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REVIEW ARTICLE

'Non-Criteria' Neurologic Manifestations of Antiphospholipid Syndrome: A Hidden Kingdom to be Discovered

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Abstract: Neurological manifestations or disorders associated with the central nervous system are among the most common and important clinical characteristics of antiphospholipid syndrome (APS). Although in the most recently updated (2006) APS classification criteria, the neurological manifestations encompass only transient ischemic attack and stroke, diverse 'non-criteria' neurological disorders or manifestations (*i.e.*, headache, migraine, bipolar disorder, transverse myelitis, dementia, chorea, epileptic seizures, multiple sclerosis, psychosis, cognitive impairment, Tourette's syndrome, parkinsonism, dystonia, transient global amnesia, obsessive compulsive disorder and leukoencephalopathy) have been observed in APS patients. To date, the underlying mechanisms responsible for these abnormal neurological manifestations in APS remain unclear. *In vivo* experiments and human observational studies indicate the involvement of thrombotic events and/or high titers of antiphospholipid antibodies in the neuro-pathogenic cascade of APS. Although different types of neurologic manifestations in APS patients have successfully been treated with therapies involving anti-thrombotic regimens (*i.e.,* anticoagulants and/or platelet antiaggregants), antineuralgic drugs (*i.e.,* antidepressants, antipsychotics and antiepileptics) and immunosuppressive drugs alone or in combination, evidence-based guidelines for the management of the neurologic manifestations of APS remain unavailable. Therefore, further experimental, clinical and retrospective studies with larger patient cohorts are warranted to elucidate the pathogenic linkage between APS and the central nervous system in addition to randomized controlled trials to facilitate the discovery of appropriate medications for the 'non-criteria' neurologic manifestations of APS.

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INTRODUCTION

Antiphospholipid syndrome (APS) or Hughes syndrome is a systemic autoimmune disease that was first described in 1983 [1]. APS is clinically characterized by the presence of thrombotic events (arterial and/or venous) and/or pregnancy morbidity co-existing with any one of the three antiphospholipid antibodies (aPLs), *i.e.,* lupus anticoagulant (LA), anticardiolipin antibody (aCL) and anti-β2glycoprotein I (anti-β2GPI) [2]. APS is considered 'primary' (PAPS) when there is no other underlying disease apart from at least one clinical and one laboratory APS feature [3]. Secondary APS (SAPS) co-exists with other autoimmune disorders, most commonly systemic lupus erythematosus (SLE) [4]. Catastrophic APS (CAPS) is the most aggressive form of APS and is characterized by thrombi development in the

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small blood vessels of multiple organs that result in multiple organ failure and is thus considered the most common reason for the high mortality rate of APS [5]. The incidence of APS is approximately five new cases per 100,000 persons per year, the prevalence is approximately 40 - 50 cases per 100,000 persons, and females are 3.5 times likely to be affected than males [6].

As systemic disease, APS affects multiple organs including the central nervous system (CNS) [7]. According to the most recently updated (2006) APS classification criteria [2], only transient ischemic attack (TIA) and stroke have been accepted as the 'criteria' for neurological manifestations. However, in addition to stroke and TIA, APS patients display a wide variety of neurologic symptoms [8]. 'Non-criteria' neurological manifestations, such as bipolar disorder (BD) [9], dementia [10], chorea [11], epilepsy [12], psychosis [13], cognitive impairment [14], transient global amnesia (TGA) [15], Parkinsonism [16] and dystonia [17], have been observed in patients with APS. The occurrence of thrombotic events is believed to be among the primary causes of the development of neurological symptoms, such as stroke and TIA, in patients with APS [18]. However, many of the CNS manifestations, including psychosis, cognitive dysfunction, headaches, migraines, depression, chorea, epilepsy, transverse myelitis (TM) and optic atrophy, cannot be solely explained by thrombotic events or hypercoagulability [19, 20].

Additionally, some APS patients with neurologic symptoms do not exhibit any lesions on computerized tomography (CT) scans or brain magnetic resonance imaging (MRI), which further suggests that neuro-thrombotic events are not solely responsible for the neurologic disorders associated with APS [21]. In addition to the indirect role of aPLs that is mediated via the activation of thrombogenic and/or immunogenic components, the direct action of aPLs against neural tissues has been proposed to support the development of cognitive and behavioral abnormalities in APS [22, 23]. In contrast, elevated levels of aPLs (LA and/or aCL and/or anti-β2GPI) have been reported in patients suffering from different types of neurological disorders, such as migraine [24], multiple sclerosis (MS) [25, 26], Tourette's syndrome (TS) [27, 28] and obsessive compulsive disorder (OCD) [29] without any underlying APS clinical criteria, which indicates the existence of an area related to APS that has yet to be explored.

The objective of this review was to explore the 'non-criteria' neurological manifestations of APS based on existing knowledge from human and animal studies to provide a potential source for the forthcoming APS classification criteria that will strengthen the link between APS and the CNS.

METHODOLOGY

Clinical evidences of 'non-criteria' neurologic manifestations associated with APS were retrieved from PubMed, Web of Science and Google Scholar databases by following a systematic search strategy (Appendices). Articles published in only English language between January 1983 and March 2016 were considered.

PATHOGENIC LINKAGE BETWEEN APS AND CNS

Although the complete pathogenic mechanisms of the abnormal neurological manifestations of APS remain unclear, a summary of the information from a total of 12 *in vivo* studies (between 1997 and 2015) is provided in Table **1**. This information indicates the involvement of aPLs and the activations of different inflammatory mediators. Additionally, positive or elevated titers of LA, aCL (IgG and/or IgM) or anti-β2GPI (IgG and/or IgM) have been observed in almost all of the neurological manifestations exhibited by patients with PAPS, SAPS or CAPS (Table **2**). In addition to the postulated pathogenic contribution of aPLs, different types of thrombotic events, including TIA [20, 30, 31], cardiac valve thickening or dysfunction [32], the presence of livedo reticularis [33] and rheumatic fever (RF) [11, 34], have also been confirmed to contribute to the neurological manifestations of APS in the presence of diverse types of aPLs. In contrast, the presence of aPLs without any underlying neuroimaging findings has been confirmed in some studies [9, 35, 36]. Taken together, these findings indicate that the presence of aPLs and/or thrombotic events with other underlying pathogenic conditions are likely to be responsible for the development of different types of abnormal neurological features in APS patients.

NEUROLOGICAL DISORDERS/MANIFESTATIONS IN APS

1. Headache and Migraine

Headache is one of the prominent neurological complaints of patients with APS [37]. In 2014, Zhu *et al*. [38] observed that among the neurological features of APS patients (n=16), the incidence of headache was significantly ($p<0.05$) elevated compared with the rheumatologic features governing APS (n=35). A 43-year-old woman with CAPS from Afghanistan presented with a severe headache that she described as the 'worst headache of her life' upon admission to the emergency department [39], and another 22-year-old African American woman with APS exhibited headache associated with bilateral vision loss [40]. These scenarios confirm the pathogenic links between APS and headache.

According to the 'Euro-Phospholipid Project', migraine is the most frequent (20.2%) neurologic manifestation of APS patients [41]. During the diagnoses of Latin American APS patients, Garcia-Carrasco *et al*. [42] observed migraine in 25% of the patients. Migraine has been addressed as one of the most common 'non-criteria' neurologic features of APS [43] and has a higher prevalence in females [44]. Migraine was one of the main manifestations reported in a 14-year retrospective cohort study of PAPS (n=128) and was present in 40% of the patients. A retrospective study (n=428) established a significant ($p<0.05$) association between the presence of aPLs and migraine [45], but no significant association was established between aPLs and migraine-discordant monozygotic twins (214 individuals) [46]. However, a comparative case study [24] of migraineurs (n=284) revealed that those who suffered from migraine (with or without aura) had a significantly higher prevalence ($p=0.0004$) of aPL positivity (LA, IgM aCL or anti-β2GPI) than those who did not, and anti-β2GPI was the most

Table 1. Animal models investigating the pathogenesis of neurological manifestations in APS.

No.	Animal (Sex)	Model	Aim of the experiment	Neurological Tests*	Outcome/Prediction	Year, References
1	Mice (Female)	Balb/C	To identify if structural alterations of hippocampal neurons are associated with the neurological symptoms of APS	Staircase test and Y-maze alternation test	Increased antiphospholipid antibody (aPL) titers presented with abnormal behavior and impaired short term memory in addition to reduction of dendritic complexity of hippocampal CA1 neurons	2015, [129]
2	Mice (Female)	Balb/C	To identify whether the observed behavioral features are dependent on a critical aPL concentration	Staircase test	High levels of aPLs are required for neuropsychiatric manifestations in APS	2014, [130]
3	Mice (Female)	C57BL/6	To observe the interactions between genetically and autoimmune-mediated coagulopathies in APS	Staircase, elevated plus-maze and swim T-maze tests	The gene associated with coagulopathies increase the risk of developing coagulation-targeted autoimmune responses and aPL antibody level contributes to neurodegeneration	2013, [131]
4	Mice (Female)	C57B6/SJL	To elucidate the neurodegenerative pathological processes associated with APS	Staircase test, swim T-maze tests	Both APP genotype and increased level of aPLs are risk factors to development of Alzheimer's disease in APS	2011, [132]
5	Mice (Female)	Balb/C	To explore the behavioral alterations in APS due to the intracerebroventricular (ICV) administration of whole-serum with IgG aPLs	Staircase test	IgG and/or other serum components may be associated with the neurological manifestations of APS	2009, [133]
6	Mice (Female)	Balb/C	To assess the association of thrombotic and inflammatory perivascular factors and standard APS therapies (enoxaparin and aspirin) with CNS manifestations in APS	Staircase test	Both inflammation [via elevated tumor necrosis factor-α (TNF-α) and prostaglandin E (PGE)] and thrombosis (via low levels of intrinsic brain thrombin inhibitors) in the brain are associated with brain dysfunction in APS and enoxaparin attenuates behavioral alteration better than aspirin	2008, [134]
7	Rat (-)	Sprague-Dawley	To elucidate whether there are β_2GPI alike proteins in rat brains	None	Histidine-rich glycoprotein (HRGP) is 68.0% similar with β_2GPI and therefore it may be involved with the neurological features of APS	2007, [135]
8	Mice (Female)	Balb/C	To explore the pathological processes underlying neurological dysfunctions in APS	None	Thrombotic occlusion of capillaries in combination with mild inflammation may be associated with APS neurological defects	2004, [136]
9	Mice (Male)	C3H	To investigate the pathogenic role of aPL by intracerebroventricular administration of IgG	Swim maze	aPLs which gain access to the CNS may play a direct role in the pathogenesis of neurological manifestations of APS	2003, [137]
10	Mice (Female)	Balb/C	To elucidate whether the production of antibodies against complex of phospholipids and β_2GPI exerts any neurological manifestations in APS	T-maze tests	Increased antibodies against negatively charged phospholipids and β_2GPI may be associated with neurological impairments in APS	2002, [138]
11	Mice (Female)	Balb/C	To examine the aPL-mediated behavioral changes in APS	Staircase test	aPL may have a crucial pathogenic role in the emergence of diverse behavioral deficits in APS	2001, [139]
12	Mice (Female)	Balb/C	To elucidate the mechanism underlying the neurological changes associated with APS	Open field test and rotarod treadmill test	aPLs are probably involved in the neurological and behavioral APS defects	1997, [140]

*Staircase test: Hyperactivity and Anxiety; Y-maze alternation test: Short term memory, general locomotor activity and stereotypic behavior and spatial memory; Swim T-maze test: Cognitive function; Elevated plus-maze test: Behavioral features of anxiety; Open field test: Emotionality; Rotarod treadmill test: Performance test (evaluating balance, grip strength and motor coordination).

Table 2. Association of aPLs with neurological manifestations of APS.

Antiphospholipid Antibody		Neurological Manifestations		References
LA		i.	Migraine	[24]
		ii.	Bipolar disorder	[9]
		iii.	Dementia	[10]
		iv.	Chorea	[11, 73]
		v.	Psychosis	[36, 90]
		vi.	Cognitive Impairment	[14]
		vii.	Tourette's Syndrome	[27, 28]
		viii.	Parkinsonism	[16, 101, 106]
		ix.	Dystonia	[17]
		x.	Transient Global Amnesia	[15, 112]
		xi.	Leukoencephalopathy	[118]
aCL	Undefined (IgG or IgM)	i.	Dementia	[10, 62]
		ii.	Chorea	[73]
		iii.	Multiple Sclerosis	[25, 26, 85]
		iv.	Psychosis	[91]
		v.	Cognitive Impairment	[14]
		vi.	Leukoencephalopathy	[118]
	IgG	i.	Bipolar disorder	[35]
		ii.	Dementia	[65]
		iii.	Chorea	[11]
		iv.	Epilepsy	[79, 80]
		v.	Psychosis	[36, 90]
		vi.	Cognitive Impairment	[96]
		vii.	Tourette's Syndrome	[27, 28]
		viii.	Parkinsonism	[16, 101, 103, 106]
		ix.	Dystonia	[17, 104, 108, 109]
	IgM	i.	Transient Global Amnesia	[112]
		ii.	Leukoencephalopathy	[115]
		iii.	Migraine	[12, 24, 47]
		iv.	Chorea	[11]
		v.	Psychosis	[13]
		vi.	Parkinsonism	[16, 103, 106]
		vii.	Dystonia	[104, 109]
		viii.	Leukoencephalopathy	[115]
Anti-β2GPI	Undefined (IgG or IgM)	i.	Migraine	[24]
		ii.	Chorea	[11, 12]
		iii.	Multiple Sclerosis	[26]
		iv.	Psychosis	[36]
	IgG	i.	Epilepsy	[12]
		ii.	Dystonia	[17]
	IgM	i.	Epilepsy	[12]
		ii.	Multiple Sclerosis	[25, 84]
		iii.	Dystonia	[17]
		iv.	Leukoencephalopathy	[116]

(Table 2) Contd….

Antiphospholipid Antibody		Neurological Manifestations		References
Undefined aPLs (LA and/or aCL and/or anti-β2GPI)	Undefined (IgG or IgM)	i.	Migraine	[45]
		ii.	Transverse Myelitis	[56, 57]
		iii.	Dementia	[61]
		iv.	Chorea	[37]
		v.	Epilepsy	[67]
		vi.	Multiple Sclerosis	[83]
		vii.	Psychosis	[87]
		viii.	Cognitive Impairment	[93]
		ix.	Obsessive Compulsive Disorder	[29]
		x.	Leukoencephalopathy	[116]

LA: Lupus Anticoagulant; aCL: Anticardiolipin Antibody; β2GPI: β2glycoprotein I; IgG: Immunoglobulin G; IgM: Immunoglobulin M; aPLs: Antiphospholipid Antibodies.

prevalent antibody (80.8% of the patients; p=0.004). Another recent report (2013) confirmed the prevalence of aPLs among migraineurs is greater than that among non-migraineurs. aPLs was predominantly detected in PAPS patients with IgM aCL (p=0.017) and not in those with LA (p=0.014) [47]. A prospective study of APS patients (n=333) revealed a significant association (p=0.016) between IgM aCL and migraineurs with PAPS [12]. Interestingly, severe migraine has been observed in the majority of APS patients with thrombotic events, TIAs or stroke [20, 30]. A retrospective study (n=284) revealed a significant (p=0.002) association between cardiac valve thickening or dysfunction and migraine [32]. Toubi *et al*. [33] observed a highly significant (p=0.002) association of migraine with livedo reticularis, which is one of the 'non-criteria' manifestations of APS.

Therefore, additional experimental studies are required to investigate whether there are any thromboembolic links between APS and headache or migraine that are mediated via elevated levels of aPLs with the goal of clarifying whether migraine or headache is one of the early predictors of APS diagnosis.

2. Bipolar Disorder (BD)

BD (also known as manic-depressive illness) is a mental disorder that is characterized by periods of elevated mood and periods of depression that affect the level of energy, irritability and the ability to function. Yearly, approximately 1% of the American population (more than 2 million) is diagnosed with BD (age ≥18) [48, 49]. To the best of our knowledge, there are only two reported cases of bipolar disorder in APS patients. In 2008, the first case of BD was described by Raza *et al*. [9] in a 31-year-old male who had a pulmonary embolism and recurrent LA positivity. He experienced manic episodes, cognitive problems, including poor focus and concentration, and significant psychosocial stress with family histories of both thrombotic events (the patient's father and uncle died of fatal cerebrovascular ischemia and a massive pulmonary embolism, respectively) and BD (the patient's father had bipolar disorder). The second case of non-familial BD was reported in 2012 by Avari *et al*. [35]. This case involved a 61-year-old male APS patient who experienced two episodes of deep vein thrombosis and persistent IgG aCL elevation. In addition to the depressive episodes, mania was a prominent and high scoring (30) psychological symptom as assessed with the Folstein mini mental state examination (range: 0-30). Neither of the cases presented any signs of cerebrovascular thrombotic episodes on neuroimaging findings of CT scans or MRIs, which indicated that the aPLs may directly contribute to the development BD without promoting a hypercoagulable state.

3. Transverse Myelitis (TM)

TM is a neurological disorder that is characterized by thickening of spinal cord (T5-T8 areas) due to inflammation across the white matter. Inflammation of the spinal cord causes damage to the myelin sheath (the fatty insulating substance that covers nerve cell fibers) that consequently disrupts the communications of the spinal nerves with the rest of the body and manifests as dysfunctions of the motor and autonomic nerves, weakness, muscle paralysis and sensory abnormalities [50]. Although 60% of TM patients are idiopathic, the presences of bacterial/viral infections, systemic autoimmune disorders and aPLs have been found to be associated with the development of TM [18, 51, 52]. In 1985, the co-occurrence of TM and APS was first described in a 45-year-old women [53]. Although TM is commonly observed in SLE and Sjogren's syndrome [54], the prevalence of TM in APS is <1.0% [6]. Among the different types of APS, TM was found to predominate in PAPS (64.3%) with a mortality rate of approximately 7% [55]. Because the prevalence of aPLs is as high as 73% in patients with TM [56], it can be postulated that aPLs provide a considerable pathogenic contribution to the development of immune-mediated inflammatory response against the myelin sheaths of the spinal cord. Some studies have reported direct interactions between aPLs and the phospholipids of the spinal cord [57, 58]; however, there is no firm conclusive evidence of this pathogenic linkage.

4. Dementia

Dementia is a broad term for a set of neurologic symptoms that are associated with loss of memory, decline

in mental abilities and emotions, difficulties in problem solving, impaired thinking abilities and language problems [59, 60]. Although dementia is not a clinical criterion of APS, according to Gomez-Puerta *et al*. [10], dementia has been observed in 37% of APS patients who are positive for LA and aCL. Mosek *et al*. [61] observed a significantly (p=0.03) elevated aPL titer in patients with dementia (n=87) compared with healthy controls (n=67). A prospective study (n=218) conducted by Juby *et al*. [62] revealed that there a significant (p=0.02) association between the presence of aCL and dementia. Of a group of PAPS patients (n=23), 56% were diagnosed with dementia [63] according to the Hachinski Ischemia Score (HIS). Moreover, prolonged persistent exposure to aPLs and aging have been found to be significant (p=0.01) risk factors for the development of dementia in APS patients. Duval *et al*. [64] presented a seronegative case of an APS-like syndrome in a 51-year-old female with dementia (Mattis dementia rating scale score: 112 out of 144) without the presence of any of the three aPLs. A case report in 2011 [65] described the co-existence of dementia with ataxia and parkinsonism in a 54-year-old male patient with APS with and elevated titer of IgG aCL. The patient had been suffering from depression and memory problems for six months. Neuropsychological tests revealed significant impairments in verbal fluency, verbal and visual learning and memory, information processing speed, sustained and rapid alternating attention, confrontational naming, abstract reasoning and visuoconstruction. All of these symptoms suggested dysfunction of the frontal lobe. Although brain T2-weighted MRI images revealed non-specific hyperintensities in small regions of white matter, no hippocampal atrophy was visualized. Although some studies have found high titers of aPLs in patients with dementia, the influence of aPLs in the pathogenesis of dementia is not yet conclusive. Therefore, *in vivo* studies are recommended to elucidate the linkage between aPLs and dementia.

5. Chorea and Other Movement Disorders

Chorea is a group of neurological movement disorders that is primarily characterized by involuntary, irregular and non-stereotyped movements of the limbs, trunk, neck and face [66]. Chorea can be hereditary (*i.e*., Huntington's disease) or non-hereditary as in autoimmune disease-mediated cases (*i.e.,* APS and SLE) [67]. Chorea is an unusual neurologic manifestation of APS patients. According to the Euro-Phospholipid Project [41], the prevalence of chorea in APS is approximately 1.3%. According to a 10-year literature review (1985-1995), cerebral infarction is observed in 35% patients with APS and chorea [68]. Several studies have established a strong association between the presence of aPLs and chorea in the presence of RF [21, 37, 67, 69]. Chorea was the predominantly observation in 63.6% of case reports with co-existing APS and RF [11]. According to a systematic review [11], in patients with APS and RF, IgM aCL is most commonly found (71.4%) followed by anti-β2GPI (66.6%), LA (62.5%) and IgG aCL (37.5%). A recent (2012) [34] cross-sectional study with Brazilian PAPS patients (n=88) identified four patients with chorea associated with RF and thrombocytopenia. Acute severe chorea was reported in a 20-year-old Swedish PAPS woman with elevated levels of aCL, a prolonged partial thromboplastin time (PTT) and thrombocytopenia [70]. Pediatric chorea has been observed in three PAPS patients (aged between 5 and 16) [71]. According to the Pediatric APS registry, chorea is one of the most common (4%) non-thrombotic neurological manifestations [72]. Dale *et al*. [73] observed chorea in 66.6% of the Australian female pediatric patients (aged between 8 and 14) in the presence of both LA and aCL. Because positivity for aPLs has been found to be associated with chorea co-existing with APS, RF and SLE [74], a pathogenic linkage between RF and APS in the development of chorea is anticipated. Recently (2016), Schwarzbach *et al*. [75] described a 38-year-old female patient with cryopyrin-associated periodic syndrome co-occurring with APS and severe chorea in addition with two chronic inflammatory brain white matter lesions. The patient had an elevated aCL titer aCL and total protein level and anti-nuclear antibody (ANA) (1:160) positivities. Her neurologic symptoms were almost completely resolved with interleukin-1β (IL-1β) blockade with anakinra in addition to the use of conventional immunosuppressive drugs (prednisolone and hydroxychloroquine). According to the findings of a prospective study (n=333), chorea is significantly associated with anti-β2GPI (p=0.041) and with patients with SAPS (p=0.001) [12]. A case of an 89-year-old woman who presented with chorea and a high IgM aCL titer (45 MPL) in the absence of any clinical features of APS was recently reported [76]. Based on the above discussion, the predominance of chorea is clear in patients with APS. Interestingly, RF has been observed to co-exist with chorea in the presence of either APS or aPLs, which supports the notion of the common pathogenic involvement of aPLs, RF and chorea.

6. Epilepsy

Epilepsy is a group of neurological disorders that is characterized by unpredictable recurrent seizures. Epileptic seizures are the result of excessive and abnormal cortical nerve cell activity in the brain that causes strange sensations, emotions or behavior, violent muscle spasms and even the loss of consciousness [77, 78]. A strong association has been established between aPLs positivity and epilepsy. In different studies [12, 31, 67], epilepsy has been observed to occur at a significantly (p<0.05) higher frequency in SAPS (especially SAPS associated with SLE) than in PAPS. According to the latest data from the Euro-Phospholipid Project, epilepsy was present in 7% of 1000 APS patients [41], and epilepsy was the second-most frequent non-thrombotic neurologic manifestation. The prevalence of epilepsy was observed to be as high as 8.6% in a multicenter European cohort (n=538). This prevalence is nearly 20-fold greater than the prevalence of epilepsy in the general population [31]. In the same study, the prevalences of epilepsy were significantly elevated in young (26.5 ± 10.4, p<0.05), female (82.6%) and SLE-associated APS (50%) patients. A recent (2013) [12] prospective study (n=333) revealed a strong significant associations of high levels of IgM (>100 PLU/ml; p=0.00001) and IgG (>100 PLU/ml; p=0.035) with anti-β2GPI antibody levels in patients with epilepsy with PAPS and SAPS, respectively. Eriksson *et al*. [79] observed a significantly elevated (p=0.01) prevalence IgG aCL-positivity in a Finish pediatric (mean age 9 years)

epileptic cohort (n=50) compared with healthy children (n=20). Therefore, elevated aPL levels are postulated to be strongly associated with the pathogenesis of epilepsy. In a multi-center cohort (n=538), Shoenfeld *et al*. [31] observed that APS patients with epilepsy exhibited significantly elevated frequencies of focal ischemic events (54.3%, $p<0.0001$) and cardiac manifestations (43.5%, $p<0.01$). Therefore, it has been concluded that APS patients with thromboembolic events are predisposed to developing epilepsy. Additionally, Krause *et al*. [32] observed a significant ($p<0.02$) association between cardiac vegetation and epilepsy in a cohort (n=284) of Israeli patients with APS. A Finnish population-based (n=960) cross-sectional study established a significant association between IgG aCL and a prolonged history of epilepsy (≥30 years) with an increased frequency of epileptic seizures (≥1 seizure/month) [80]. Additionally, these authors concluded that ANA (a laboratory criterion for SLE) is more frequent among patients who experience ≥1 seizure per month [80], and this finding might be one of the explanations for the greater prevalence of epilepsy among SLE-associated APS cases [12, 67].

7. Multiple Sclerosis (MS)

MS is the most common immune-mediated neurodegenerative disease and is characterized by multifocal areas of myelin loss followed by axonal degeneration and progressive neuronal loss resulting in weakness, poor limb coordination, fatigue, vision problems, numbness and even paralysis [81, 82]. In a prospective case-control study [25] of MS patients (n=85), significantly elevated IgM anti-β2GPI levels ($p<0.05$) were detected in 20% of patients, and a significant correlation ($p=0.029$) was observed among patients with co-existing aCL but not among healthy controls. Another prospective case-control study [26] observed aPLs positivity in 57.1% of MS patients (n=49) among whom aCL and anti-β2GPI positivity had been established in 18% and 10%, respectively. A recent (2014) observational study [83] revealed that during the relapse phase of MS patients (n=100), the frequency of aPL (LA, aCL or anti-β2GPI) positivity was significantly elevated ($p<0.0001$) compared to the frequency in healthy controls (n=60). Bidot *et al*. [84] observed both higher levels of IgM auto-antibodies, including anti-β2GPI (82%), and greater proportions of patients who were positive for these antibodies among exacerbated MS patients (n=17), which further confirms the association of aPLs with the severity of MS. In another study, the presence of aCL was significantly elevated ($p=0.012$) among secondary-progressive multiple sclerosis (SPMS) patients compared with relapsing-remitting multiple sclerosis (RRMS) patients [85]. These reported co-existing patterns of aPLs and MS suggest that they might share a pathological linkage that confers the clinical manifestations of APS patients.

8. Psychosis

Psychosis is a serious mental disorder that is characterized by the loss of contact with the reality via episodes of delusions (false thoughts) and/or hallucinations [86]. In 1994, Kurtz *et al*. [87] elucidated the association between aPLs and psychosis in a 50-year-old woman. He postulated that psychotic symptoms could be a potential initial indicator of the developing clinical features of APS. Recently (2015), a 25-year-old female Turkish PAPS patient presented with psychotic symptoms that included auditory hallucinations (hearing voices providing commentary or voices in discussion with one another), excessive talking, sleeplessness, persecutory delusions (she thought that her mother-in-law would harm her) and agitation in the presence of IgM aCL and an infarction in the caudal part of the corpus callosum [13]. A 23-year-old Spanish girl with PAPS was reported to have two experienced delusional episodes of psychosis in addition to abnormal choreiform and hemiballistic movements [88]. Another case report confirmed the presence of psychosis (persecutory delusions, visual and auditory hallucinations) and catatonia in a 28-year-old women with APS [89]. A 9-year-old Saudi girl developed psychotic illness that included drowsiness, abnormal behavior, confusion and hallucinations in the presence of LA positivity and elevated aCL (IgG 86.9 GPL/mL) and anti-β2GPI (256.5 U/L) levels without any thrombotic manifestations [36]. Although her psychotic symptoms improved with the use of antidepressants and antipsychotic drugs, she developed a right axillary vein thrombosis five months after stopping aspirin treatment (100 mg/day). Schwartz *et al*. [90] detected high titers of aPLs in approximately 32% of untreated psychotic patients (n=34) (approximately in 24% among the IgG aCL patients, $p<0.02$; approximately 9% among the LA patients). In a study of 100 psychotic patients (exhibiting hallucinations and/or delusions), aCL was detected in the sera of 8% of the patients, and the cerebrospinal fluid (CSF) was positive for aPLs in 6% of these patients [91]. Hence, the association between the presence of aPLs and psychosis is quite clear. However, whether the thrombotic events observed in psychotic patients were aPL-induced is a matter of debate.

9. Cognitive Impairment

Cognitive impairment can occur independently without any known thrombotic manifestation in the brain, such as stroke. The common manifestations of cognitive dysfunction include difficulties learning, memorizing and problem-solving and impaired attention, perception and concentration [92]. There are only a few studies that have addressed cognitive performance in APS. Jacobson *et al*. [93] observed significant cognitive impairments ($p<0.01$), including impairments in verbal learning and memory, working memory, visuospatial abilities and complex executive functioning, in a group of aPL-positive subjects (n=27) compared with healthy controls (n=27). In another cohort of patients with APS (n=60; 39 PAPS and 21 SAPS), the cognitive alterations included impairments of complex attention and verbal fluency was observed in 42% of APS patients ($p=0.005$) [94]. Aharon-Peretz *et al*. [95] observed mild cognitive deficits in 93% of APS patients. Neuropsychological dysfunction was found in approximately 23% of the subjects who were positive for IgG aCL despite the lack of any anatomical abnormalities on MRI [96]. Fukui *et al*. [14] reported a case of SAPS (positive LA and aCL) that co-existed with multiple cognitive impairments. Cognitive impairments are observed in patients with APS without any thrombotic events; therefore, aPLs might exert a

direct action on the development of the symptoms of cognitive impairment.

10. Miscellaneous

i. Tourette's Syndrome (TS)

TS is a neurobehavioral disorder that usually begins during childhood or adolescence and is characterized by chronic vocal and/or motor tics [97]. For the first time in 1994 [27], the presence of aPLs (LA and IgG aCL) was confirmed (44.4%) in a group of children (12.0 ± 1.8 years) with TS. Later in 2008 [98], a 25-year-old Spanish male presented with TS along with APS (stroke was a clinical feature and LA was a laboratory feature) in addition to epileptic seizures. The patient responded positively to treatment with levetiracetam (an antiepileptic drug). However, in another study, the presence of aPLs was described as an epiphenomenon because Singer *et al*. [28] observed LA and IgG aCL positivity in only 5% and 16%, respectively, of the non-APS children and adolescents with TS (n=21). Therefore, the influence of aPLs on the development of TS is still debatable.

ii. Parkinsonism

Parkinsonism is a group of neurological disorders that are characterized by bradykinesia, postural instability, resting tremor and cogwheel rigidity. Despite the fact that nigrostriatal hypodopaminergism is the fundamental basis of parkinsonism, the pathogenic causes of >80.0% Parkinson's patients are believed to be idiopathic [99]. Parkinsonism can be caused by systemic autoimmune diseases, such as SLE and/or APS [100]. Parkinsonism was found to co-exist with APS in a 51-year-old Taiwanese woman who presented with elevated levels of both IgG and IgM aCL and LA positivity [16]. Two female APS patients aged 56 and 44 years with high IgG aCL (30.9 GPL and 62.2 GPL, respectively) levels and LA positivity were found to have parkinsonism [101, 102]. Additionally, three aPL-positive male patients aged 50 years (IgG aCL 30.0 GPL and IgM aCL 35.0 MPL) [103], 60 years (IgM aCL 80.0 MPL) [104] and 53 years (IgG aCL 62.0 GPL) [105] were confirmed to have parkinsonism. Chen *et al*. [106] designated LA as neurotoxin that possibly favors dopamine-related movement disorders, such as parkinsonism, because these authors observed co-occurrence of parkinsonism and LA in patients with PAPS.

iii. Dystonia

Dystonia is a neurological movement disorder that is characterized by twisting and repetitive movements or abnormal postures due to nonstop, repetitive and patterned muscle contraction [107]. A 79-year-old woman with a diagnosis of PAPS presented with a left foot focal dystonia associated with LA positivity, a high IgG aCL titer (>91 GPL) and a high anti-β2GPI titer (IgG 95.5 U/mL and IgM 45.2 U/L) [17]. A pediatric case (a 5-year-old boy) of dystonia of the right upper extremity presented with high titers of both APS-mediated antibodies [IgG aCL (75 GPL) and IgA aCL (85 APL)] in combination with SLE-associated autoantibodies [(ANA, anti-double stranded (ds) DNA and anti-Smith (Sm) antibodies)] [108]. Dystonic posturing of the right hand involving all fingers (in addition to severe pain and continuous spasms) was observed in a 60-year-old male PAPS patient with an increased IgM aCL titer (80 MPU) [104]. A retrospective study of patients (n=13) with acquired hemidystonia since childhood revealed that 33.3% had PAPS with IgG and/or IgM aCL positivity [109]. Therefore, the pathogenic linkage between aPLs and the development of dystonia is quite clear.

iv. Transient Global Amnesia (TGA)

TGA is a neurological disorder that is characterized by a temporary but almost complete disruption of short-term memory, difficulty accessing older memories and the inability to acquire new information [110]. There are only a few reported cases of amnesia in patients with APS. A 45-year-old woman with PAPS was described as having TGA with the presence of LA in addition to the clinical manifestations of ischemic events caused by multiple arterial thromboses [15]. TGA has been observed to exist at significantly higher frequency (p=0.004) in a Latin American mestizo population with APS (n=100) [111] than the Euro-Phospholipid cohort (n=1000) [6]. Persistently high titers of aCL (IgG 90 GPL) and LA positivity have been observed in a 52-year-old Spanish man suffering from TGA [112].

v. Obsessive Compulsive Disorder (OCD)

In 1999, OCD was observed for the first time in a 7-year-old Chinese-American girl with an elevated aPLs level (IgG 72) [29]. Later, the co-existence of PAPS and OCD was confirmed in a 15-year-old Belgian boy in addition to an infarction in the caudate nucleus of the basal ganglia [113]. Therefore, the presence of a hypercoagulative state and/or aPLs can be two of the causes for OCD in patients with APS.

vi. Leukoencephalopathy

Leukoencephalopathy is a neurodegenerative disorder that is characterized by degeneration of the white matter in the brain with typical clinical manifestations that include decreased alertness, visual loss, seizures, headache and altered mental functioning [114]. An Italian male PAPS patient with prolonged APTT and persistently high aCL titers (both IgG and IgM) presented with a posterior white matter hypodensity [115]. Another 32-year-old Italian woman exhibited leukoencephalopathy co-existing with PAPS [in addition to venous thrombosis, a high titers of IgM aPL (63.4 MPL) and IgM anti-β2GPI (57.5 mg/dL)] [116]. Leukoencephalopathy has also been observed in patients with CAPS with elevated aPLs titers including LA and aCL [117, 118]. Therefore, aPLs might be involved in the degeneration of the brain via direct interactions with the white matter.

TREATMENT OF THE NEUROLOGIC MANIFESTATIONS OF APS PATIENTS

To date, there are no evidence-based guidelines available for the treatment of APS patients with neurological manifestations. Immunosuppression and/or immunomodulation therapies, antidepressants, antipsychotic, antiepileptic drugs and steroids are commonly used treat the CNS manifestations of APS in combination with secondary

prophylaxis (anticoagulation and/or platelet anti-aggregator (Fig. **1**)).

A complex migraine phenomenon was resolved in an APS patient with a subtherapeutic international normalized ratio (INR; 1.22 - 1.95) via the administration of vitamin K-dependent anticoagulant therapy (warfarin) maintaining the target INR between 2.5 and 3.5 [119]. Low-molecular weight heparin (LMWH) completely abolishes headaches in 90.5% of APS patients [120]. Anticoagulant therapy is a potential treatment for severe headache and migraine [121, 122].

A patient exhibiting chorea with an aPLs level was treated with aspirin (81 mg/day) for 3 months and reported no significant change in the intensity or pattern of chorea [76]. However, in another aPL-elevated patient, chorea disappeared completely following nine months of combined treatment with aspirin (75 mg/day) and risperidone (an antipsychotic medication) [123]. A patient suffering from aPL-induced TM recovered due to a combined therapy with high-dose steroids and LMWH [124]. A low-dose steroid has also been effective when used in addition to an oral anticoagulant therapy against the worsening of TM [125]. Additionally, acute psychotic symptoms disappeared in an aCL-positive patient following treatment with 20 mg/day olanzapine (an antipsychotic drug) [13].

The psychiatric manifestations of a pediatric APS patient were significantly improved following a combined treatment with antipsychotics, antidepressants, aspirin (100 mg/day) and hydroxychloroquine (100 mg/day) [36]. Psychotic symptoms were abolished in another APS patient following a combined treatment with anticoagulation, haloperidol, venlafaxine (an anti-depressive drug) and immunosuppressive drugs (azathioprine and prednisolone) [89]. Furthermore, in another study, in the absence of any psychotropic medication, an anticoagulant drug (warfarin) alone was able to elicit the remission of the psychotic symptoms of an APS patients [126]. In a recent (2014) retrospective study, all of the APS patients (n=16) with neurologic manifestations (headache, epilepsy and cognition impairment) were administered anticoagulant therapy (*i.e.,* warfarin), and proportions of the patients were treated with a platelet anti-aggregator (*i.e.,* aspirin), immunosuppressive drugs (*i.e.,* azathioprine) or steroids (*i.e.,* glucocorticoids), and these treatments resulted in the recoveries of 94% of the patients' from the neurological symptoms. In another study, a female PAPS patient with epileptic seizures and psychosis was treated with phenytoin (an antiepileptic drug, 100 mg, twice daily) and quetiapine (an antipsychotic drug, 300 mg/daily) in addition to LMWH and acenocoumarol (an anticoagulant) [127]. This combined therapeutic strategy resulted in significant improvements in her seizures and psychosis. APS patients with bipolar disorder was treated with both warfarin (15 mg) and lamotrigine (an anticonvulsant or antiepileptic drug, up to 200 mg/day), which resulted in significant improvement in the depressive symptoms [35]. Memory functions have also been found to be clinically improved in APS patients treated with heparin [120]. The neurological features of MS were improved in a group of patients with aPLs positivity (n=11) following

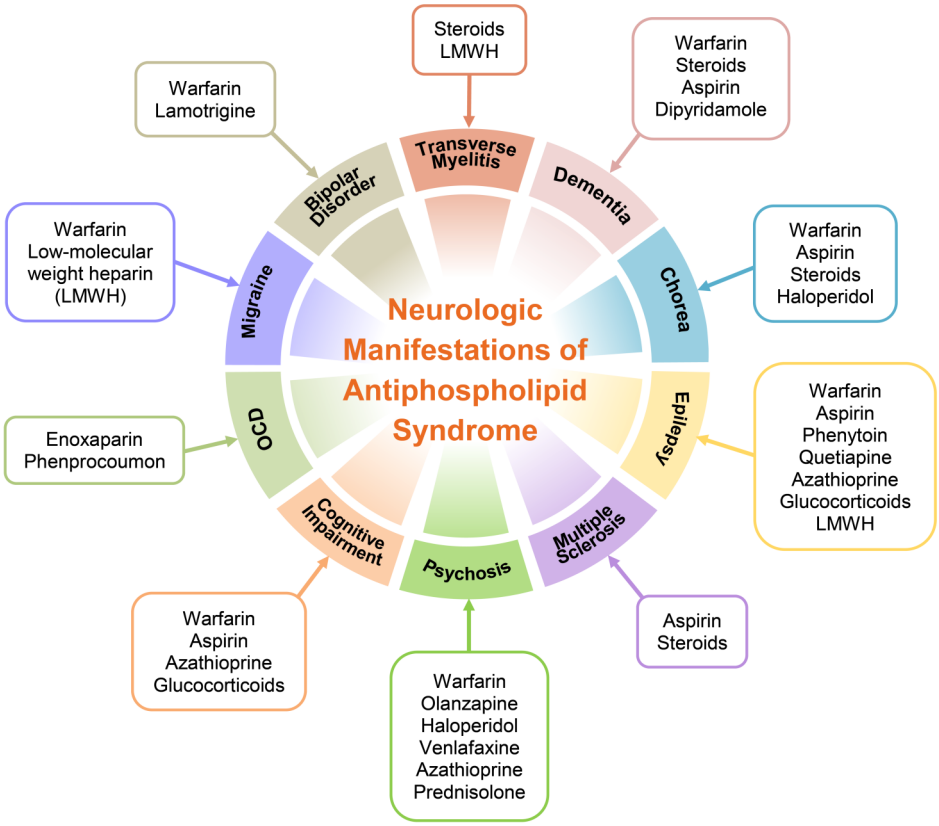

Fig. (1). Successful treatment strategies of APS-associated neurologic manifestations.

treatment with aspirin (100 mg/day) and the occasional use of steroids [128].

FUTURE DIRECTIONS AND CONCLUSION

To elucidate the group of the most frequently occurring neurological manifestations in APS patients, observational, retrospective or prospective studies with large cohorts patients should be conducted. The associations of aPLs with the pathogeneses of developing CNS manifestations remain matters of open debate. Therefore, additional precisely designed animal model studies are warranted to understand the pathogenic linkages between aPLs and the neurologic symptoms observed in patients with APS. Genetic studies of APS patients with neurological disorders can be another potential area of research that could elucidate the genetic and molecular linkages between APS and CNS. Additionally, a systematic review and meta-analysis is warranted to reveal whether the presence of aPLs is a causative factor in the development of neurologic manifestations.

According to a recent report (2014), the misdiagnosis rate of neurologic APS is very high (87.5%) [38]. Therefore, the formation of a multi-disciplinary team consisting of rheumatologists, neurologists and hematologists is recommended to reach accurate diagnoses and achieve proper patient management. Although the role of the use of anticoagulants alone for the treatment of psychiatric symptoms remains controversial, it has not been properly investigated and may be an area for further studies. In the meantime, psychiatric disorders in APS patients are treated with standard psychiatric therapy regimens for symptom management. Randomized controlled trials may help clarify the roles of anticoagulants, platelet anti-aggregators, antidepressants, antiepileptics, antipsychotics and immunosuppressive drugs in the treatment of different neurological features of APS.

LIST OF ABBREVIATIONS

aCL	=	Anticardiolipin Antibody
Anti-β2GPI	=	Anti-β2glycoprotein I
aPLs	=	Antiphospholipid Antibodies
APS	=	Antiphospholipid Syndrome
BD	=	Bipolar Disorder
CAPS	=	Catastrophic Antiphospholipid Syndrome
CNS	=	Central Nervous System
LA	=	Lupus Anticoagulant
MS	=	Multiple Sclerosis
OCD	=	Obsessive Compulsive Disorder
PAPS	=	Primary Antiphospholipid Syndrome
SAPS	=	Secondary Antiphospholipid Syndrome
SLE	=	Systemic Lupus Erythematosus
TGA	=	Transient Global Amnesia
TIA	=	Transient Ischemic Attack
TM	=	Transverse Myelitis
TS	=	Tourette's Syndrome

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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APPENDICES

Search Strategy

(Antiphospholipid Syndrome **OR** Anti Phospholipid Antibody Syndrome **OR** Anti Phospholipid Syndrome **OR** Antiphospholipid Antibody Syndrome **OR** Anti-Phospholipid Antibody Syndrome **OR** Antiphospholipid Antibody Syndromes **OR** Anti-Phospholipid Syndrome **OR** Hughes Syndrome **OR** antiphospholipid antibody **OR** antiphospholipid antibodies **OR** anti-phospholipid antibody **OR** anti-phospholipid antibodies **OR** aPL **OR** aPLs **OR** anticardiolipin antibody **OR** anticardiolipin antibodies **OR** anti-cardiolipin antibody **OR** anti-cardiolipin antibodies **OR** aCL **OR** aCLs **OR** lupus anticoagulant **OR** lupus anticoagulants **OR** LA **OR** anti beta2 glycoprotein 1 **OR** anti-beta2 glycoprotein 1 **OR** anti-beta2-glycoprotein 1 **OR** anti-beta-2-glycoprotein 1 **OR** β2GP1 **OR** β2-GP1 **OR** β-2-GP1 **OR** β2glycoprotein 1 **OR** β2-glycoprotein 1 **OR** β-2-glycoprotein 1) **AND** (Neurology **OR** Neurologic **OR** Neurological **OR** Headache **OR** Migraine **OR** Bipolar disorder **OR** Transverse myelitis **OR** Dementia **OR** Chorea **OR** Movement disorders **OR** Epilepsy **OR** Multiple sclerosis **OR** Psychosis **OR** Cognitive impairment **OR** Tourette's syndrome **OR** Parkinsonism **OR** Dystonia **OR** Transient global amnesia **OR** Obsessive compulsive disorder **OR** Leukoencephalopathy).

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