

REVIEW

Hughes syndrome and Multiple sclerosis

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Multiple sclerosis (MS) and antiphospholipid syndrome (APS) share common clinical, laboratory and radiological features. We reviewed all the English papers on MS and APS published in the literature from 1965 to 2014 using PubMed and Google Scholar. We found that APS can mimic antiphospholipid antibodies (aPL)-positive MS in many ways in its clinical presentation. Nevertheless, APS diagnosis, clinical manifestations and management differ from those of MS. aPL were found in MS patients with titers ranging from 2% to 88%. The distribution and volume of lesions on magnetic resonance imaging (MRI) may help to differentiate MS from primary APS. In addition, atypical MS presentation can guide physicians toward an alternative diagnosis, especially when features of thrombosis and/or history of connective tissue disease are present. In that case, an anticoagulation trial could be worthwhile. *Lupus* (2015) 24, 115–121.

Key words: Hughes syndrome; antiphospholipid syndrome (APS); multiple sclerosis (MS); antiphospholipid antibodies (aPL)

Introduction

Antiphospholipid (Hughes) syndrome (APS) was first described in 1983.¹ It is defined as a state of hypercoagulability resulting in venous or arterial thrombosis, pregnancy loss, and thrombocytopenia. These clinical events are associated with the presence of serum antiphospholipid antibodies (aPL), which include lupus anticoagulant (LA), anticardiolipin (aCL) and anti-beta-2-glycoprotein I (anti-β2GPI).^{1–4} APS can exist as either a primary disease or secondary to a connective tissue disorder (mostly systemic lupus erythematosus).⁵

Multiple sclerosis (MS) is the most common immune-mediated neurodegenerative disease of the human central nervous system (CNS), characterized by multifocal areas of myelin loss disseminated in time and space, and followed by axonal degeneration and progressive neuronal loss.^{6–8}

CNS association is one of the most prominent clinical manifestations of APS; it involves arterial and venous thrombotic episodes, psychiatric events

and a range of other non-thrombotic neurologic features such as headache, migraine, epilepsy, chorea and dementia.⁵ The clinical presentation may mimic MS symptoms and therefore lead to a challenge in the diagnosis.^{9–13} aPL have been reported in MS patients in various frequencies; their clinical significance is still unclear, probably linked to an augmented autoimmune humoral response.¹⁴ Some studies describe higher frequencies of certain types of aPL in MS and their association with different clinical subtypes of the disorder such as spinal cord involvement and optic neuritis.^{15–17} As the association of APS with MS is still unclear, the objective of this review is to describe and identify this correlation by reviewing published articles on this topic.

Epidemiology

MS and APS predominately affect women of child-bearing age,^{6,18–20} yet the female-to-male ratio is lower in MS (2:1) compared to APS (5:1).^{6,19–21} The worldwide prevalence of MS differs by geographic region; it is high in the Northern countries (80–300/100,000 residents) and low in some regions of Asia, Africa and South America

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(five per 100,000 residents).^{22,23} The prevalence of aPL positivity in healthy people ranges between 1% and 5% and increases with age, particularly in elderly with chronic diseases.²⁴ Several studies reported the presence of aPL in serum of MS patients with wide variability (2%–88%).^{10,14–17,25–34}

Diagnosis of APS

APS is characterized by thromboembolic brain disease, whereas demyelination is the hallmark of MS.¹¹ APS is classified using the Sydney criteria,³⁵ which is the modification of the Sapporo APS classification criteria.³⁶ At least one clinical and one laboratory criterion is required.³⁵

There is no single diagnostic test or clinical feature sufficient for diagnosis of MS. Instead, a combination of clinical and paraclinical studies are required.^{5,6,9,19,37–42} Brain and spinal magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) examination with immunoglobulin (Ig)G index, visual evoked potential (VEP), immunoelectrophoresis, and autoantibody serology contribute to the diagnosis.¹² Nevertheless, the main criteria used for diagnosis is highlighted by McDonald *et al.* (2001), where neurological attacks have to be separated by time and space.^{6,19,40,43} “MS,” “possible MS,” or “not MS” now substitute for the terms “probable MS” and “clinical MS.” “Possible MS” is used when there is no access to MRI or CSF analysis until two clinical attacks in two separate regions are detected.⁴⁰

aPL in MS

The prevalence of aPL ranges between 2% and 88%.^{10,14–17,25–34} Noteworthy, several studies reported a predominance of IgM over IgG subtypes,^{17,26,33,44} maybe due to patients not having antibody class switch yet. Though aPL frequency was higher in MS patients with exacerbations, the significance of this autoantibody titer elevation is still not fully understood.³³

aCL prevalence in MS patients varied between 6% and 28% in a number of studies.^{14,16,29,31,33,44} There was no significant difference in clinical characteristics of MS when comparing aCL-positive and -negative MS patients.^{31,33} Another set of studies found that 2% to 28% of MS patients had positive anti- β 2GPI antibodies when compared to controls; both aCL and anti- β 2GPI were of

IgM type.^{14,29,33,44} Bidot *et al.* (2007) showed that 82% of MS patients in exacerbation were positive for aCL and anti- β 2GPI compared to 28% of patients in remission.³³ LA was studied to a lesser extent and Garg *et al.* (2007) found only one LA-positive case among 78 MS patients tested.⁴⁴ More studies are needed to elucidate the true prevalence of LA in MS patients. Table 1 summarizes the studies conducted thus far.

MS and/or APS features

MRI findings

Neurodegeneration in MS patients develops along with inflammatory demyelination as emphasized by histological and *in vivo* studies using MRI. Although this pathology affects the entire brain, different distributions in white and gray matter can be noted.⁴⁷ Hughes *et al.* (2005) described that lesions seen on repeat MRI in APS do not change in shape and size over time in contrast to the lesions seen in MS. Predilection of the lesions to the subcortical area and their improvement with anticoagulation better supports an APS etiology. Periventricular lesions, particularly in the corpus callosum, with an elongated ovoid shape (Dawson’s fingers) and “black holes” are more commonly found in MS.^{5,39,41,42,48–52}

Stosic *et al.* (2010) studied MRI findings on patients diagnosed with MS and compared them to those of patients diagnosed with primary APS (PAPS). MS patients presented with severe and extensive tissue damage compared to PAPS patients. MRI of MS patients showed significantly higher T1- and T2-lesion volumes (LVs) and T2-LV magnetic transfer ratio (MTR), lower brain parenchymal fraction (BPF) and gray matter fraction (GMF), and higher mean parenchymal diffusibility (MPD) than PAPS patients.^{46,53}

More studies showed that contrast dyes, such as gadolinium, could distinguish MS lesions from vascular lesions, often similar on normal MRI, with dye-enhanced lesions in MS generally smaller than those in APS.^{10,48} Single photon emission computerized tomography (SPECT) revealed low perfusion areas that improved with anticoagulation treatment in APS patients⁵⁴ but failed to be conclusive in patients with MS.^{55,56} Other differences on MRI include MS patients having widespread white matter disease, whereas a predilection of abnormalities to the putamen was found in aPL-positive patients.¹⁰

Table 1 Summary of studies showing prevalence of aPL in MS patients

<i>First author and date</i>	<i>Population</i>	<i>Antibodies</i>	<i>Titers</i>	<i>Comments</i>	<i>Type of study</i>
Fukazawa <i>et al.</i> , 1993 ¹⁵	38 MS pts	aCL	aCL: 5.3%	SSD	Prospective, case-control
Sugiyama <i>et al.</i> , 1996 ²⁶	32 MS pts	aCL	aCL: 44% IgM and 9% IgG	SSD	Prospective, case-control
Karussis <i>et al.</i> , 1998 ¹⁶	100 MS pts (30 atypical)	aCL	aCL: 5% in classic and 20% in atypical MS	SSD	Prospective, follow-up
Cordoliani <i>et al.</i> , 1998 ²⁷	62 MS pts	aCL and anti-β2GPI	aCL and anti-β2GPI: 8%	SSD	Prospective, case-control
Tourbah <i>et al.</i> , 1998 ²⁸	161 MS pts (84 atypical)	aCL and LA	aCL and LA: 6.2%	NSSD	Prospective, follow-up
IJdo <i>et al.</i> , 1999 ¹⁷	322 pts; 23 MS or MSL pts	aCL and LA	aCL: 59% of all pts and 88% of MS or MSL pts LA: 21%	Pts included have aPL-related symptoms on initial visit	Prospective
Cuadrado <i>et al.</i> , 2000 ¹⁰	27 atypical MS pts	aCL and LA	aCL: 100% (74% IgG and 77% IgM) LA: 33%	Pts turned out to have primary APS or SLE	Retrospective, case-control
Roussel <i>et al.</i> , 2000 ²⁹	89 MS pts	aCL and anti-β2GPI	aCL or anti-β2GPI: 32.6% aCL: 21% (79% IgG) anti-β2GPI: 15% (85% IgM)	NSSD in clinical presentation	Prospective, case-control
Sastre-Garriga <i>et al.</i> , 2001 ³⁰	251 MS pts and 45 MSL pts	aCL and anti-β2GPI	aCL: 2% anti-β2GPI: 1%	NSSD	Retrospective, case-control
Heinzlef <i>et al.</i> , 2002 ³¹	285 MS pts	aCL	aCL: 15% (76% IgM)	NSSD in clinical presentation	Prospective, case-control
Vilisaar <i>et al.</i> , 2005 ⁴⁵	41 OCB-ve pts and 206 OCB+ve pts	aCL and anti-β2GPI	OCB+ve; aCL: 19% (57% IgM and 69% IgG) anti-β2GPI: 8% OCB-ve; aCL: 78% (66% IgM and 98% IgG) anti-β2GPI: 34%	SSD	Prospective, case-control
Garg <i>et al.</i> , 2007 ⁴⁴	111 MS pts and 26 CIS pts	aPL, aCL, and anti-β2GPI	aPL: 55% in MS pts and 59% in CIS pts aCL: 6% in MS pts and 0% in CIS pts anti-β2GPI: 2% in MS and 4% in CIS	Nine out of the 14 CIS aPL+ve pts were -ve on repeated testing SSD	Prospective combined with retrospective (medical chart review)
Bidot <i>et al.</i> , 2007 ³³	24 RR MS pts; seven in rem. and 17 in exc.	aCL and anti-β2GPI	Rem.; aCL: 28% anti-β2GPI: 28% Exc.; aCL: 28% anti-β2GPI: 82%	All antibodies detected were of IgM subtype SSD	Prospective, cohort
Carrillo-Mora <i>et al.</i> , 2010 ³⁴	12 MS pts	anti-β2GPI	anti-β2GPI: 0%	No anti-β2GPI detected in serum or in CSF	Prospective, case-control
Stosic <i>et al.</i> , 2010 ⁴⁶	49 MS pts	APE, aCL, aPL, and anti-β2GPI	APE: 32% aCL: 18% aPL: 18% anti-β2GPI: 10%	Tests repeated after six months SDD	Prospective, case-control
Szmyrka-Kaczmarek <i>et al.</i> , 2012 ¹⁴	85 MS pts or CIS pts	aCL, aPL, and anti-β2GPI	anti-β2GPI: 20% (IgM only) aPL: 22% aCL: 6%	SDD	Prospective, case-control

Pts: patients; MS: multiple sclerosis; MSL: multiple sclerosis-like; OCB: oligoclonal bands negative; -ve: negative; +ve: positive; CIS: clinically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis; rem.: remission; exc.: exacerbation; aCL: anticardiolipin; anti-β2GPI: anti-beta-2-glycoprotein I; LA: lupus anticoagulant; aPL: antiphospholipid; APE: anti-phosphatidylethanolamine; IgM: immunoglobulin M; IgG: immunoglobulin G; SSD: statistically significant difference; NSSD: no statistically significant difference.

Clinical findings

Most often, clinical findings cannot clearly distinguish between MS and APS.⁹ Strokes, transient

ischemic attacks (TIA), seizures and headaches, which are the most common neurological manifestations of APS, are not usually present in MS patients. On the other hand, some of the

uncommon syndromes such as transverse myelitis, optic neuritis, Devic's syndrome, brainstem/cerebellar syndromes and diplopia are often identified as the first manifestation of MS.¹² APS is considered as an alternative diagnosis for MS patients with previous connective tissue disease-like features.¹⁷ In addition, features such as thrombosis, miscarriages, pregnancy morbidity, livedo reticularis, and thrombocytopenia are suggestive of APS rather than MS. Karussis et al. (1998) found that MS patients with atypical features had much higher prevalence of aPL than patients with classic MS and slower progression of the disease.¹⁶ Hypocomplementemia, frequently described in APS, is not present and prompts the diagnosis to be reconsidered if detected in MS patients.¹⁷

In cases where MRI or clinical presentation are atypical,⁴³ CSF findings such as mild lymphocytic pleocytosis, high IgG index or oligoclonal bands are common in MS and not usually found in APS.¹²

The only neurophysiological test ruled as sufficient to discriminate MS from APS diagnosis is the Visual Evoked Potential (VEP) test.¹⁹ It is especially useful for cases where the clinical features and imaging studies are not distinctive.⁴⁰ It is unusual to find an MS patient with normal evoked potential.^{6,19,40} Paran et al. (2006) compared evoked potentials in APS and MS patients who had similar neurological symptoms, physical findings, laboratory tests and MRI studies. They found that abnormal prolonged VEP as well as other evoked potentials are unusual in APS, thus a normal VEP test in patients with MRI findings compatible with either APS or MS supported the APS diagnosis.⁵⁷

Cuadrado et al. (2000) suggest that anticoagulation treatment can help in the diagnosis of APS when there is an overlap with MS because the remission of neurological manifestations in APS patients is frequently noted contrary to MS.¹⁰

Striking features of MS-complicating APS

The implications of aPL on the clinical presentation of MS and their role in its pathogenesis are still widely debated.^{17,29,58} Garg et al. (2007) compared aPL-negative and -positive MS patients and found the latter group to have a longer span of the disease (15.0 vs 10.6 years) and higher Extended Disability Status Scale (EDSS). MRI findings demonstrated T2-LV differences between the two groups (15.1 ml in the aPL-positive group vs 6.7 ml in the aPL-negative group); all results were significant

with correction for disease duration in generalized linear model analysis. Conversely, findings on BPF, T1-black hole LV, frequency and distribution of spinal cord lesions were not significantly different.⁴⁴ Zivadinov et al. (2012) highlighted discrepancies in response to treatment with interferon-beta1 between aPL-positive and -negative patients of relapsing-remitting (RR) MS. Response of aPL-positive patients was weaker compared to that of aPL-negative patients. The aPL-positive group showed worse MRI findings and more severe clinical deterioration over the three-year follow-up period.⁵⁹

Another study conducted by Bidot et al. (2007) found positive correlation between MRI findings and the presence of IgM anti-factor 7, phosphatidylcholine (PC) and phosphatidylserine (PS). Therefore, some aPL may be involved in the pathogenesis of MS by targeting these antigens on the blood brain barrier (BBB) and compromising its integrity.³³ Some studies reported that anti-β2GPI promotes the expression of adhesion molecules, endothelial cell activation,⁶⁰ and adherence to CNS cells,⁶¹ thus facilitating interaction and access of lymphocytes to CNS cells.²⁹ However, no significant correlation between MRI findings and aCL, anti-β2GPI, or anti-phosphatidylethanolamine antibodies was found.^{26,29,31,33,45}

Findings of higher disability in aPL-positive patients suggest aPL as a marker of CNS injury. This may be due to immune-mediated B-cell reaction,⁴⁴ where molecular mimicry of aPL-target antigens with myelin, myelin-related proteins and brain phospholipids leads to cross reactivity,^{16,62} prothrombotic states⁶³ and induced vasospasm.⁶⁴

Management of APS-MS

Interferon-beta1, anticoagulation, and aspirin

In MS patients, interferon-beta1 is the treatment of choice, reducing relapses by 30%. However, it is expensive, can activate Th-2 lymphocytes and exacerbate lupus.^{6,65-67} Corticosteroids therapy is the mainstay in managing acute exacerbations of MS. The risk of exposing aPL-positive MS patients to interferon-beta1 is not elucidated yet; studies did not show elevation of serum aPL, though other autoantibodies such as anti-tertioglobulin and anti-microsome were significantly raised.⁶⁸⁻⁷⁰ According to Colosimo et al. (1997), short-term treatment of MS with interferon-beta1 is safe.⁶⁸ Side effects of interferon-beta1 in MS therapy are uncommon;⁷¹

however, acute toxicity manifested as autoimmune reactions, capillary leak syndrome, anaphylactic shock, and thrombotic-thrombocytopenic purpura may limit its use.⁷² Milder adverse effects include headache, alopecia, insomnia and depression.^{72,73} Interferon-beta1 must be cautiously administered and its effects should be further studied in APS patients with MS features.

Several authors described a good clinical response in aPL-positive patients presenting with MS-like syndrome after anticoagulation therapy, mainly with warfarin.^{9,10,17,39,42,74–76} Fernández-Fernández *et al.* (2006) reported two cases of APS simulating MS with positive aCL whose symptoms remitted after oral anticoagulation.¹³ Ferreira *et al.* (2005) suggest that anticoagulation to international normalized ratio (INR) of 3–4 for six months is reasonable and cost effective in MS patients with persistently positive aPL and/or atypical features.¹²

Karussis *et al.* (1998) treated MS patients presenting with atypical features and positive aPL with 100 mg once a day (o.d.) acetylsalicylic acid (aspirin) and occasional steroids that improved the condition of four and stabilized that of nine patients, while only two patients' conditions deteriorated. The authors attributed the stabilization of this "MS subtype" to aspirin therapy.¹⁶

On the other hand, a cohort by Sastre-Garriga *et al.* (2001) found aPL only in six out of 296 MS and clinically isolated syndrome patients; the authors recommended neither screening nor treating aPL-positive MS patients unless other APS features are present.³⁰

Corticosteroids and intravenous immunoglobulin (IVIG)

Frohman *et al.* (2003) successfully managed bilateral autoimmune optic neuropathy in an aCL-positive child with corticosteroids, aspirin, and IVIG.⁷⁷ Furthermore, Chapman (2004) treated 12 MS-APS patients with IVIG. They reported improvement in some and long-term stabilization in all patients.⁷⁰ Large controlled studies, however, are required to better clarify this effect. Fukazawa *et al.* (1993) administered corticosteroids to two MS patients with aCL antibodies; one patient completely recovered from the acute attack while the second only mildly improved.¹⁵ Ruiz-Argüelles *et al.* (1998) effectively treated an aCL-positive patient presenting with refractory hiccups (due to transverse myelitis) with corticosteroids.⁷⁸

Conclusion

Different types of aPL coexist with MS in highly variable frequencies; however, the clinical significance of this coexistence is still unclear and large sample-size population studies are further needed. APS and aPL-positive MS may have similar clinical presentation, yet the criteria for diagnosis and management are different and definitive diagnosis is challenging. APS should be strongly considered in atypical MS patients. Screening for aPL in these patients is highly recommended. In addition, a positive response to anticoagulation strongly aids in APS diagnosis and could be lifesaving as it can stop disease progression.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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