Review

Neurological manifestations of anti-phospholipid (Hughes) syndrome

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ABSTRACT

In the 21 years since the description of the antiphospholipid syndrome (APS), neurological features have become recognised as some of the most important and common aspects of the syndrome. Recognition of the relationship between APS and central nervous system impairment could open the door to improved treatment and outcomes in some neurological syndromes.

Introduction

The anti-phospholipid syndrome was first described in 1983 by Graham Hughes, and is characterised by thrombosis that can affect any vascular bed (arterial and venous), recurrent fetal loss and the presence of circulating antibodies against phospholipids (1). Originally it was recognised in patients with systemic lupus erythmatosus (SLE) but it immediately became evident that it could also appear in patients without underlying disease, the so-called "primary anti-phospholipid syndrome" (PAPS) (2). It is a non-inflammatory autoimmune disease with a significant prothrombotic risk, and because any size of vessel can be affected, the clinical manifestations are very heterogeneous (Table I), often mimicking other syndromes (3, 4).

The central nervous system (CNS) is a major target organ in APS and a selective susceptibility of the brain vascular endothelium may play an important role (4, 5). Stroke is the most important manifestation but there are many other neurological symptoms including migraine, memory loss, epilepsy, myelopathy, chorea and "multiple sclerosis-like" features. The identification of the syndrome can offer a better prognosis for some of those patients, who can improve considerably with anticoagulant therapy (4, 6).

In this review we focus on some of the manifestations that have been reported in association with the APS.

Neurological clinical manifestations

Cerebrovascular disease

Stroke and transient ischaemic attacks are considered the second most common clinical manifestations of APS after venous thrombosis (7-9). The middle cerebral artery territory is the most frequently affected but ischaemic events can occur in any vascular territory. Amaurosis fugax, transient paraesthesias, motor weakness, vertigo and transient global ischaemia are manifestations. In extreme cases the recurrent infarction can produce a multi-infarct dementia with cognitive impairment (7).

Table I. Clinical neurological manifestations of the antiphospholipid syndrome.

Transient ischemic attack
Cerebrovascular accident (thrombolic or embolic)
Cerebral venous thrombosis
Seizures
Migraine
Cognitive dysfunction
Multi-infact dementia
Chorea and other movement disorders
Transverse myelitis
Pseudotumour cerebri
Mononeuritis multiplex
Amaurosis fugax

Cardiac emboli may be an infrequent cause of stroke in patients with antiphospholipid antibodies (aPL) (8). Cerebral ischemic events are more frequent in patients with valvular heart disease and it has been shown that the prevalence of valvular abnormalities is higher in SLE patients with aPLthan in those without aPL (predominantly mitral valve thickening) (10, 11).

As well as arterial ischaemia this syndrome is also associated with sagittal venous sinus thrombosis and acute ischaemic encephalopathy, although these features are uncommon manifestations in APS patients (7).

Epilepsy

Soon after the description of APS it was recognised that patients with SLE had more seizures if they were positive for aPL (12). Later reports supported the association between epilepsy and aPL in patients affected by SLE. There were also studies that found an increased prevalence of aPL in patients with epilepsy without any manifestation of connective disease or APS, and unrelated to the anti-epileptic drugs (7, 13, 14).

As well as a thrombotic mechanism, there may also be a primary immunological basis for seizures in some SLE patients with aPL owing to an aPL-brain phospholipid interaction (15,16). Anticardiolipin antibodies (aCL) obtained from patients with SLE who had seizures have been shown to reduce a gamma-aminobutyric acid (GABA) receptor-mediated chloride current in snail neurons, suggesting the possibility that the aPL might be involved in a mechanism that lowers the seizure threshold (17).

Headache and migraine

In clinical practice headache is one of the most common symptoms in patients with APS, and can vary from classic intermittent migraine to almost continuous incapacitating headache (18). Migraine is one of the most prominent features of APS, yet surprisingly the results of different studies vary widely (19). The aPL, especially IgG aCL, appears to be related to the occurrence of chronic headache in patients with SLE, but not to a particular subtype of headache (20, 21).

Cuadrado *et al*. recently reported 5 patients with APS and intractable headaches treated with a 7-day course of daily low-molecular-weight heparin. None had significant brain MRI lesions, but all had features of APS, notably previous venous thrombosis, livedo, previous recurrent pregnancy loss and thrombocytopenia. All 5 patients had a moderate-to-high titre aPL. In all 5 there was a marked improvement (with total disappearance in 3) of the headache, in the majority within 48 h of starting heparin. The headache returned in all 5 patients on cessation of heparin treatment. The authors recognized that the decision to try anticoagulation treatment for an essentially non-thrombotic clinical feature is debatable, but speculated that a possible future approach in aPL patients without major thrombosis and chronic intractable headache could be to treat with low-dose warfarin (22).

It seems pertinent to test the presence of aPL in migraine or recurrent headaches, especially in young women (3, 4).

Cognitive dysfunction

Cognitive impairment, together with headache, is probably the predominant neurological feature of Hughes syndrome, ranging from mild cognitive dysfunction to severe dementia. Whether these cognitive deficits result from recurrent cerebral ischemia or there are other underlying mechanisms remains unknown (4). Frequent complaints in these patients are poor concentration or forgetfulness, verbal memory deficits, decreased psychomotor speed and decreased overall productivity (23). The application of formal neuropsychological tests facilitated the recognition of a positive link between aPL and cognitive dysfunction (23,24). One of these studies found that there was no association between the results of neuropsychological tests and levels of anti-DNA or C3 levels, supporting the hypothesis that aPL play a primary role in the aetiology of the cognitive impairment in this syndrome (7,25). The underlying pathophysiologic basis for cognitive impairment and other more diffuse neurological manifestations may be related to reduced cerebral blood flow or a direct effect of aPL on neuronal function (25, 26).

While the current evidence does not support the introduction of aggressive anticoagulation as a strategy to prevent subclinical cognitive impairment, there may be a role for more benign therapies such as low-dose aspirin, antimalarials, or even low intensity warfarin (3, 4).

Dementia

A chronic multifocal disease, defined as a recurrent or progressive neurological deterioration attributable to cerebrovascular disease, can produce multi-infarct dementia (7). This dementia itself does not have any special characteristics so it cannot be differentiated from other kinds of dementia such Alzheimer's disease, senile dementia or metabolic/toxic conditons involving the brain (3,27,28). Sometimes only the presence of features like livedo reticularis and other concommitant thrombotic events point to a diagnosis of APS.

Luminal occlusion by thrombi, and marked endothelial hyperplasia and thrombosis of small arterioles was found in a brain biopsy from a patient with dementia and APS (29). Another patient with PAPS and dementia, examined by positron emission tomography (PET), showed a considerable diffuse impairment of cortical glucose metabolism combined with reduced cerebral perfusion in the arterial border zones. The MRI from the same patient showed cerebral atrophy and a moderate number of white matter hyperintensities (30). These findings indicate that a mechanism of immune-mediated intravascular thrombosis can be implicated in the pathogenesis (8).

Chorea

This feature has been strongly associated with the presence of antiphospholipid antibodies and it can occur in both primary and secondary APS (3). This movement disorder is a rare manifestation of SLE (1-3%) and has also been documentated in the pregnancy/postpartum period and as a complication of oral anticontraceptives (7).

The precise pathophysiology of the chorea is unclear. While ischaemia is most likely, it is also possible that aPL can cause chorea by antibody-binding phospholipid in the basal ganglia (31). Several patients with chorea were also studied with PET, revealing a transient hypermetabolism in the basal ganglia, suggesting an underlying excitatory rather than ischemic pathophysiologic mechanism (32).

Multiple sclerosis

Clinical syndromes mimicking multiple sclerosis (MS), mainly in its relapsing-remitting pattern, are reported to occur in association with aPL. It can be difficult to differentiate between MS and APS (6). Indeed, in a recent questionnaire of patients attending our clinic, they were asked: "Did any of your doctors at any stage of your illness consider the diagnosis of MS?" No less than 28.8% of 90 patients with positive aPL tests recorded a positive response compared with 8.4% of aPL negative patients (33). It appears that patients with similar clinical patterns like progressive myelopathy, spinocerebellar syndrome or neuromyelitis optica but also with unusual features for MS such as persistent headaches and absence of oligoclonal bands, were frequently positive for aCL (34). Another study attempted to identify parameters that might differentiate the two entities, and found that laboratory findings and MRI studies were not useful to distinguish APS from MS. It was concluded that a careful medical history, a previous history of thrombosis and/or fetal loss, and a favourable response to anticoagulant therapy might be helpful in the differential diagnosis (6). We recommend testing for aPL in patients with atypical features of MS, because some patients with APS have marked clinical improvemment, especially with regard to visual symptoms (i.e. amaurosis fugax), headache and seizures (7).

Recently, Lampropoulos *et al.* found a significantly higher prevalence of abnormal electroencephalography (EEG) in patients with neuropsychiatric manifestations and APS, compared to SLE patients (aPL negative) with neuropsychiatric features. In this study of 81 patients, 17 had APS and all of them showed EEG abnormalities, mainly slow temporal activity. Two of these patients had also the diagnosis of MS with small periventricular lesions that could not explain the alterations found in the EEG. In this study, the EEG appeared to be more sensitive in detecting neuronal dysfunction due to vascular insufficiency than brain MRI, where this can be seen only when the lesions are already advanced, such as multifocal lesions and small vessel disease (submitted for publication). This can be useful to differentiate some patients with the features of both APS and MS, and may offer an objective means of measuring the outcome of anticoagulation therapy.

Transverse myelitis

Many studies have reported an association between aPL and transverse myelitis (35-37). It is sometimes associated with optic nerve ischaemia (Devic's disease). The pathophysiology of spinal cord damage in aPL-associated myelopathy is uncertain; however both ischemic and antibody-mediated interactions have been postulated (7). The observation of vessel thrombosis in the spinal cord of paraplegic mouse-models for APS supports the concept that the addition of anticoagulation to the conventional steroids and immunosuppressives should be considered (38).

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension is also known as pseudotumour cerebri. The term is used to describe the occurrence of raised intracranial pressure that is not due to mass lesions, obstruction of cerebrospinal fluid flow or focal structural abnormalities in alert and oriented patients. The term "idiopathic" requires the exclusion of intracranial venous sinus thrombosis.

Idiopathic intracranial hypertension is frequently associated with aCLand can be the presenting symptom. Its true incidence is still unknown (39, 40).

Sensorineural hearing loss

Many authors have described the association of sudden sensorineural hearing loss with aPL(41-43). It is possible that the acute onset of sensorineural hearing loss in the presence of aPL may be a manifestation of APS, and that anticoagulation treatment should be recommended for these patients (44). A well-defined explanation for this feature is still lacking, but an impaired circulation of the inner ear has been suggested (4).

Ocular syndromes

Ocular vaso-occlusive disease is frequently found in patients with APS (45, 46). Patients usually complain of transient blurred vision or amaurosis fugax, transient diplopia, decreased vision or transient field loss associated with headache. It is important to distinguish this thrombotic retinopathy from that seen in SLE patients as a result of vasculitis (4). APS patients appear to develop unilateral optic neuropathy more commonly than patients with SLE (47).

Other neurological manifestations

Guillain-Barré syndrome was associated with the aPLin the original descriptions of the Hughes syndrome (8). Other symptoms such as transient global amnesia, neuropathy (peripheral and cranial) and Dystonia-Parkinsonism have all been reported in APS (3, 48, 49).

Treatment

It is clear that antiphospholipid antibodies constitute a significant risk for thrombosis, including stroke. Among other studies, a 10-year retrospective analysis showed that almost 50% of the patients with positive antibodies went on to develop thrombosis (49).

A more difficult decision is whether to use aspirin alone or to anticoagulate with warfarin as a primary prevention therapy. Currently most of the data available point to the superiority of warfarin (3, 51-53).

The traditional fear of cerebral haemorrhage has almost certainly resulted in the undertreatment of many patients with APS (3).

It is also important to recognise that the aCL and LA (lupus anticoagulant) levels can fluctuate over time and titers can decrease during the acute phase of the thrombotic event. For this reason

the presence of aPL should be confirmed at least 1 to 3 months after the thrombotic event (8, 54).

Another challenging point is the treatmant of "non-thrombotic" neurological features, for example patients with severe headaches and positive antiphospholipid antibodies who have not suffered a previous thrombotic event. It is a common observation that these patients often improve when they are treated with warfarin (3). To prove the veracity of this observation more detailed and prospective studies are required.

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