

REVIEW

Migraine, memory loss, and “multiple sclerosis”. Neurological features of the antiphospholipid (Hughes’) syndrome

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The antiphospholipid syndrome (APS, Hughes’ syndrome), first described in 1983, is a prothrombotic disease in which neurological events feature prominently. Strokes, transient ischaemic attacks, and headaches (including migraine) are important complications. However, it is clear that other neurological symptoms, including diplopia, memory loss, ataxia, and “multiple sclerosis-like” features are common. A notable feature of Hughes’ syndrome is the clinical response to anticoagulants; features such as headache and memory loss often improving dramatically with appropriate warfarin dosage. APS may well become recognised as an important (and potentially treatable) cause of neurological disease.

away the commonest symptom reported was headache: not evidence based medicine perhaps, but a pointer to the importance of this symptom.⁵

The history is remarkably similar in many patients with teenage headaches that are frequently migrainous—often premenstrual—often disappearing for 10–20 years only to return in the 30s or 40s. There is, significantly, a strong family history of headaches or of migraine in many of our patients, pointing to genetic influences. In some patients the headaches are accompanied by visual or speech disturbance, or by transient ischaemic attacks.

It is my view that antiphospholipid antibody testing should be among the armamentarium of those investigating migraine or recurrent headache.⁶

It is now recognised that antiphospholipid syndrome (APS) is a major neurological disease.¹ The syndrome, first described in 1983, is characterised by recurrent thrombosis (both venous and arterial), recurrent miscarriage, neurological disease, including stroke, and the presence of circulating antibodies against phospholipids.²

Our early studies focused on lupus, but we recognised that the syndrome was just as prevalent outside lupus and called this syndrome the antiphospholipid syndrome. The title is not strictly correct—the antibodies are in fact directed against phospholipids and proteins.

The syndrome is now recognised as a common and important prothrombotic condition with ramifications into almost all spheres of medicine, surgery, and obstetrics.

While our earliest descriptions highlighted the neurological aspects of the syndrome (strokes, chorea, myelopathy, headaches, memory loss, and dementia),^{3,4} the full impact of the syndrome on neurology is now becoming more widely recognised.

CLINICAL FEATURES

This short review addresses these nervous system features, their pathogenesis, and their management.

Headache and migraine

Recently, we set up a patients’ website on APS (www.hughes-syndrome.org). In the first week of operation we received over 20 000 hits. Far and

Memory loss

All those dealing with large numbers of patients with the syndrome recognise memory loss as possibly the most important feature. Unfortunately, as yet, there have been few formal psychometric studies of these patients—for example, before and after anticoagulation treatment is started.

In some patients, the disease, if untreated, progresses to widespread brain infarction, grossly abnormal magnetic resonance images and, ultimately, multi-infarct dementia.

In the majority of patients, the memory loss is less extreme—though sufficiently frightening for the patient to worry about the possibility of Alzheimer’s disease.⁷ It is this aspect of the syndrome which—like headaches—often improves when anticoagulation is started.

Epilepsy

Seizures are a feature of APS: indeed in a patient with lupus presenting with seizures, APS is the most likely underlying pathology—an observation with therapeutic implications.

All ages are affected, and all forms of epilepsy are seen, as are subclinical (abnormal electroencephalogram) forms. The association of antiphospholipid antibody with epilepsy, first reported in 1985,⁸ may be of significant importance in the investigation of seizures in general.⁹

Abbreviations: APS, antiphospholipid syndrome; INR, international normalised ratio

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A typical scenario

A 39 year old woman complained of headaches, fatigue, and memory loss. She was concerned about a possible diagnosis of Alzheimer's disease.

Two years earlier, she had suffered from similar headaches, associated with gait disturbance and ataxia. She had been investigated for multiple sclerosis but brain magnetic resonance imaging had been normal.

Her past history included a strong teenage tendency to headaches, often migrainous.

In her 20s she had been investigated for infertility, but on two occasions had conceived only to suffer a miscarriage at three months. At the age of 35 she had a successful pregnancy.

In view of the possible diagnosis of APS (Hughes' syndrome), blood tests for antiphospholipid antibodies were ordered and found to be strongly positive.

She was treated initially with aspirin 75 mg daily, with moderate though incomplete resolution of the headaches. Ultimately, in view of the known prothrombotic nature of APS, and especially its neurological and obstetric sequelae, the patient was anticoagulated with warfarin.

Not only did this treatment result in disappearance of the headaches, but the patient noted a marked improvement in memory. Interestingly, these two major symptoms returned whenever the international normalised ratio (INR) fell below 2.5.

Stroke

The commonest serious complication of APS is stroke. Indeed, the syndrome is becoming recognised as a major, and potentially preventable, cause of stroke. It has been estimated that up to one in five of all young (under 45) strokes are associated with Hughes' syndrome, although all ages can be affected. The clinical spectrum ranges from transient ischaemic attacks and focal lesions—such as amaurosis fugax—to widespread cerebral infarction, ataxia, bladder, and gait disturbance and—in extreme cases—multi-infarct dementia.

More than anything else, it is this propensity to (arterial) stroke which marks out Hughes' syndrome from the other less serious coagulopathies such as factor V Leiden deficiency.

Myelopathy

Transverse myelopathy is a rare but well recognised feature of APS. It is sometimes associated with optic nerve ischaemia (Devic's disease). The pathology of the myelopathy is poorly understood. However, some interesting observations have come from the mouse model of APS. Some of these animals which develop an APS-like disease became paraplegic. Histology of the spinal cord in these animals showed vessel thrombosis.¹⁰ These observations might be taken to support the suggestion that anticoagulation may have to be considered in addition to the more conventional steroid and immunosuppressive regimens generally given to some lupus patients with myelopathy, for example.

Multiple sclerosis

Not surprisingly, a number of patients with APS have carried a working diagnosis of "multiple sclerosis". In a recent study from our unit, 28 APS patients were reviewed in whom an original diagnosis of multiple sclerosis had been made.¹¹

Some interesting lessons were learnt. Firstly, differential diagnosis was difficult—in this particular study the magnetic resonance imaging did not clearly distinguish the two conditions. Secondly, with hindsight, there had been clues to the underlying diagnosis, notably recurrent headaches, previous thrombosis, or recurrent miscarriage. Thirdly, and perhaps

most significantly of all, in the majority of the patients ultimately correctly diagnosed and appropriately anticoagulated, there were no further neurological events.

Clearly, there will be many similar studies to come. However, it seems probable that a small percent of patients diagnosed with multiple sclerosis do in fact have Hughes' syndrome, a condition with totally different treatment and prognosis.

Chorea

Our original studies in 1983 included chorea. Although rare, this feature has been strongly associated with the presence of antiphospholipid antibodies—indeed, the combination in some APS patients of joint pains, heart murmurs and chorea has led, not unexpectedly, to a label of "rheumatic fever". Although the precise pathophysiology of the chorea is unclear, an interesting clinical observation has been made that in a small number of patients, the chorea has ceased with the institution of anticoagulants.

Neuropathy

Possibly one of the more surprising findings has been the association in some patients between antiphospholipid antibodies and neuropathy, both peripheral and cranial. In classical lupus, peripheral neuropathy is relatively uncommon, and larger numbers will be required before this possible association can be confirmed.

Behavioural disorders

A number of cases of frontal lobe ischaemia, with its attendant behavioural disorder, have been seen (this author was referred one 3 year old boy with an aggressive behavioural disorder found to be associated with multiple cerebral infarcts). To date there have been surprisingly few studies detailing the neuropsychiatric manifestations of APS.

Treatment

Anticoagulation is required. Current experience shows that antiphospholipid antibodies constitute a significant risk for thrombosis, including stroke. For example, in our clinic, in a 10 year retrospective analysis, no fewer than 50% of those individuals (mainly lupus patients or women with recurrent miscarriage) with positive antibodies in 1985 had developed thrombosis by 1995.¹²

A more difficult decision is whether to use aspirin alone or to anticoagulate with warfarin. Most data currently available point to the superiority of warfarin if there has been clear cut cerebral ischaemia.

Khamashta *et al* analysed APS patients over a 10 year period.¹³ Of those treated with aspirin alone, over half developed further thrombosis. Likewise, in those treated with warfarin to an INR of less than 3, one half developed further thrombosis. Only in those maintained at an INR of 3 or over was there a significant 10 year benefit.

Our study had two possible weaknesses. Firstly, it was retrospective. Secondly, it was directed mainly to patients with arterial rather than venous thrombosis—it could be argued that subsets of patients with venous thrombosis alone might require less aggressive anticoagulation.

One point, however, is clear. The danger of thrombosis and stroke in these patients far outweighs the risks of anticoagulant induced bleeding. The traditional fear of cerebral haemorrhage has, almost certainly, resulted in the under-treatment of many patients with APS.

Finally, what of the "non-thrombotic" neurological features? What of the patient with severe, recurrent headaches who has antiphospholipid antibodies but who has not had a previous thrombosis. It is a common observation that warfarin treatment when finally given (for example, for a deep vein thrombosis) results in dramatic improvement in headache.

Recently, we have introduced a "clinical trial" of heparin in this situation. A two week trial of self administered heparin (for example, Fragmin 5000 units daily) is both safe, and, in our preliminary studies, has provided a clear indication (for example, immediate disappearance of the headaches) as to whether anticoagulation might be suitable.⁵⁻¹⁴ We are involved in a prospective controlled trial of this treatment in APS associated headache and migraine.

RESEARCH AND SPECULATION

Epidemiology

APS (Hughes' syndrome) may well prove to be a much more common neurological diagnosis than hitherto realised. Multi-centre studies are now in progress in migraine, multiple sclerosis, memory loss, epilepsy, and stroke clinics. The observation that some patients have strong family histories of APS features (especially migraine) suggests that genetic studies should broaden the clinical spectrum beyond "classical" cases.

Why the brain?

The 20 year experience of the syndrome has shown that the central nervous system appears to be particularly at risk. The reasons (if this observation proves correct) are uncertain. However, interactions between brain and clotting processes have a long history.

The coagulation mechanism within the central nervous system has clear differences from that found in other organs. For example, the brain endothelium expresses little thrombomodulin, unlike other endothelial surfaces. While some experimental work has suggested that antiphospholipid antibodies may have direct antineuronal ties, at the present time, the available evidence suggests that the major underlying mechanism in the cerebral features of Hughes' syndrome is either vascular thrombosis or sludging.

Future trends

As imaging techniques improve, so presumably will the diagnostic yield. Conventional magnetic resonance imaging may be normal in some cases of classical APS (as in the case presented at the beginning of this review).

The standard blood tests—anticardiolipin and lupus anticoagulant—are reasonably standardised internationally, but do have limitations. To date, the addition of other tests such as IgA anticardiolipin, anti-β2 GP1, antiprothrombin, and antiphosphatidyl serine, for example, have not added much in the way of further clinical definition.¹⁵

Health economics

The links between APS and stroke, migraine, and epilepsy are well established. The links between APS and memory loss and

between APS and multiple sclerosis are recognised but require further validation. In any event the diagnosis of this prothrombotic condition, and its response to anticoagulation, has major therapeutic and economic implications.

Up to one in five of all strokes in the under 45 year olds are associated with APS and are potentially preventable. The economic cost of strokes per annum in the UK has been estimated at £2.3 billion and in the USA at £23 billion. More frequent and earlier diagnosis of APS and precise anticoagulant therapy could have an impact on these costs, both economic and human.

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