In 1983, Poser et al.\(^1\) established their criteria for the diagnosis of multiple sclerosis (MS). In the same year, Hughes\(^2\) described the association between thrombosis, abortion, cerebral disease and lupus anticoagulant. These reports have eventually become connected. Today, almost 20 years later, there are enough data to consider antiphospholipid syndrome (APS), or Hughes’ syndrome, as a major differential in the diagnosis of definite or probable MS according to Poser’s criteria.

Arterial thrombosis is a major feature of Hughes’ syndrome, central nervous system vessels being among the most frequently affected.\(^3\) The resulting clinical event is generally a stroke. However, more complex manifestations may include multifocal sensory, motor or cognitive dysfunction, optic neuritis, transverse myelitis and a combination of the last two (Devic’s syndrome). Different areas are often affected during the progression of the disease. Magnetic resonance imaging (MRI) studies in these patients frequently show multiple T2 hyperintense brain lesions. This combination—relapsing/remitting multifocal neurological symptoms plus the MRI findings—may closely resemble MS.

In recent years, the number of patients in the medical literature diagnosed with MS and later shown to have antiphospholipid antibodies (aPL) has grown substantially. In 1994, Scott et al.\(^4\) reported four patients presenting with multiple neurological manifestations, including vertigo, aphasia, unilateral visual loss, diplopia or hemiparesis, in different combinations over several years, with variable degrees of recovery after the episodes. All had white-matter lesions and all had received the clinical label of MS. Anticardiolipin antibodies (aCL) of the IgG isotype were positive at medium to high levels in the four patients, and lupus anticoagulant (LA) was also found in three of them. In addition, all but one patient had previous clinical manifestations suggestive of APS, such as venous thrombosis, recurrent miscarriages and thrombocytopenia.

In 1998, Djo et al.\(^5\) published a series of 23 patients with the clinical suspicion of MS. Seventeen of them met Poser’s criteria for definite or probable MS. The most frequent manifestations were transverse myelitis and optic neuritis, which were seen, alone or in combination, in 12 patients. Twenty-two of the 23 MRI studies performed were abnormal. After being re-evaluated by a radiologist unaware of the previous reading, 12 studies were labelled as diagnostic or compatible with MS, whilst in the remaining 11, MS was not the leading diagnosis, but could not be excluded. aPL were positive in all patients (it was an inclusion criteria); 14 had IgG and/or IgM medium/high titres and/or LA. Twelve patients had clinical features suggesting the presence of APS or systemic autoimmune disease, such as Raynaud’s, livedo reticularis, miscarriages, rash, arthritis or sicca syndrome.

Also in 1998, Karussis et al.\(^6\) published a neurologists’ perspective on this issue. They identified a cohort of 100 patients with MS according to Poser’s criteria but with unusual features, such as headaches, progressive myelopathy and absence of oligoclonal bands in the cerebrospinal fluid (CSF). Twenty of these patients were found to have persistently positive aCL of the IgG isotype. Nineteen had MRI findings typical of MS, including T2 hyperintense lesions in the white matter, without enhancing after gadolinium injection in any of the 13 patients with myelopathy. Spinal cord involvement was also frequent in this series, (15 patients). Optic neuritis and cerebellar lesions were the two other main forms of presentation. The clinical course of this cohort was different from ‘classical’ MS, including a slower rate of progression, a higher incidence of headaches and a frequent absence of oligoclonal bands.

Recently, we have reported on a group of 27 patients who were initially diagnosed by a neurologist as having MS, but were referred to our Unit due to atypical features.\(^7\) All of them were subsequently found to have aCL IgG and/or IgM in medium/high titres and/or LA. Assuming the ischaemic nature of their neurological symptoms, all of them fulfilled the classification criteria for APS,\(^8\) 16 primary and 11 secondary to systemic...
lupus erythematosus. Transverse myelitis was the presenting feature in 22% of patients of this series. Other manifestations included optic neuritis (with myelopathy in three cases), vertigo, ataxia, aphasia, focal weakness and numbness. MRI studies were abnormal in 23 patients. Blinded comparison of these MRIs with those from a group of 25 controls with definite MS without aPL could not distinguish which patients belonged in which group.

Some ‘negative’ studies that appear to refute the association between APS and MS-like clinical features have also been published. Rombos et al.9 compared the levels of IgG and IgM aCL in two groups of patients with MS (n=42) and myasthenia gravis (n=21) and 210 healthy individuals. They did not find any difference in the mean titres of aCL among the three populations. Tourbah et al.10 evaluated the presence of manifestations suggestive of autoimmune disease in 161 patients with definite MS. Eight of the patients with a prolonged follow-up had aCL, but no specific clinical features were found in this subgroup. However, what both studies confirmed is that aPL are found in only a minority of patients with MS. In keeping with this, the group of Karussis found aPL in only 5.7% of patients from their cohort with classical MS.6

To what degree do these antibodies represent an alternative diagnosis rather than an incidental finding? The answer to this question is not straightforward, since no gold standard can differentiate MS from Hughes’ syndrome with cerebral involvement. However, some clues suggest the existence of two different conditions. Migraine is a frequent complaint in the aPL-positive group of patients,6,7 whilst the presence of oligoclonal bands in the CSF is found much more rarely than in classical MS.6,6 Both facts point to vascular rather than inflammatory pathogenetic mechanisms. Other clinical manifestations in aPL-positive patients include livedo reticularis, sicca syndrome, Raynaud’s, miscarriages5 or even the presence of overt SLE.7 However, the strongest evidence for the presence of two different diseases is the striking response to oral anticoagulation seen in the different groups of patients with aPL: The neurological symptoms did not recur, respectively, in 3/3,4 9/95 and 8/12 patients without SLE2 treated with warfarin. Six out of nine patients with SLE in our series also responded to anticoagulation.7 All these facts suggest that a proportion of patients with APS is actually mislabelled as having MS. Accordingly, both IgG and IgM aCL and LA should be routinely included in the evaluation of any patient presenting with symptoms suggesting MS.

The absence of oligoclonal bands in the CSF should be regarded as evidence against the diagnosis of classical MS,6 although its presence does not necessarily exclude APS, since a small number of patients in the above series exhibited this feature.4-6 More specific neuroimaging techniques are being developed, and a recent study by Rovaris et al.11 suggested that magnetization transfer imaging combined with standard MRI can detect microscopic brain tissue damage and discriminate between patients with MS and those with APS. However, in this study the images obtained in a group of SLE patients with neurological symptoms were indistinguishable from those of MS patients. The authors did not report the nature of the neurological symptoms in this group with SLE, nor did they comment on the presence of aPL in them. However, positivity for aPL is very high in SLE patients with white-matter lesions,12 so the diagnosis of secondary APS can not be excluded in Rovari’s SLE group. Accordingly, no single test discriminates between ischaemic (secondary to APS) and inflammatory (secondary to MS) white-matter lesions.

Recommendations about treatment can only be based on the limited evidence of the above series, and can not therefore be considered absolute. Obviously, in patients who are consistently positive for aPL (aCL IgG and/or IgM at medium to high titres and/or LA), anticoagulation can be considered. The presence of clinical features such as migraine, thrombocytopenia, previous thrombosis, livedo reticularis, recurrent early miscarriages or an unexplained fetal loss, or a concomitant diagnosis of SLE or Sjögren’s syndrome, make the possibility of a thrombotic cause for the neurological manifestations more likely. In this group, as in other APS patients with neurological features such as stroke, anticoagulation can stop the progression of the symptoms and substantially improve the prognosis of the disease.

G. Ruiz-Irastorza
M.A. Khamasht
Lupus Research Unit
The Rayne Institute
St Thomas’ Hospital
London

References


