Multiple sclerosis (MS), systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are chronic, immune-mediated, relapsing–remitting disorders affecting young adults, the pathogenesis of which is still largely unknown. Neurological manifestations and magnetic resonance imaging (MRI) can be indistinguishable and there are no specific diagnostic tools. Treatment and prognosis are quite different. There is controversy about the prevalence and significance of antiphospholipid antibodies (aPL) in MS. A significant number of patients with APS/SLE are misdiagnosed as MS but evidence suggests they are distinct nosological entities. However, it is essential to differentiate them since APS may be responsive to anticoagulation. When assessing MS patients, clinicians should consider APS/SLE, especially if the MS has atypical features. A trial of anticoagulation might be worthwhile in some patients with atypical MS and consistently positive aPL.

**KEY WORDS:** multiple sclerosis, multiple sclerosis-like illness, neuropsychiatric lupus, antiphospholipid syndrome, differential diagnosis.

Multiple sclerosis (MS) is the commonest cause of neurological disability in young adults [1–3]. Its aetiology and pathogenesis are unknown [1–10]. The course and prognosis are variable and there is no definitive long-term treatment [1–3].

Systemic lupus erythematosus (SLE) is a multisystem disease and central nervous system (CNS) involvement occurs in about 50% of patients and carries a poor prognosis [1, 11–13]. A wide spectrum of neurological and psychiatric features are recognized [11–15]. Demyelinating syndromes resembling MS are a rare feature of SLE (‘lupoid sclerosis’) and are a diagnostic challenge [12–21]. The pathophysiology of CNS lupus remains poorly understood [1, 11–13, 22, 23] but there is increasing evidence that it is often associated with antiphospholipid antibodies (aPL) and only rarely caused by vasculitis [12–14, 22–32]. This is particularly true for myelopathy [27–29, 32, 34]. Combined therapy with immunosuppression and anticoagulation is often required [32–34].

Antiphospholipid (Hughes) syndrome (APS) was first described in 1983 [35] and it can occur on its own (primary APS; 53%) or in association with other diseases (secondary APS), most commonly SLE (36%) [11–13, 36, 37]. It is characterized by thrombosis (venous or arterial) and/or pregnancy morbidity in the presence of persistent aPL [37, 38]. Although only stroke and transient ischaemic attack (TIA) are included in the classification criteria [37, 38], more complex neurological manifestations are being recognized [12, 13, 19–21, 39–47] and multifocal white matter lesions on brain magnetic resonance imaging (MRI) are common [12, 13, 46]. In the Euro-Phospholipid Project cohort of 1000 European APS patients (primary and secondary), myelopathy and optic neuropathy were rare manifestations (0.4 and 1%, respectively) [36]. However, the number of patients diagnosed with MS and later shown to have APS has grown substantially [45–47] and the true prevalence of aPL in unselected MS populations is controversial [20, 21, 47–58]. Anticoagulation is very effective both in treatment and prevention of APS [59, 60].

The immunological nature of these diseases, the affected population, the relapsing–remitting course, the neurological manifestations and the presence of multifocal white matter lesions on MRI can make them indistinguishable [19–21, 45–49]. Some authors even question whether they could represent the same nosological entity [21]. It is important to clarify these issues since cost-effective treatments may be useful in young patients who would otherwise be disabled. Here we review the literature with a view to improving differential diagnosis. Three clinical groups are considered: MS, primary APS (PAPS) and neuropsychiatric lupus with/without APS (NPLE/APS).

**Epidemiology**

MS, SLE and APS mainly affect women of childbearing age [1–3, 11, 37] but there is a lower female to male ratio in MS (2:1 versus 9:1 in SLE and 5:1 in PAPS) [1–3, 36]. Black and Japanese populations are rarely affected by MS [1–3] but they have one of the highest incidences of SLE [1, 11].

SLE is a relatively common autoimmune connective tissue disease [1, 11] and neurological involvement is common (25–70%) [1, 11–13] and frequently associated with aPL/APS (50–60%) [12–14, 25–32, 44, 45]. The rising incidence of both diseases is possibly due to better recognition [1–3, 11]. At the...
same time, there has been a marked increase in the diagnosis of MS variants with the widespread use of MRI [48]. The potential significance of aPL and its variable prevalence in MS [20, 21, 46–58] will be explored later in this review.

Pathophysiology

The pathophysiology of MS, neuropsychiatric lupus erythematosus (NPLE) and APS remains largely unknown. Immunological mechanisms in genetically predisposed individuals, triggered by environmental factors, are a reasonable explanation for both MS and SLE [2, 23]. Thrombosis is a key feature in APS and vessels of the CNS are frequently affected [13, 37, 44–47]. The pathogenic role of aPL in the development of thrombosis is supported by experimental models [61, 62]. However, the possible effects of aPL are unlikely to be exclusively thrombotic and cross-reactivity with cerebral structures, inflammation, vasculopathy and accelerated atherosclerosis are all potential mechanisms [22, 23].

SLE is a B-cell-mediated disorder in which these cells are hyperactive and spontaneously produce a range of immunoglobulins against self antigens [22, 23]. Neurological injury in lupus is multifactorial but aPL seem to play a major role [22–26]. There could be a direct injury to neurons or glia (immune complex- or complement-mediated) and antibody-induced rheological disturbances leading to infarction and possible microvasculopathy [22, 23]. Toubi et al. [24] studied an unselected SLE population of 340 patients and found a significant difference in aPL positivity between patients with/without CNS involvement (55 vs 20%, respectively; P < 0.001). The presence of aPL was also strongly associated with less lupus activity and with small high-density lesions on brain MRI.

This study and the pathological observations clearly favour a thrombotic hypothesis, which has major therapeutic implications. However, antineuronal antibodies have also been found both in serum and cerebrospinal fluid (CSF) of patients with NPLE [23, 63]. When injected into experimental animals, circulating immune complexes can increase permeability of the blood–brain barrier, facilitating the entry of pathogenic autoantibodies into the brain which is normally protected from a potentially deviant host immune response [23]. Reversible glial cell injury following exposure to specific antibody has been described in vitro in SLE, with evidence for a comparable phenomenon in vivo in MS [23]. Vessel wall necrosis and thrombosis predominate in pathological studies of patients with APS/SLE [23, 49] but demyelination has been reported [53].

MS has long been recognized as an autoimmune disorder in which myelin is seen as foreign [2, 4–7, 9, 10]. This concept was reinforced by experimental animal models in which immunization with myelin, myelin protein or myelin protein peptides induced destruction of CNS myelin [2]. Recently, Lucchinetti et al. [6] described four patterns of disease: the first two (I and II) resembling a T-lymphocyte-mediated response, with demyelinating antibodies and complement playing a major pathogenic role and patterns III and IV resembling a primary oligodendrocyte with subsequent demyelination. They also observed a different clinical course, with a more classic relapsing–remitting disease in pattern II and a primary progressive form in pattern IV.

The hallmark of MS is the demyelinating plaque consisting of a hypocellular area with oligodendrocyte and myelin loss, axon degeneration, gliotic scars and perivascular inflammatory infiltrate mainly composed of lymphocytes and macrophages [2, 4, 9, 10]. However, there are few pathological studies and these usually analyse chronic lesions not necessarily reflecting the disease pathogenesis [6]. Barnett and Prineas [10] recently reported clinical and pathological findings in 12 patients with relapsing–remitting MS who died during or shortly after a relapse. They suggested that oligodendrocyte apoptosis may be the first event in the type III MS pattern. Other authors observed similar findings in acute white matter stroke [8]. They speculated that a hypoxia-like metabolic injury may contribute to inflammatory white matter damage in a subset of patients with MS [8]. However, small vessel infarctions have not been reported [8, 10].

These findings suggest that MS has a multifactorial aetiology. Alternatively it may be a series of syndromes with different causes and pathogenic mechanisms [2, 6, 7, 9, 10]. The resulting clinical picture is one of a chronic demyelinating disease, but the target of injury (myelin or oligodendrocytes) and the mechanism of demyelination seem to be different in subgroups of patients [6, 7, 9, 10]. This may have major therapeutic implications [6, 7, 9, 10].

The mechanisms by which aPL may induce an MS-like illness include ‘molecular mimicry’ with myelin or other CNS antigens, microvascular thrombotic events/vasculopathy and an autoimmune ‘vasculitis’ similar to that seen in SLE [21]. Antiphospholipid antibodies have demonstrated cross-reactivity with myelin, myelin-related proteins and brain phospholipids (cephalin, sphingomyelin) [18, 21, 50]. Sun et al. [64] found that anticardiolipin antibodies (aCL) bound to mouse brain tissue and inhibited astrocyte proliferation in vitro.

Diagnosis

Clinically, a clear distinction between MS, NPLE and APS can be difficult since the clinical manifestations, MRI lesions and laboratory features are often indistinguishable (Fig. 1) and have a similar relapsing–remitting course [20, 21, 45–49]. Diagnosis is challenging because there are neither pathognomonic features nor gold standard diagnostic tools [45–47] but some findings can suggest one of the diagnoses [2, 3, 12, 13, 45–47, 65] (Table 1).

MS can only be diagnosed when there is objective evidence of central neurological dysfunction ‘disseminated in space and time’, i.e. more than one affected area and more than one episode, and other possible explanations have been excluded [2–4, 65]. These points were highlighted by MacDonald et al. [65] in the revised diagnostic criteria of MS, but specific recommendations to distinguish it from PAPS and NPLE were not given.

Patients can be labelled as ‘not MS’ (diagnostic evaluation ruled out MS), ‘definite MS’ or ‘possible MS’ (at risk but diagnostic evaluation equivocal) and, in many cases, accurate diagnosis can only be made after long-term follow-up [65].

Clinical manifestations

An acute isolated neurological syndrome is the main diagnostic problem, since it is the most common picture in MS (90%) [2, 3, 64, 65] but can also be the only feature in APS/SLE [12, 13, 47–50]. Long-term follow-up studies indicate a wide range (30–80%) of progression to definite MS raising questions about the accuracy of the initial diagnosis [66].

The most common neurological manifestations of APS/SLE (stroke, TIA, seizures, headaches) [12, 13] and psychiatric disorders are not seen in MS [2, 3, 45–47]. However, some uncommon reported syndromes [transverse myelitis, optic neuritis alone or associated with transverse myelitis (Devic’s syndrome), brainstem/cerebellar syndromes, diplopia] [12, 13, 15–21, 27–32, 36] are often the first manifestation of MS [2, 3, 46, 47]. Demyelinating syndrome and myelopathy are two of the 19 recently defined syndromes in NPLE [15]. Transverse myelitis has been increasingly reported in association with APS with or without SLE [12, 13, 27–32, 34, 48] and significant
improvement after oral anticoagulation has been observed [20, 32, 34, 47, 49, 50]. SLE patients with transverse myelitis have a higher prevalence of aPL than SLE patients without it [29]. MS patients with aPL may present with myelopathy alone or associated with optic neuritis [21, 48, 49, 52, 53]. An ischaemic aetiology of visual symptoms is suggested by the abruptness of onset and shorter duration [13, 30, 43]. Optic neuritis associated with APS is usually unilateral but in SLE as in MS it may be bilateral [30].

Symptoms suggestive of peripheral nervous system involvement suggest SLE since MS only affects the CNS [2, 3]. Other manifestations would suggest underlying APS (thrombosis, miscarriages, pregnancy morbidity, livedo reticularis, thrombocytopenia) or connective tissue diseases (photosensitivity, rash, arthralgias or sicca syndrome) [12, 13, 32, 42-49].

**Diagnostic tests**

There is no specific diagnostic test [2, 3, 12, 13, 45-47, 65] but the most useful are brain and spinal MRI, CSF examination including immunoglobulin G (IgG) index and immunoelectrophoresis, visual evoked potentials and autoantibody serology.

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**FIG. 1. MRI from a patient with antiphospholipid syndrome. A, B: Brain MRI showing periventricular lesions indistinguishable from those seen in MS. C, T2-high-signal widespread lesions in spinal levels C2–5, T1–3, T5–7.**
MRI. MRI is an important diagnostic tool but small strokes in the white matter may produce lesions resembling demyelinating plaques in the brain and spinal cord. Similar multifocal white matter lesions can be found in MS, NPLE and APS (30–70%) [12, 13, 46, 67–73] and they are often ‘clinically silent’ [25, 41, 46]. Gadolinium enhancement is more suggestive of inflammation but immune complexes can also induce leakage of the blood–brain barrier [68–70] and MRI is unable to ascertain inflammation but immune complexes can also induce leakage of the blood–brain barrier [68–70] and MRI is unable to ascertain the inflammatory nature of the underlying disease [48, 65, 68–70].

The MRI criteria of Barkhof et al. [67] provide the best combination of sensitivity and specificity for an accurate diagnosis of MS [2, 65, 67]. MRI should be periodically repeated (ideally every 3 months) when there is no definite diagnosis and whenever new neurological symptoms appear [2, 65, 67]. The absence of multifocal lesions on brain MRI has a good negative predictive value for later development of MS [68]. Lesion distribution could be helpful, since subcortical lesions predominate in APS/SLE and periventricular and especially corpus callosum lesions are more common in MS [12, 13, 43–46, 68–70]. Elongated ovoid shaped lesions (‘Dawson’s fingers’) and ‘black holes’ are more characteristic of MS but they are not pathognomonic [68–70]. In our experience, the lesions seen in association with APS are usually static on repeat MRI compared with the dynamic nature of lesions seen in MS. Furthermore, lesions associated with APS may improve with anticoagulation [73].

CSF examination. CSF examination may be useful when clinical or imaging features are unusual [65] and it is the only method that can directly assess inflammation [2, 3, 65]. Mild lymphocytic pleocytosis, high IgG index or oligoclonal bands not present in serum (intrathecal production) are common in MS and NPLE and they are not usually found in primary APS [21, 49, 54, 55]. However, their presence does not exclude that diagnosis [20, 21, 49]. The absence of oligoclonal bands makes the diagnosis of MS unlikely [2, 3, 65].

Visual evoked potentials. Of the neurophysiological tests, only visual evoked potentials have shown sufficient discriminative diagnostic usefulness [3]. They are particularly helpful when MRI abnormalities are few (e.g. primary progressive form with progressive myelopathy) or have less specificity (e.g. older patients with risk factors for microvascular ischaemic disease) [65]. Normal visual evoked potentials are unusual in MS [2, 3, 65].

Antinuclear antibodies. The frequency of antinuclear antibodies (ANA) in MS and their significance are uncertain [48, 53, 74–76]. Variable prevalences have been reported [74–76] probably reflecting differences in patient selection and sensitivity of techniques [49, 54]. Barred et al. [74] retrospectively studied 150 patients with MS and found 27% to be positive for ANA. Similar findings were reported in a prospective study [54]. Other authors also found a positive correlation between titre/persistence of ANA and MS activity [75]. These data were not corroborated by others [76] and ANA can be found in healthy individuals (2–8%) and in infections, neoplasms and even after administration of some drugs, where they are usually transient and not related to thrombotic events [37, 50].

Antiphospholipid antibodies. Antiphospholipid antibodies are present in 2–5% of the general population, usually at low titre and without symptoms [21, 37] but they are associated with increased cardiovascular risk [77–79]. They also can be found in infections, neoplasms and even after administration of some drugs, where they are usually transient and not related to thrombotic events [37, 50].

Higher prevalences are reported in autoimmune diseases, mainly in SLE (36%) [11–13, 36, 37] where they are associated...
with CNS involvement (50–60%) [12–14, 25–32]. aPL have been described in neurological conditions such as myasthenia gravis, Lambert–Eaton syndrome and migraine [50]. They also have been reported with variable frequency in patients with MS [20, 21, 45–58], especially of the neuromyelitic type [21, 49, 50]. Whether this is an incidental finding, an epiphenomenon reflecting underlying immune activation, the result of nervous system damage or is in fact pathogenic is a matter of discussion. Specific characteristics of the selected populations and study protocols, utilization of different techniques and interlaboratory variation, type of aPL measured (lupus anticoagulant (LA) not determined in most cases) and no uniform cut-off value for positive results are possible explanations for the wide variability of the results. aPL titres can fluctuate and they are sometimes negative in the acute phase [48] but most studies have not measured aPL sequentially. There is also no consensus about routinely measuring aPL in patients with MS but some authors have suggested it would be important to add aPL testing to diagnostic criteria [54]. The most relevant published studies are summarized in Table 2.

In the United States, Scott et al. [20] reported four patients diagnosed as MS. aCL of the IgG isotype were positive at medium to high titre in all patients. LA were also found in three, and all but one patient had previous clinical manifestations suggestive of APS. In Japan, SLE is very common [1, 11] while MS is rare [1–3] and characterized by a high incidence of neuromyelitis optica and transverse myelitis [80]. Fukazawa et al. [51] studied a Japanese MS population and found a significant prevalence of aPL (5.3%, two of 38 patients) when compared with controls. Both patients presented with recurrent optic neuritis and transverse myelitis. Both had normal brain MRI, swelling of the spinal cord, no oligoclonal bands on CSF examination, abnormal visual evoked potentials and no evidence of connective tissue disorders. Similar results were reported by others in a similar population but with a predominance of the aCL IgM isotype [52]. Karusis et al. [21] found an aPL prevalence of 5.7% in patients with classic MS but much higher (20%, mainly of IgG isotype) in patients with atypical features (myelitis alone or associated with optic neuritis/cerebellar signs, migraine, absence of oligoclonal bands in CSF). MRI findings typical of MS were found in the majority of these patients. This group had a slower progression and the authors suggested it may represent a specific subset of patients with MS or a different nosological entity. All patients were treated with acetylsalicylic acid (100 mg o.d.) and most remained stable.

In a study involving 322 patients referred to a rheumatology clinic, 59% (n = 189) had positive aPL and 8% (n = 26) had a previous diagnosis of MS [48]. In these patients transverse myelitis and optic neuritis were common. Most of them were aPL positive (23/26 (88%), most commonly of IgM isotype). Almost all MRI studies were abnormal, but only 50% were labelled as diagnostic or compatible with MS by a radiologist blind to the diagnosis. Also, 50% of patients had previous manifestations suggesting APS/SLE. Cuadrado et al. [49] corroborated these data when evaluating 27 female patients with atypical MS (symptoms suggesting underlying connective tissue disease, uncommon findings for MS on MRI, atypical evolution, aPL positivity). All were aPL positive and fulfilled the classification criteria for APS (16 PAPS, 11 secondary to SLE). Transverse myelitis was the commonest presenting feature and most of them had MRI abnormalities indistinguishable from the patients with definite MS. These findings suggest that a significant number of patients with aPL are initially diagnosed as MS and the authors advised screening for aPL in MS population, at least when atypical features are present.

Some ‘negative’ studies have also been published and the authors argued that occasionally higher prevalences of aPL in MS populations are merely an epiphenomenon [50, 53–58]. They do not recommend screening for aPL in MS patients but they agree that APS should be considered in the differential diagnosis.

Tourbah et al. [53] found that about 50% of an unselected MS population of 161 patients had atypical features (e.g. isolated clinical abnormalities, ANA and/or aCL positivity). No significant difference was found between them and patients with classic MS. However, after 5 yr of follow-up, a diagnosis of MS was not established in about 20% of patients in the atypical group. These were characterized by a combination of clinical, biological and MRI abnormalities suggesting APS/SLE as an alternative diagnosis (positive ANA in combination with positive aPL in about 40%; anti-DNA antibodies in about 30%; punctiform or diffuse T2 hyperintense lesions in about 40%).

Roussel et al. [54] studied a population of 89 MS patients and about 30% had aPL, either aCL (21%) or β2-glycoprotein (GPI) (16%) but, contradicting other studies, they did not observe a different clinical presentation or evolution in these patients. Nevertheless, they actually found one of the highest prevalences of aPL in an unselected MS population, even higher than in patients with stroke. Heinzlef et al. [55] reported similar results in a larger unselected MS population, but only patients with definite MS were included. Sastre-Garriga et al. [56] studied the largest unselected MS population to date and they did not find either a higher prevalence of aPL than in general population (2%) or specific characteristics in the positive patients. Similar findings have been reported by other authors in smaller populations [50, 57, 58].

Despite discordance in these results, because APS is a treatable disease and aPL screening is a non-invasive, widely available and inexpensive diagnostic test, it seems reasonable to consider it in patients with MS, especially in those with atypical features. Repeated negative results make a diagnosis of APS unlikely. Consistently positive aPL might suggest a different treatment approach.

Other diagnostic tests. More specific neuroimaging techniques are being developed. The application of single photon emission computed tomography has been studied in patients with APS where it can show focal low-perfusion areas that improve with anticoagulation [49, 81]. Rovaris et al. [72] suggested that magnetization transfer imaging combined with standard MRI could discriminate MS from APS, but images were indistinguishable from SLE.

Some neurophysiological studies in MS found an increase of slow frequencies (δ and θ) in the left frontotemporal-region and decrease of the α band, the significance of which is not well understood [82–84]. Similar studies in SLE reported δ and θ slowing and sharp wave activity suggesting selective damage to the left temporolimbic region [85]. Seizures were reported in SLE associated with APS [86] soon after the first description of the syndrome [35]. Recently, Lampropoulos et al. (unpublished data) observed a significantly higher prevalence of abnormal electroencephalograms (EEGs) in APS patients when compared with those who were only aPL positive and with patients with SLE without aPL (100, 71 and 39.1%, respectively). Two patients (2/81) who were also diagnosed as MS had focal slow activity and small periventricular lesions which are unlikely to explain those abnormalities on EEG. The authors suggested that EEG may be useful since a normal recording is less compatible with APS.

Treatment

The classic treatment for MS is interferon-β which reduces relapses by 30%, but delay in disability progression or long-term benefit is not proven [1, 2]. It is an expensive parenteral therapy [1, 2] and it may potentially induce or aggravate lupus activity [87].
<table>
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<tr>
<th>Authors, date, country</th>
<th>Study protocol</th>
<th>Population</th>
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<td>Positive studies</td>
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<td>Fukazawa et al., 1993 [51], Japan</td>
<td>Prospective, case–control</td>
<td>38 patients (25 F; 40.2 yr)</td>
<td>aCL (ELISA), LA N.D.</td>
<td>5.3% in MS population. 67% in ON/TM</td>
<td>SSD</td>
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<td>Sugiymama et al., 1996 [52], Japan</td>
<td>Prospective, follow-up (12-36 mo)</td>
<td>100 patients (12 F; 45.3 yr)</td>
<td>aCL (ELISA), LA N.D.</td>
<td>5.7% in classic MS, 20% in atypical MS (most IgG)</td>
<td>SSD</td>
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<td>Karussis et al., 1998 [21], Israel</td>
<td>Prospective</td>
<td>322 patients, 189 aPL+, 26 MS or MSL (25 F; 41 yr)</td>
<td>aCL (ELISA), LA RVVT</td>
<td>59%, 88% in MS or MS-like (most IgM)</td>
<td>SSD</td>
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<td>Sugiyama et al., 1996 [52], Japan</td>
<td>Retrospective, case–control</td>
<td>27 atypical MS (27 F; 38.4 yr)</td>
<td>aCL (ELISA), LA (RVVT)</td>
<td>100%</td>
<td>SSD</td>
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<td>Ijdo et al., 1999 [48], USA</td>
<td>Prospective</td>
<td>32 patients</td>
<td>aCL (ELISA), LA (Kao/APTT), GPI (ELISA)</td>
<td>32.6% (21% aCL; LA none)</td>
<td>SSD for IgG. Prevalence higher than for stroke. MSSD in clinical presentation or evolution</td>
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<td>Karussis et al., 1998 [21], Israel</td>
<td>Prospective</td>
<td>100 patients</td>
<td>aCL (ELISA), LA (Kao/APPTT), β2 GPI (ELISA)</td>
<td>15% (most IgM)</td>
<td>SSD in clinical manifestations or evolution</td>
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<td>Rombos et al., 1990 [50], Greece</td>
<td>Prospective, case–control</td>
<td>42 patients (28 M; 33 yr)</td>
<td>aCL (ELISA), LA N.D.</td>
<td>Not reported</td>
<td>SSD</td>
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<td>Cordoliani et al., 1998 [57], France</td>
<td>Prospective, case–control</td>
<td>62 patients (37 F; 43.4 yr)</td>
<td>aCL (ELISA), LA N.D., β2 GPI (ELISA)</td>
<td>8%</td>
<td>SSD</td>
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<td>Baraczka et al., 2002 [58], Hungary</td>
<td>Prospective, case–control</td>
<td>35 patients (13 SLE with MS-like (12 F), 22 MS (20 F) (36.6 yr)</td>
<td>aCL (ELISA), β2 GPI (ELISA), LA N.D.</td>
<td>Not reported</td>
<td>SSD</td>
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M, male; F, female; yr, years old (mean age); Kao/APTT, kaolin and activated partial thromboplastin clotting times; RVVT, Russel viper venom time; N.D., not determined; MSSD, no statistically significant difference; ON, optic neuritis; SSD, statistically significant difference; TM, transverse myelitis.
Choice of the most appropriate treatment for NPLE is always challenging because it is difficult to be certain of the underlying mechanism [12, 13, 33] and combined therapy is often required (immunosuppressive drugs and anticoagulation) [32–34, 46]. Cyclophosphamide is the recommended agent in severe cases, with good results [33]. Azathioprine, mycophenolate mofetil or methotrexate can be used to maintain remission [33]. Corticosteroids are used in both SLE [33] and MS [1, 2], mainly to control symptoms during the acute phase.

High-intensity anticoagulation with warfarin (international normalized ratio (INR) 3–4) is the most effective treatment for APS, with a low haemorrhagic risk [37, 59, 60]. Primary prevention with anti-aggregation or even low-dose oral anticoagulation is probably suboptimal [39, 59]. Some patients with MS-like illnesses and aPL with or without SLE had a significant improvement after anticoagulation, both clinically and radiologically [20, 32, 34, 45–49]. This suggests that in patients with MS and persistently positive aPL and/or atypical features, a trial of anticoagulation with a target INR of 3–4 for 6 months might be cost-effective. Clearly the patients should be carefully counselled about the risks of anticoagulation.

### Prognosis

The course of MS is largely unpredictable but about 50% will need help with walking 15 yr after diagnosis and 70% will have secondary progression despite treatment [1–4].

Recent studies have shown a reduction in mortality in SLE [88, 89] probably because of earlier recognition and treatment. NPLE [12, 13] and secondary APS [12, 50] carry a worse prognosis, suggesting potential benefit from combined therapy.

Primary APS is being increasingly recognized and treated, and even healthy individuals with aPL are now regarded as a population at risk [37, 59]. Treatment definitely improves prognosis [37, 59].

### Conclusion

Evidence suggests that MS, APS and NPLE are distinct entities. Epidemiological data differ and some APS/SLE clinical features are unusual in MS. The striking response to anticoagulant therapy in some patients with ‘MS’ and aPL is probably the strongest argument for distinguishing the two diagnoses.

However, as seems evident from the literature and from the everyday practice of those working with APS/SLE, a significant number of these patients are probably mislabelled as MS. Transverse myelitis and multifocal white matter lesions seem to be the most common confounding factors.

APS primary or secondary to SLE is an essential differential diagnosis of MS because treatment in this young population may improve both quality of life and mortality. When dealing with potential diagnoses. Screen for aPL, especially if atypical features are present.

- Consider APS/SLE as possible differential diagnoses. Screen for aPL, especially if atypical features are present.
- Consider a trial of anticoagulation if aPL are persistently positive.

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