Antiphospholipid Syndrome

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The antiphospholipid syndrome is an illness characterized by recurrent venous or arterial thrombosis, recurrent fetal loss, and thrombocytopenia. It is diagnosed by the presence of antiphospholipid antibodies, such as anticardiolipin antibody or lupus anticoagulant. Although the antiphospholipid syndrome affects a significant number of patients, these patients may be unrecognized because the syndrome has not been well reported in the primary care literature.

Key words. Antiphospholipid; antiphospholipid syndrome; antibodies, anticardiolipin; lupus coagulation inhibitor.
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Although the antiphospholipid syndrome (APS) affects a significant number of patients and is receiving increasing research attention from multiple specialties in a wide array of centers worldwide, little has been written about this syndrome in primary care–based journals. APS is characterized by recurrent venous or arterial thrombosis, recurrent fetal loss, and thrombocytopenia in the presence of autoantibodies to negatively charged phospholipids such as anticardiolipin antibody (aCL) and lupus anticoagulant (LA) (Table 1). Primary care physicians are often the first to see these patients.

Much confusion surrounds APS, some of which can be attributed to its historical evolution. In 1906, Wassermann developed the VDRL, a complement fixation procedure using saline extracts from the liver of fetuses with congenital syphilis. Subsequently, false-positive tests were found to be associated with some of the collagen vascular diseases, most notably lupus erythematosus. Over the next few decades, the acidic phospholipid component of the VDRL was identified and named *cardiolipin*. In 1952, Conley and Hartmann[1] described two patients who had lupus erythematosus and a hemorrhagic disorder with circulating anticoagulants. Feinstein and Rapaport[2] coined the term *lupus anticoagulant* for these circulating anticoagulants, but since the majority of patients with LA do not have lupus erythematosus, this term is a misnomer. In addition, although the antibodies cause an in vitro prolongation of the activated partial thromboplastin time, they tend to be thrombogenic in vivo.

During the 1970s and early 1980s, there were multiple reports of thromboembolic disease, recurrent fetal loss, and thrombocytopenia among patients with LA.[3–7] Observing that many of these patients also had a false-positive VDRL, Harris et al[8] developed a solid-phase radioimmunoassay for antibodies against cardiolipin. The concept of a syndrome emerged, and the condition was termed *antiphospholipid syndrome*.[9] It was soon evident that the results of the anticardiolipin test did not completely correspond with those of the LA, as only 60% to 70% of patients were positive for both. Research subsequently showed that LA and aCL are different antibodies that can be distinguished by affinity chromatography.[10,11] In the late 1980s, there were reports of a significant number of patients with APS who did not have underlying lupus erythematosus or other collagen vascular diseases. The term *primary antiphospholipid syndrome* was coined for this subset of patients.[12–14] Since these early beginnings, case reports and case-cohort studies have provided increasingly better characterization of APS and the subset of patients with primary antiphospholipid syndrome.

In spite of the growing knowledge base, there is still much controversy concerning APS. The syndrome is likely a heterogeneous group of diseases with multifac-

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Table 1. Terms and Their Acronyms Used in Discussing Antiphospholipid Syndrome

APS—	Antiphospholipid syndrome (APS): syndrome that is characterized by thromboembolic phenomena, recurrent fetal loss, and thrombocytopenia associated with an antiphospholipid antibody.
PAPS—	Primary antiphospholipid syndrome (PAPS): APS that is not secondary to systemic lupus erythematosus or other collagen vascular diseases.
aPL—	Antiphospholipid (aPL) antibody: antibody that reacts with negatively charged phospholipids; two primary aPLs measured are lupus anticoagulant and anticardiolipin antibody. Also known as APA.
LA—	Lupus anticoagulant (LA or LAC)
aCL—	Anticardiolipin antibody (aCL, ACA, or ACLA)
SLE—	Systemic lupus erythematosus (SLE)

torial causation, but current understanding is based primarily on case reports rather than strong study designs. There is controversy concerning the strength of association of several of the reported manifestations. Understanding of the natural history is further complicated by the vacillation of antibody levels between positive and negative over time in a single patient. Finally, lack of standardization of the LA and aCL tests has resulted in a wide range of reported prevalences and therapeutic outcomes. With the development of international working groups, these variances have gradually decreased.

Epidemiology

To date, there has not been a prospective study on APS in a primary care–based population. The generally accepted prevalence of antiphospholipid antibodies in healthy populations is 2% to 5%. This rate is based on studies using blood donors as representative of the population.[15] For all patients with APS, the ratio of female to male patients is approximately 2:1 for primary antiphospholipid syndrome and 9:1 for cases associated with systemic lupus erythematosus (SLE).[12,16,17] The presumed female preponderance may represent selection bias, since the exclusion of patients with recurrent fetal loss results in a fairly equal distribution between men and women.[18] Mean and median ages of patients in most reports have been 35 to 45 years.[13,16,17,19] Worldwide case reports include a wide ethnic distribution, but in the United States, the syndrome is more common among whites.[12,20] Little is known about hereditary patterns.

Association with Lupus and Other Rheumatic Diseases

Between 40% and 50% of patients with SLE are positive for aCL or LA, but only one half of these manifest recurrent thromboembolic disease.[19,21–23] Titers of aCL in patients with SLE are directly related to the likelihood of thromboembolic disorders. Although the correlation is controversial, higher titers of aCL tend to correlate with increased SLE activity.[24] Antiphospholipid antibodies also occur with a lower prevalence in other collagen vascular diseases, including rheumatoid arthritis, Behçet's syndrome, and Sjögren's syndrome, but it is uncertain what percentage of these patients will have thromboembolic disease.[25–27]

Other Special Groups

Approximately 25% of patients with recurrent fetal loss (±3) have APS.[28–30] The prevalence of APS in the general pediatric population, like that among adults, is not known, but there have been several case reports of children with cerebral or myocardial infarctions.[31–34] Similar to the adult population, about one half of pediatric patients with SLE have antiphospholipid antibodies.[35] As with other autoantibodies, geriatric patients are more likely to have antiphospholipid antibodies without disease.[36,37]

Patients with Antiphospholipid Antibodies Without APS

The presence of aCL and LA in low titers without other manifestations of APS has been reported in patients with HIV and various malignancies.[16,38,39] Similarly, antiphospholipid antibodies have been reported in patients who are being treated with certain medications, including phenothiazines, procainamide, and hydralazine.[38,40]

Pathophysiology

Because of the heterogeneity of aCL and LA and the various sites of the body affected, several different pathophysiologic mechanisms have been suggested, including alterations of endothelial cell function, the coagulation regulatory system, and erythrocytes and platelets.[13,41–45] A cofactor, β_2 glycoprotein-I (β_2GPI), is required and enhances the binding of aCL to cardiolipin.[44,46,47] It is well documented that the process does not include vasculitic changes.

Table 2. Clinical Manifestations of Antiphospholipid Syndrome

Neurologic	Dermatologic
Cerebrovascular accident	Livedo reticularis
Transient ischemic attack	Leg ulcers
Severe migraine	Necrotizing purpura
Chorea	Distal cutaneous ischemia/ gangrene
Seizures	Widespread cutaneous necrosis
Multi-infarct dementia	
Ischemic encephalopathy	Obstetric
Peripheral neuropathy	Recurrent fetal loss
Myasthenia gravis	Intrauterine growth retardation
Sneddon's syndrome	Preeclampsia
	Chorea gravidarum
Cardiovascular	Postpartum syndrome
Myocardial infarction	
Valvular lesions, mitral and aortic	Miscellaneous
Pseudoinfective endocarditis	Avascular necrosis
Intracardiac mass	Nonthromboembolic pulmonary hypertension
Hematologic	
Thrombocytopenia	
Coombs' positive hemolytic anemia	
Leukopenia	

Clinical Manifestations

The clinical manifestations of APS are summarized in Table 2.

Thromboembolic Disease

The primary pathologic consequence of the antiphospholipid antibody is noninflammatory thromboembolic disease. Virtually all venous and arterial systems have been cited, including large, medium, and small vessels. The most common site for venous thrombosis is in the lower extremity in the femoral and popliteal systems, whereas cerebral ischemia, manifested as embolic cerebrovascular accidents and transient ischemic attacks, is the most commonly reported arterial presentation. Harris[48] reported that of the thousands of patients' serum samples analyzed by a reference laboratory, 50% of patients with a moderately positive aCL had a history of thrombosis. Of those with a highly positive aCL, 75% had a history of thrombosis. The recurrence rate for thromboembolic disease is not known; however, it is likely to be high. In a recent report of the clinical course of 70 patients with APS, there were 31 recurrences of venous or arterial thrombosis in 33 untreated patients over a 5-year period.[17]

Hematologic Disorders

Hematologic manifestations include thrombocytopenia, hemolytic anemia, leukopenia, and disseminated intravascular coagulation. Thrombocytopenia is a common manifestation of APS, occurring in about 15% to 20% of patients with the syndrome.[17,19,49] Coombs' positive hemolytic anemia and leukopenia also have been noted in patients with APS.[19] A questionable association of antiphospholipid antibodies with disseminated intravascular coagulation has appeared in case reports.[50]

Neurologic Associations

One third of patients with APS have neurological manifestations, including cerebrovascular accident, transient ischemic attack, severe migraine, multi-infarct dementia, myasthenia gravis, peripheral neuropathy, seizures, and acute ischemic encephalopathy.[49,51–57] About 6% of the general stroke population have antiphospholipid antibodies (aPL).[58,59] In younger patients with evidence of cerebral ischemia, the prevalence of APS is much higher.[51,52,60] The majority of cerebral ischemic events are believed to be cardioembolic in nature with a wide distribution of sites and vessel sizes affected.[20,52,55,61] Patients with APS and previous stroke have an increased rate of recurrence: 18.7% per year recurrence for cerebrovascular accident and 15.2% per year recurrence for transient ischemic attack.[20] There is a marked association of aPL in patients with Sneddon's syndrome, an interesting neurological disease consisting of cerebral ischemia with livedo reticularis.[62]

Cardiac Abnormalities

Of patients with APS, 25% to 35% have valvular abnormalities.[63–66] Left-sided lesions are much more common than right-sided, and mitral valve involvement is more common than aortic. Echocardiographically, mitral valve thickening, often with associated regurgitation, is the most common finding. Patients with SLE are more likely to have valvular disease if they have aCL.[63] As mentioned previously, mitral and aortic valve abnormalities increase the risk of cerebral ischemia. Patients with arterial thrombosis seem more likely to have valvular abnormalities than do patients with venous thrombosis.[66] As with cerebral ischemia, young patients (≤45 years old) with myocardial infarction are often found to have elevated antiphospholipid antibodies.[67,68] Studies of general myocardial infarction populations of all age groups do not show an association with aPL antibodies.[69,70]

Dermatologic Manifestations

Cutaneous manifestations include livedo reticularis, leg ulcers, necrotizing purpura, distal cutaneous ischemia,

Table 3. Diagnostic Criteria for Antiphospholipid Syndrome

Clinical		Laboratory		Interval
Venous thrombosis* or Arterial thrombosis or Recurrent fetal loss or Thrombocytopenia	plus	IgG aCL (moderate to high) or IgM aCL (moderate to high) or Positive LA	plus	aPL positive at least twice with an interval greater than 8 weeks

**More than one episode of unexplained deep venous thrombosis if no other clinical manifestations.*
IgG denotes gamma G immunoglobulin; aCL, anticardiolipin antibody; aPL, antiphospholipid antibody; IgM, gamma M immunoglobulin; LA, lupus anticoagulant.

widespread cutaneous necrosis, purpura, and peripheral gangrene.[19,49,71–73] About 25% to 40% of patients with APS have a cutaneous manifestation. Livedo reticularis, a violet discoloration of skin in a reticular or lattice-like pattern, is a frequent finding, occurring in about 20% to 30% of patients. Livedo reticularis generally occurs on the thighs, shins, or forearms and is believed to be caused by stagnation of the blood in superficial capillaries and venules. Cutaneous ulceration secondary to thrombosis of the dermal vessels is another common dermatologic manifestation.[71,74] The ulcer is usually painful, has distinct margins, has a propensity for the lower extremities, and heals leaving a white, atrophic scar. Digital ischemia is common and can result in digital gangrene.[71]

Obstetric Complications

Historically, obstetric complications were among the initial clinical manifestations noted with APS. Obstetric complications associated with aPL antibodies include recurrent fetal loss, severe preeclampsia, premature delivery, chorea gravidarum, intrauterine growth retardation, and postpartum syndrome.[29,30,75] About 3% of the general obstetric population have measurable aCL, though generally in low titers and without known clinical significance. In patients without previous fetal loss, a single, mildly elevated aCL is not predictive of fetal demise.[76] However, there is a strong association of moderate to high titers of aCL or presence of LA with fetal loss. About one fourth to one third of patients with recurrent fetal loss (≥3 spontaneous abortions or fetal losses) have elevated aCL titers or LA.[28–30,77,78] Triplett and Harris[30] report that by 1989, there was a fetal loss rate of 87% in 689 pregnancies among 191 women with LA who were untreated. An unusual postpartum syndrome has been described in patients with an uneventful pregnancy who subsequently developed pleuropulmonary disease, fever, and cardiac manifestations with associated aPL antibodies.[75] The incidence of venous or arterial thrombosis during pregnancy in patients with APS is roughly 40%.[30]

Miscellaneous

Case reports of other diseases with a questionable association of aPL antibodies and APS include primary pulmonary hypertension and avascular necrosis.[79,80]

Diagnosis

Criteria for the diagnosis of APS have been recommended by Harris[41] and modified by others (Table 3).[19,72,81] A clinical diagnosis of APS can be made if the patient has experienced an unexplained thromboembolism, thrombocytopenia, or recurrent fetal loss in conjunction with persistently elevated titers of aCL or LA. Patients in whom more than one site is involved or more than one manifestation has occurred are more likely to experience recurrence.[24] It is important to remember that stricter diagnostic criteria are useful for clinical studies. However, patients can have APS manifestations with low positive titers of aCL.

As an increasing number of patients are evaluated for the presence of aPL antibodies, there is growing awareness that there are possibly two or three subsets of patients. Initially, APS was described largely in SLE populations. About one half of patients with SLE have aPL antibodies, with a significant number demonstrating the clinical manifestations of APS. Likewise, APS has been noted to be associated with other collagen vascular diseases, such as rheumatoid arthritis, Behçet's and Sjögren's syndromes.

Another subset of patients are those without underlying SLE or another collagen vascular disease. These patients, classified as primary antiphospholipid syndrome (PAPS), tend to be younger, with a less pronounced preponderance of female patients than among lupus patients with APS (APS/SLE). The incidence of venous or arterial thrombosis is 87% in patients with PAPS as compared with 61% in patients with APS/SLE.[16] Initially, these patients were thought to represent a prelupus phase. However, 5 to 10 years of follow-up shows that

only a small percentage of patients with PAPS subsequently develop SLE. It is important to realize that patients with APS have a multitude of clinical courses, regardless of whether the patient has APS/SLE, APS secondary to other collagen vascular diseases, or PAPS.

Laboratory Evaluation

False-positive VDRLs, which were one of the initial markers for disease, occur in only 30% to 40% of patients with APS. Although there is some discordance in the results of LA and aCL measurements, they are the best confirmatory tests. Current recommendations for interpretation of these tests are described below.[82–86]

Lupus Anticoagulant

Lupus anticoagulant is more specific but less sensitive than aCL. Testing for LA antibodies consists of three basic steps: screening tests, inhibitor identification, and confirmatory tests.[82–85] The test is reported as positive if LA is present. LA cannot be tested if the patient is receiving heparin therapy, and the blood should not be drawn from a line with heparin flush.

Anticardiolipin Antibody

There are three major isotypes of aCL: IgG, IgM, and IgA. Although all three have been found in patients with thromboembolic manifestations, IgG is much more common, especially subclasses IgG_2 and IgG_4.[87] IgA by itself is fairly rare, and some recommend testing for it only if the patient has clinical findings of APS but is negative for IgG and IgM aCL.[88] Drug- and infection-induced aCL is usually a low titer IgM.

Standard control samples are compared with the optical density of the sample and reported in IgG phospholipid units (GPL) and IgM phospholipid units (MPL). One GPL unit is the binding activity of 1 μg/mL IgG. Likewise, an MPL unit corresponds to the binding activity of 1 μg/mL IgM. Rather than using a set cutoff point, it is recommended that the aCL be reported as low positive (GPL <15; MPL <6), medium positive (GPL 15 to 80, MPL 6 to 50), and high positive (GPL >80, MPL >50).[86]

Treatment

Appropriate therapy is effective in reducing the rate of recurrence of thromboembolic disease with APS. However, there are reported treatment failures with each modality.[17,72,88,89] Treatment plans using immunosuppression, anticoagulation, and antiplatelet therapy have met with varying success. Because there are still little prospective, randomized data concerning the different treatment modalities, and because little is known about the natural history of patients with APS, it is difficult to select the optimum treatment modality. Regardless of which therapy is used, it is imperative to reduce any other risk factors the APS patient might have (eg, smoking, hypertension, diabetes mellitus, hyperlipidemia).

Treatment of Venous or Arterial Occlusion

Intravenous heparinization is the standard treatment for acute thromboembolic manifestation. Long-term use of anticoagulants, primarily warfarin sodium, has been more successful than immunosuppressants in preventing recurrence of thromboembolic phenomena.[17,72,88,89] Warfarin is recommended for use after the initial therapy for all arterial occlusions. Because of the inherent risks with anticoagulant therapy and because a recurrence is likely to affect the same venous system, there is debate about whether long-term warfarin therapy should be started in a patient with APS after the first occurrence of a deep venous thrombosis without other manifestations. It is recommended that these patients be given warfarin for 3 to 6 months and aspirin thereafter. There is insufficient data to recommend high vs low doses of aspirin. Warfarin is recommended for long-term therapy after the second occurrence of a deep venous thrombosis and after the initial episode of any other venous occlusion. Because some patients experience warfarin resistance, it is recommended that an International Normalized Ratio (INR) of 3 is optimum for preventing recurrence of both arterial and venous occlusion.[17,72,88]

Because of the high INR required and the erratic nature of anticoagulation in some patients, it is important to schedule frequent follow-up visits with regular evaluation of the prothrombin time. The role of retesting for aCL and LA in the long-term follow-up of a patient with APS is not well understood. Echocardiographic evaluation may be helpful for patients with an arterial occlusion because of the increased incidence of left valve abnormalities.[65,66]

Prophylactic Therapy

Subcutaneous heparin is recommended for prophylaxis in patients who have APS and are undergoing surgery. If the patient is being treated with warfarin, it should be discontinued 2 to 3 days before surgery. The recommended dosage of heparin is 5000 to 8000 units every 8

hours. The higher dosage is suggested because some patients experience recurrence postoperatively on the standard dosage of 15,000 units per day.[72]

Prevention of Fetal Loss

Although corticosteroids have not demonstrated much success in preventing recurrent thromboembolic disease, they have proved useful in preventing fetal loss in the obstetric population.[29,90–92] There is disagreement about whether prednisone or heparin therapy is more effective in preventing fetal loss.[90–94] Multicenter trials to evaluate the optimum therapy are currently in process.

If corticosteroid therapy is used, prednisone is generally begun early in pregnancy at a dosage of 40 mg/d. This dosage is continued for 4 weeks, then slowly tapered to 10 mg/d or every other day. Several studies have followed the activated partial thromboplastin time (APTT) or the kaolin clotting time to determine the rate of tapering.[29] A change in titer of aCL does not correlate well with disease, and therefore is not a good indicator of disease activity.

If heparin therapy is chosen instead, the recommended dosage is 15,000 to 20,000 units per day, divided into two or three doses and administered subcutaneously.[93,94] Because of the prolongation of the APTT with heparin, it is not helpful to follow the APTT or kaolin clotting time during pregnancy.

Use of aspirin by itself has not been very successful in preventing recurrent fetal loss, but because of its theoretical advantage of inhibiting platelet aggregation, it has been used in conjunction with either corticosteroids or heparin. A low dosage of aspirin is begun early in pregnancy.

Other Therapies

The use of more potent immunosuppressants, such as cyclophosphamide and azathioprine, has been reported in a limited number of cases. Plasma exchange in combination with cyclophosphamide can decrease aCL titers, but rebound with cessation of therapy is common. Although little is known concerning the usefulness of these other modalities, further research may reveal that they play a role in the overall therapeutic regimen.

Recommendations for the Primary Care Physician

A thorough examination of patients with APS is necessary because of the significant morbidity and mortality of APS, which often occur in young patients. Because many of the clinical manifestations in patients with APS are noted initially by primary care physicians, it is important to establish a reasonable plan for evaluation and treatment (Tables 4 and 5).

Primary care physicians can also play a vital role in the understanding of APS. To date, information about APS is based on patients seen at tertiary care centers. Such patients often have the most severe forms of illnesses and may have self-selected the tertiary referral center for treatment, thus creating a bias. It is very likely that a significant number of patients with APS are being seen and followed by primary care physicians away from

Table 4. Evaluation of a Patient with Antiphospholipid Syndrome

Patients to evaluate	If Patient Has APS
1. Patient with more than one unexplained fetal loss	1. Check ANA; rule out antiphospholipid syndrome/ systemic lupus erythematosus
2. All young patients with idiopathic venous thrombosis	2. Check complete blood count; evaluate for thrombocytopenia or hemolytic anemia
3. All young patients with idiopathic arterial thrombosis or embolism	3. Evaluate liver and renal function
4. Older patients with thromboembolic disease without significant risk for cardiovascular disease	4. Evaluate for dermatologic manifestations
5. All patients with systemic lupus erythematosus	5. Echocardiogram for patients with arterial thrombosis (consider in patients with venous thrombosis)
6. Patients with idiopathic: Thrombocytopenia Livedo reticularis Leg ulcers Hemolytic anemia	

ANA denotes antinuclear antibody test.

Table 5. Treatment Recommendations for Patients with Antiphospholipid Syndrome

Circumstance	Treatment
Following single episode of deep venous thrombosis (DVT)	Aspirin
Following recurrence of DVT or with initial episode of any other venous occlusion	Warfarin
Following occurrence of arterial occlusion	Warfarin
Preoperatively	Heparin, subcutaneous
During pregnancy	Low dose aspirin with prednisone or heparin

tertiary care sites. Data concerning these patients and the course of their disease can make an important contribution to the body of knowledge about this disease. Primary care research centers can also play a vital role in conducting studies necessary to obtain prospective data evaluating the prevalence and incidence of APS in the general population.

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