Neurologic Manifestations of the Antiphospholipid Syndrome

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Antiphospholipid syndrome is an important cause of neurologic morbidity. The clinical criteria for antiphospholipid syndrome include only cerebrovascular arterial and venous thrombosis, but many other neurologic manifestations have been associated with antiphospholipid antibodies (aPL). This review discusses the role of aPL in cerebrovascular manifestations and in some of the other neurologic manifestations commonly associated with these antibodies, as well as data pertaining to the pathophysiology of aPL-associated neurologic manifestations and treatment issues.

Introduction

The diagnosis of antiphospholipid syndrome (APS), also known as antiphospholipid antibody syndrome, requires an episode of arterial or venous thrombosis leading to tissue ischemia or recurrent fetal loss, as well as the presence of antiphospholipid antibodies (aPL) of moderate to high titer or a lupus anticoagulant (LA) on at least two occasions at least 12 weeks apart (Table 1) [1••]. APS is classified as primary if it occurs in individuals without systemic lupus erythematous (SLE) or some other connective tissue disease and secondary in individuals without these disorders. Primary and secondary APS are clinically indistinguishable [2]. In this paper, we review aPL-associated stroke as well as some of the many other neurologic manifestations listed in Table 2.

Pathophysiology and Pathogenesis

Antibodies to negatively charged phospholipids make up a large and heterogeneous family of autoantibodies with heterogeneous aPL disease-causing mechanisms. A variety of effects on platelets, coagulation proteins, and endothelial cells, including tissue factor upregulation, have been ascribed to aPL, making them not only serologic markers for APS, but also direct contributors to the development of thrombosis and other clinical manifestations. Evidence is emerging that aPL binding to phospholipid complexes on various cells including platelets and vascular endothelium also results in their activation through the Fc-gamma receptor. Campbell et al. [3] demonstrated the induction of a dose-dependent increase in the activation and aggregation of human platelets using aPL from patients with APS.

Passive and active immunization of normal laboratory mice with either aPL or anti–β_2 glycoprotein (GP)-1 results in the induction of an experimental APS, including thrombocytopenia, placental infarction and fetal loss, myocardial infarction, and neurologic dysfunction [4]. Normal mice immunized with viral protein fragments with β_2GP-1 sequence homology develop aPL and suffer intrauterine fetal death, spinal cord infarction, and thrombosis [5], suggesting that infection may well be the trigger for pathogenic aPL antibody production. A larger clot size with a longer time to dissolution is seen in mice treated with human aPL compared to control immunoglobulin G (IgG) using a pinch clamp injury model [6]. Taken together, these studies provide important evidence that antibodies to phospholipids and phospholipid-binding proteins like β_2GP-1 can cause thrombosis and other antibody-mediated clinical manifestations. Pierangeli et al. [7••] have shed some light on a possible mechanism for both cell activation by aPL and potential treatment strategies. The group discovered that intracellular signaling of the p38 mitogen-activated protein kinase (p38 MAPK) phosphorylation is stimulated by aPL, and that when reversed using p38 MAPK inhibitors, thrombosis manifestations are also inhibited [7••].

A "second hit" hypothesis has been postulated to explain how aPL might lead to thrombosis. This hypothesis proposes aPL induction of a prothrombotic state, in which thrombosis is triggered by an otherwise insufficient local trigger [8], explaining why patients with persistent serum autoantibodies display clotting events only occasionally and in the absence of detectable immunoglobulin deposits.

Neurologic Manifestations Associated with aPL

Ischemic stroke and aPL

Cerebral ischemic events in patients with aPL can occur in any vascular territory. A variety of cardiac valvular

Table 1. Classification criteria of antiphospholipid antibody syndrome

Clinical criteria
Vascular thrombosis
One or more clinical episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ. Thrombosis must be confirmed via imaging, Doppler studies, or histopathology, with the exception of superficial venous thrombosis.
Pregnancy morbidity
One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with normal fetal morphology documented by ultrasound or exam;
One or more premature births or a morphologically normal neonate at or before the 34th week of gestation because of preeclampsia or severe placental insufficiency; or
Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and exclusion of maternal and paternal chromosomal causes.
Laboratory criteria
aCL antibody of IgG and/or IgM isotype and measured by a standardized enzyme-linked immunosorbent assay for β_2GP1–dependent aCL or anti–β_2GP-1 of IgG and/or IgM isotype in blood, present in medium or high titer on two or more occasions at least 12 weeks apart.
LA present in plasma on two or more occasions 12 weeks or more apart and detected according to the guidelines of the International Society of Thrombosis and Hemostasis, in the following steps:
Demonstration of a prolonged phospholipid-dependent coagulation screening test (eg, aPTT, KCT, DRVVT, dPT, Textarin time)
Failure to correct the prolonged screening test by mixing with normal platelet poor plasma
Shortening or correction of the prolonged screening test by the addition of excess phospholipid
Exclusion of other coagulopathies as appropriate (eg, factor VIII inhibitor, heparin)

aCL—anticardiolipin; aPTT—activated partial thromboplastin time; dPT—dilute prothrombin time; DRVVT—dilute Russell viper venom time; GP—glycoprotein; IgG—immunoglobulin G; IgM—immunoglobulin M; KCT—kaolin clotting time; LA—lupus anticoagulant.
(*Data adapted from* Miyakis et al. [1••].)

Table 2. Neurologic syndromes associated with antiphospholipid antibodies

Cerebrovascular ischemia
Stroke
Transient ischemic attack
Cerebral venous sinus thrombosis
Ocular ischemia
Dementia
Acute ischemic encephalopathy
With Sneddon's syndrome
Without Sneddon's syndrome
Seizures
Transverse myelopathy
Headache
Demyelinating disease
Chorea
Guillain-Barré syndrome
Peripheral neuropathy
Sensorineural hearing loss
Sudden onset
Progressive
Transient global amnesia
Psychiatric disorders
Orthostatic hypotension

lesions have been associated with aPL, making cardiac emboli a possible stroke mechanism in some patients. Two-dimensional transthoracic echocardiography is abnormal in one third of patients, typically demonstrating nonspecific left-sided valvular (predominantly mitral) lesions characterized by valve thickening (reviewed by Tenedios et al. [9]). These may represent a potential cardiac source of stroke.

Although aPL antibodies are well-established as risk factors in a first ischemic stroke, their role in recurrent stroke is less clear. All but one of the case-control and prospective studies that evaluated aPL as a stroke risk factor in young adults showed an increased risk for incident ischemic stroke (reviewed by Brey [10]). The study failing to find an association only tested for anticardiolipin (aCL) antibodies, whereas the other studies evaluated for both aCL antibodies and LA. The presence and magnitude of the ischemic stroke risk associated with aPL antibodies in older populations is more evenly split between finding an increased risk and no increased risk; however, of the studies where both aCL antibodies and LA were tested, all but one found an increased risk (reviewed in [11]). This finding suggests that aPL antibodies may be a more important stroke mechanism in young people, whereas in older populations, other stroke risk factors take on more importance. Alternatively, the presence of LA may be more important in determining stroke risk at any age than aCL antibodies alone. Most of these studies either excluded cardioembolic disease or did not distinguish between cardioembolic, artery-to-artery embolic, or thrombotic mechanisms.

Two large studies have evaluated the risk for recurrent stroke and aPL antibodies in young adults (reviewed in

[12]). One study evaluated both aCL antibodies and LA and found an increase in recurrent stroke risk attributable to aPL antibodies. The other, more recent study, which also evaluated for both aPL and LA, found no increased recurrent stroke risk [13]. Two studies done in pediatric populations, likewise, found no increased recurrent stroke risk [14,15]. In older adults, evidence for an increased recurrent stroke risk is also weak (reviewed by Brey [11]).

The Euro-Phospholipid Project Group began a study of the clinical and immunologic manifestations and patterns of disease expression of APS in a cohort of 1000 patients in 1999 [2]. Primary APS was present in 53.1% of patients, and secondary APS was present in 46.9% of patients. At study entry, deep venous thrombosis was the most common thrombotic manifestation occurring in 317 (31.7%), and stroke was the most common arterial thrombotic manifestation in 135 (13.5%) patients. Additional cerebrovascular ischemic events were seen as well: transient ischemic attack in 70 (7%) patients and amaurosis fugax in 28 (2.8%) patients. The remaining patients had fetal loss. Although some clinical differences existed between primary and secondary APS patients, none of these differences included thrombotic manifestations. Follow-up on this extremely well-characterized cohort is ongoing.

In another European collaborative study, the European Working Party on SLE, the morbidity and mortality in patients with SLE over a 10-year period was studied in a cohort of 1000 patients [16]. This is the best study of the risk of thrombotic events and aPL antibodies in people with SLE. At the beginning of this study, there were 204 (20.4%) patients with aCL IgG, 108 (10.8%) patients with aCL IgM, and 94 (9.4%) patients with LA. Thromboses were the most common cause of death in the last 5 years of follow-up and were always associated with APS [17]. The most common thrombotic events in these patients were strokes (11.8%), followed by myocardial infarction (7.4%) and pulmonary embolism (5.9%). This finding suggests an important role for aPL and recurrent thrombosis in patients with SLE.

Evaluation of patients with aPL and stroke

It is difficult to say whether the presence of aPL in a given stroke patient is the major risk factor for stroke. It is always important to evaluate for other stroke etiologies in every patient regardless of the presence of any aPL. Given the conflicting data regarding the importance of aPL as a risk factor for recurrent stroke, it is even less clear which patients should have aPL testing performed routinely in the evaluation for stroke etiology. We recommend routine testing for aPL (to include aCL, anti–β_2GP-1, and LA testing) in stroke patients with any of the following features: younger than 45 years of age; concomitant diagnosis of SLE; other features of APS; and presence of thrombocytopenia, a prolonged activated partial thromboplastin time, or positive venereal disease research laboratory test. Patients who have only weakly positive aPL antibodies on two or more occasions do not have APS, and these antibody results do not need to be taken into consideration for treatment decisions.

Cognitive dysfunction associated with aPL: without SLE or other collagen vascular disease

An association between high aCL titers and cognitive dysfunction has been found in patients without SLE or other collagen vascular disease [18–22]. For example, Schmidt et al. [21] found subtle neuropsychologic dysfunction in otherwise normal elderly people with increased levels of aCL IgG. De Moerloose et al. [19] evaluated the prevalence of aCL in 192 elderly patients. The overall prevalence of aCL was 10.9% and decreased by decade in patients 70 to 99 years of age from 18% to 10% to 7%, whereas the prevalence of antinuclear antibody positivity increased by decade from 22% to 32% to 42%. No association was seen between the presence of aCL and decreased survival. In contrast and in keeping with previous findings, Cesbron et al. [18] found a trend toward an increased prevalence of aCL by decade in 1042 elderly subjects between the ages of 60 and 99 years. In addition, high aCL levels were associated with increased physical disability in this population independent of age, gender, visual or hearing abnormalities, Mini Mental State Examination scores, or history of cerebrovascular or cardiovascular disease. In the first study of the relationship between aPL and cognitive dysfunction in a non-elderly population, Jacobson et al. [22] found a significant association between aCL IgG levels and cognitive dysfunction.

Cognitive dysfunction associated with aPL: with SLE

Multiple studies have shown an association of aPL with cognitive dysfunction measured by neuropsychologic testing in SLE [23–27,28••]. Elevations of aPL have been associated with several different patterns of cognitive dysfunction in patients with SLE, depending on the study. Verbal memory deficits, decreased psychomotor speed, and decreased cognitive efficiency/productivity have all been significantly correlated to elevated aPL levels.

Three longitudinal studies have evaluated the relationship between serially obtained aPL levels and cognitive dysfunction in SLE patients [24,26,28••]. All studies demonstrated that cognitive dysfunction was significantly associated with persistently positive aPL. Menon et al. [26] reported that SLE patients with persistently elevated IgG aCL levels over 2 to 3 years performed significantly worse than SLE patients with occasionally elevated or never elevated titers on a variety of neuropsychologic tests. These results were not observed with anti-DNA antibody titers or C3 (complement) levels. Attention and concentration, as well as psychomotor speed, were the domains most affected. Hanly et al. [24] followed 51 female SLE patients over a 5-year period and found that persistent aCL IgG elevations were associated with decreased psy-

chomotor speed, whereas persistent aCL IgA elevations were correlated with problems with executive functioning and reasoning abilities. They also found no association between cognitive deficits and anti-DNA antibodies. Interestingly, no cross-sectional relationship between cognitive dysfunction and aPL was found in this same population. Our group prospectively studied the relationship between aCL and anti–β_2GP-1 antibodies in 123 SLE patients over 3 years [28••]. Factors significantly associated with cognitive decline were persistently positive aPL levels, prednisone use, diabetes, higher depression scores, and less education.

Headache/migrainous-like events

Headache is a common complaint of patients with aPL positivity [29–32]. The association of migraine and aPL is controversial with varying results in different series. Some authors have reported such an association with LA or aPL [30], but others have not [31,32]. So far, all prospective studies using appropriate control groups failed to demonstrate the association of aPL and migraine [31,32]. One retrospective study found aPL to be independently associated with headaches (though not necessarily migraine) in patients with SLE (OR 2.04, 1.17–3.55, $P = 0.01$) [30]. Thus, no clear evidence exists that aPL are important in the pathophysiology of headache.

Multiple sclerosis–like illness

Clinical syndromes and MRI closely resembling multiple sclerosis (MS) have been associated with aPL in some but not all studies. Tourbah et al. [33] prospectively studied 161 patients with probable or definite MS for 5 years. Researchers saw no differences in MS patients with or without a positive antinuclear antibody or aPL test. In the two largest studies to date, both cross-sectional, no relationship was found between aPL and clinical course in patients with probable or definite MS [34,35]. Although some small studies suggest that aPL positivity in SLE patients with an "MS-like" illness may have a more severe disease course [36], more work is required to determine the best treatment strategies for these patients.

Transverse myelopathy

No large studies have been conducted on transverse myelopathy (TM) and aPL, probably due to the rarity of TM. Kovacs et al. [37] evaluated 14 patients with SLE and TM and 91 additional cases published in the literature. Forty-three percent of their patients and 64% of the previously reported patients were aPL positive, confirming the strong association between TM and aPL. Transverse myelitis only occurs in 1% of patients with SLE; therefore, the number of patients described in this report is remarkable. Few cases of aPL-associated TM have been reported in patients without SLE, suggesting that aPL may be a more important risk factor for the development of TM in patients with SLE than in those without it.

Seizures

As reviewed in Cimaz et al. [38], aPL have been reported with increased frequency in SLE patients with epilepsy. Moderate-to-high titers of IgG aCL are strongly implicated in relation to the appearance of seizures, whereas the IgM isotype appears to be less specific. A recent prospective by Appenzeller et al. [39] found that aPL were associated with seizures at disease onset as well as during follow-up in a cohort of 519 SLE patients. In addition, in the 1.9% of the cohort who developed epilepsy, aPL were the only predictive factor [39].

Similar to studies with SLE patients, a relationship between aPL and epilepsy has been found in patients without SLE. In addition, the prevalence of the antibodies is independent of the type of epilepsy and the antiepileptic medications. Some animal data support the possibility of a primary immunologic basis for seizures associated with aPL, which have been demonstrated to bind directly to ependyma and myelin of cat brain and rat brain. Also reviewed by Cimaz et al. [38], aPL obtained from patients with SLE who had seizures have been shown to reduce a GABA receptor-mediated chloride current in snail neurons. This inhibitory effect suggests a direct and reversible mechanism through which aPL might lower seizure threshold.

Brain Imaging

Brain MRI studies in patients with APS (primary or secondary) have revealed small foci of high signal in subcortical white matter scattered throughout the brain. This type of pattern is seen in many other disease processes and is, as such, nonspecific. The correlation between MRI lesions in patients with aPL and clinical nervous system symptoms is reported to be high by some investigators and not by others (reviewed by Brey [11]).

Toubi et al. [40] performed brain MRI studies in 53 patients with secondary APS and nervous system manifestations and found high-density lesions in 33 of them, which were interpreted as "suggestive of vasculopathy." Some patients had nonfocal nervous system manifestations such as seizures, psychiatric disorders, and cognitive impairment, suggesting that aPL-associated neurologic manifestations may be due to an aPL-brain phospholipid interaction in addition to thrombosis. However, other studies have found white matter lesions on brain MRI scans only in patients with focal neurologic manifestations, [31,41–43]. In a recent study, Csepany et al. [43] evaluated 81 SLE patients with and without aPL and evaluated brain MRI findings in both groups. MRI abnormalities were also more common in SLE patients

who had LA positivity versus those without it ($P < 0.01$), especially if hypertension was also present ($P = 0.00041$). Patients with hypertension were a mean of 6 years older at the time of MRI examination ($P = 0.033$) and had more frequent MRI abnormalities suggestive of stroke than normotensive patients ($P = 0.0015$). These data support the "second hit" hypothesis described earlier.

Sun et al. [44] evaluated Technitium-99m hexamethylpropylene amines oxime (^{99m}Tc HMPAO) to examine the effects of anticoagulant therapy on regional cerebral blood flow in patients with primary APS and brain involvement in 16 patients. This was a highly selected group, all with decreased regional blood flow demonstrated on ^{99m}Tc HMPAO prior to anticoagulant therapy. After 1 month of anticoagulant therapy, 11 (68.8%) patients had complete recovery five (32.1%) patients had partial recovery of regional blood flow. Further studies are needed to determine whether this response is predictive of future clinical events.

Treatment Issues

Treatment of APS can be directed at thrombo-occlusive events using antithrombotic medications or at modulating the immune response with immunotherapy. In the case of thrombotic manifestations, both approaches have been used. Therapies aimed at modulating the immune response in preventing both thrombotic and nonthrombotic neurologic manifestations of APS also have variable success. A better understanding of the aPL-target tissue interaction in an individual patient would help guide more rational therapeutic decision making.

Treatment of aPL-associated cerebrovascular ischemia

No data are available that address the use of any specific treatment strategies for primary prevention of aPL-associated stroke. For patients who have persistently positive LA or moderate- to high-titer aPL, we recommend the use of aspirin (325 mg/day), with the understanding that no data support this strategy.

Treatment such as platelet antiaggregant and anticoagulant therapy for secondary stroke prevention have both been used in APS and in cerebrovascular disease associated with aPL [45–48]. Two groups have retrospective data to suggest that high-intensity warfarin treatment (versus low- or moderate-intensity warfarin or aspirin treatment) is associated with better outcomes in selected cohorts with various types of thrombotic events [46,47]. Patients in these studies did not have repeat aPL testing and would not fulfill current criteria for APS.

Crowther et al. [45] performed the first randomized, double-blind, controlled trial of two different intensities of warfarin treatment on the prevention of recurrent thrombotic events in patients with APS. In this study, 114 patients were enrolled and followed for an average of 2.7 years. The average international normalized ratio (INR) values in the moderate- and high-intensity groups were 2.3 and 3.3, respectively. Recurrent thrombosis occurred in two of 58 (3.4%) patients assigned to moderate-intensity warfarin and in six of 56 (10.7%) patients assigned to receive high-intensity warfarin. No difference was reported in recurrent thrombosis or major bleeding rates between the two groups. These results suggest that high-intensity warfarin treatment is not more effective than moderate-intensity treatment in preventing recurrent thrombotic events in patients with APS. The study did not specifically address the endpoint of stroke, many of the enrolled patients had venous and not arterial thrombosis, and patients with a history of thrombotic recurrence while on warfarin therapy were excluded. Nonetheless, we recommend treating patients with an incident cerebrovascular manifestation of APS with warfarin at a dose resulting in an INR between 2 and 3.

The Antiphospholipid Antibodies in Stroke Study (APASS) group completed the first prospective study of the role of aPL in recurrent ischemic stroke in collaboration with the Warfarin-Aspirin Recurrent Stroke Study (WARSS) group [48]. Initiated in 1993, this controlled and blinded study compared the risk of recurrent stroke and other thromboembolic disease over a 2-year follow-up period in older patients (average age 62.5 ± 11.3 years) with ischemic stroke who were randomized to either aspirin therapy (325 mg/day) or warfarin therapy at a dose to maintain INR between 1.4 and 2.8. The suggested target INR was 2.2. The purpose of the study was to collect information about recurrent stroke rates in aPL-positive versus aPL-negative patients controlling for treatment.

In APASS, 882 patients were randomized to warfarin, and 890 patients were randomized to aspirin. No increased risk of recurrent thrombotic events was associated with aCL or LA baseline positivity in either the warfarin-treated patients (RR 0.97, 95% CI, 0.74–1.27, $P = 0.82$) or the aspirin-treated patients (RR 0.96, 95% CI, 0.71–1.29, $P = 0.77$). Patients with baseline positivity for both LA and aCL antibodies tended to have a higher event rate (31.7%) than patients who were negative for both antibodies (24%) (RR 1.36, 95% CI, 0.97–1.92, $P = 0.07$). No difference was seen in major bleeding complications between treatment groups. Thus it appears that for older patients with a positive aPL determination at a single timepoint at the time of ischemic stroke (ie, include low-titers of aCL and/or IgA aCL and do not meet criteria for APS), aspirin and warfarin therapy at an INR of approximately 2 are equivalent regarding stroke recurrence and major bleeding complications.

Perioperative management of patients with antiphospholipid syndrome

Surgery can be a trigger of the catastrophic antiphospholipid syndrome in patients with APS; therefore, special care must be taken for APS patients in the perioperative period. Patients with APS may also be at higher risk for

postoperative venous thrombosis [49]. Perioperative thromboses can occur for a variety of reasons including withdrawal of anticoagulation or antiplatelet therapy, increased hypercoagulability despite anticoagulation therapy, and catastrophic exacerbation of APS.

Erkan et al. [49] suggested several measures for the perioperative management of patients with APS. Preoperatively, the platelet count should be greater than 100,000, and the procedure should be done only if absolutely necessary. During the procedure, intravascular manipulation for access and monitoring should be minimized, pneumatic blood pressure cuffs should be set to inflate infrequently to minimize stasis in the distal vascular bed, tourniquets should be avoided, and a high index of suspicion should be maintained that any deviation from the normal course may represent a thrombotic event. Regarding anticoagulation, periods without anticoagulation or antiplatelet therapy should be kept to a minimum. Both pharmacologic and physical antithrombotic treatments should be used immediately after the procedure. Importantly, patients with APS may develop thrombosis despite conventional doses of anticoagulation for deep vein thrombosis prophylaxis.

Conclusions

APS is an important cause of neurologic morbidity. Although some data support the pathogenicity of aPL, a "second hit hypothesis" has been developed to explain why thrombosis occurs only intermittently in patients with persistently positive aPL. More research is needed to understand how aPL and traditional risk factors for thrombosis interact in patients to lead to thrombosis. Convincing evidence suggests that cognitive dysfunction is associated with persistently positive aPL; however, the mechanism by which this occurs is not clear. One study found that aspirin treatment may help aPL-associated cognitive dysfunction, but more studies are needed to confirm this finding. No clear evidence is available to substantiate an association between aPL and headaches. In patients with SLE, aPL and an MS-like illness appear to have a worse clinical course than in SLE patients without aPL. TM in SLE patients is also highly associated with aPL. The presence of aPL is a strong predictor of epilepsy in patients with SLE, but no clear difference has been seen in the severity of seizures or response to treatment in SLE patients with or without aPL. Treatment of cerebrovascular disease in patients meeting criteria for APS should consist of warfarin in doses that produce an INR of between 2 to 3 in most cases. People with laboratory criteria for APS but without clinical criteria should consider taking 325 mg of aspirin daily.

Acknowledgments

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