughes Syndrome/APS is very much a ‘neurological’ disease. Perhaps the most common, yet still under-recognised feature is memory loss, sometimes severe enough to suggest Alzheimer’s [3]. Another important association is epilepsy/seizures.

The link with a PL has been recognised for some time [11]. One recent review reported that individuals with positive a PL tests were found to be 11 times more likely to have seizures than patients negative for those antibodies [12]. The other reported associations include chorea and movement disorders, transverse myelitis, and ‘atypical MS’ [13]. Recently, a (possibly strong) link with autonomic disorders (including POTS) has been recognised [14].

Other less well-known but clear clinical associations include sleep disturbance, insomnia and (possibly) OCD (obsessive compulsive disorder).

**Heart**

The early reports of Hughes Syndrome/APS tended to focus on cardiac valvular disease – ranging in severity from ‘innocent’ murmurs to severe thrombotic valve degeneration (almost certainly the cause of the “Libman-Sacks endocarditis” of lupus).

While coronary thrombosis and myocardial ischaemia were recognised in APS early on [15], the importance of ‘sticky blood’ in the aetiology of ischaemic heart disease took a while to achieve widespread recognition. Recently, Greco et al reported that a group of APS women on the pill, who were a PL positive, had a relative risk of 22 times for the development of myocardial infarction [16]. Similarly Urbanus and colleagues in Holland reported a strong link between a PL, oral contraceptives, myocardial infarction and stroke in young women [2].

We have also published a series of patients with Syndrome X (angina with normal coronaries) in a group of patients with APS [17].

**Other Clinical Features**

Hughes Syndrome affects all organs, including the kidney (renal vein thrombosis, renal artery thrombosis and stenosis leading to hypertension), the adrenals, the bones (ischaemia and fracture), the eye, the skin (ulcers, livedo), the lungs (PE, pulmonary hypertension) and occasionally the blood (low platelets) [3].

The link with bone fracture is interesting. In our unit, Sangle published a series of 27 metatarsal fractures (“march fractures”) in patients with APS [18]. Since that time, histories of ‘unexpected’ fractures have been described in other areas such as the ribs.

APS may come to be recognised as an important (preventable?) cause of ‘idiopathic fracture’.

**Pregnancy**

The most well-known adverse effect of APS is in pregnancy. Secondary to placent al thrombosis (though other mechanisms have also been suggested) fetal blood supply is impaired, leading to miscarriage [19]. In a small number of cases, the effect is a later loss – stillbirth.

Slowly but surely, a PL measurement is gaining ground in routine early pregnancy testing, though for numerical (and economic) reasons, a PL testing is only advised after “two or more” pregnancy losses [3].

Nevertheless, the syndrome has had a major impact in obstetrics, Hughes Syndrome now being recognised as the commonest treatable cause of recurrent miscarriage.

**Diagnosis**

Tick 3 boxes – a CL (anti cardiolipin antibodies), LA (“lupus anticoagulant”) and anti-Beta2 GP1 (the more recent addition to the tests). Workshops and conferences are dedicated to the significance or otherwise of 1, 2 or 3 positives.

The science is still imperfect, and in busy clinical practice there are a number of patients who have, say, 5 or 10 features of the syndrome whose tests remain negative. Often these are family members who, when treated, respond just as well.

For me, the topic of “sero-negative APS” is one of the most important in our clinical repertoire [20]. Clearly, we need newer tests. And even more clearly, there are individuals attending angina, stroke and migraine clinics who could be potential responders to a diagnosis of APS.

**Aspects of Treatment**

Hughes Syndrome/APS is an autoimmune disease. Clinical experience, as well as animal studies, suggest that immunosuppression might be a logical treatment. At the present time, there are anecdotal reports of the successful use of Rituximab. However, as far as the other, earlier immunosuppressives are concerned, experience was largely negative.

Thus, at present, treatment revolves around anticoagulation – aspirin, clopidogrel, heparin, warfarin and the newer oral anticoagulant agents. Early data came mostly from pregnancy clinics where the addition of aspirin (and in later years, heparin) resulted in a significant improvement in pregnancy outcome in APS patients, many units increasing the success rate from a poor 15%-20% to over 90% [19].

Current practice is to use aspirin 75-100mgs daily in cases without major thrombosis. In many cases the clinical benefit is obvious – less mental ‘cloudiness’, fewer headaches, improved angina, for example. Low molecular heparin (e.g., dalteparin or enoxaparin) has played an important role in the management of APS.

Also, in my own clinic, heparin plays an important role in diagnosis.

In Hughes Syndrome, patients who have been started on anticoagulation for treatment of a DVT, for example, it is common to see a marked improvement in many of the APS features, notably migraine, memory loss and balance problems. Following these observations, we introduced a 3-week “heparin trial” (e.g., dalteparin 10,000 S/C daily). Although this is a ‘therapeutic trial’, it has proved a safe and very useful guide as to whether more substantive anticoagulation might be needed [21].

For more severe APS problems, including thrombosis and
neurological features such as TIAs, warfarin is the present treatment. The major lesson learnt has been that, for many, if not the majority of APS patients, a higher intensity of anticoagulation is required, many patients finding, for example, that an INR of 3.5 or even higher is needed for resolution of symptoms. For such patients, self-testing machines have proved an invaluable help in overall care [3].

The newer oral anticoagulants, such as rivaroxaban, are now being trialled in APS in a number of centres, but conclusive data regarding their use in this situation is lacking.

Predictions

At the 14th International Congress on Antiphospholipid Antibodies held in Rio de Janeiro in 2013, I was asked to make predictions for APS in 2050 [3]. Here are two:

I believe that APS will become very much more widely recognised and treated, particularly in the worlds of neurology and cardiology.

There will be new hope for a proportion of migraine sufferers – indeed, I predict that APS will be finally recognised as the ‘missing link’ between migraine and stroke.

To date, a number of studies have come up with a rough ‘1 in 5’ rule of thumb. 1 in 5 of all DVTs, 1 in 5 of young strokes, 1 in 5 recurrent miscarriages, and even 1 in 5 of idiopathic teenage epilepsies are a PL-related.

And this doesn’t take into account those patients with all the features of APS but as yet with negative tests – so called “sero-negative APS”.

How many patients are doing the rounds of neurology clinics, cardiology clinics, casualty, memory loss clinics, obstetric departments, and more, in whom simple a PL testing could lead to successful treatment?

References

3. Hughes GRV. Hughes Syndrome/APS. 30 years on, what have we learnt. Lupus. 2014; 23: 400-406.