Update on Antiphospholipid Syndrome

Michael D. Lockshin, M.D.

Abstract

This review addresses new clinical issues (revealed at the 2006 Sydney update of the 1999 Sapporo Classification criteria; cardiac, renal, and multiple sclerosis-like disease; catastrophic syndrome), mechanisms of action of antiphospholipid antibody (very likely complement mediated), current therapies (moderate dose warfarin recommended for prophylaxis, aspirin not recommended for primary prophylaxis), and potential new therapies.

Preliminary classification criteria for antiphospholipid syndrome (APS) were determined in a post-conference workshop following the 1998 Eighth International Symposium on Antiphospholipid Antibodies.[1] While clinical associations had been recognized between antiphospholipid (aPL) antibodies and, for example, events of vascular thrombosis and pregnancy loss, causation mechanisms are not well understood. This and awareness regarding the variety of disciplines contributing to the developing knowledgebase of aPls, along with the need to clarify the current bases for criteria, resulted in a consensus statement published in 1999. These new tentative clinical criteria became a basis from which further clinical and investigative work on APS could proceed more soundly. The update below addresses three aspects of APS, to include the new clinical issues, mechanisms of action, treatment recommendations, and subsequent revisions.

New Clinical Issues

The preliminary criteria for APS were revised in Sydney, Australia in 2004 (published in 2006).[2] The differences between the original and the revised criteria were: 1. the addition of exclusionary criteria, in particular, older age (males 55 and older, females 65 and older, because of competing alternative causes for thromboembolic disease in older age groups); 2. an increase in the required interval from 6 to 12 weeks, during which two consecutive tests be positive (because infection-induced auto-antibodies can be positive for more than 6 weeks); and 3. the addition, for individual diagnosis (but not for population studies) of clinical and laboratory criteria that are very uncommon, alternatively explained, or generally unavailable, except in specialized laboratories. These findings include aPL antibody-associated cardiac valve disease, livedo, thrombocytopenia, and nephropathy, as well as IgA antibody, antibody to phosphatidylserine, and other less well characterized antigens. Kaul and colleagues found elements of the revised clinical criteria to be present in 6% to 25% of patients identified by thromboembolic disease, but much less frequently in patients identified by pregnancy morbidity. IgA antibodies were not commonly present but other antibodies were.[3]

A European group recently has argued that a test for lupus anticoagulant is more valid than the enzyme linked immunosorbent assay (ELISA) for anticardiolipin and should constitute the primary criterion for diagnosis of APS.[4] Reasons to reject this argument are: 1. its proponents are primarily hematologists, with a vested interest in doing the tests; 2. consensus already exists that lupus anticoagulant is a more specific but far less sensitive test than is ELISA for anticardiolipin; and 3. the ELISA is far more reproducible and, unlike the lupus anticoagulant test, can be reliably repeated on frozen or shipped specimens. In tests of the reproducibility of the standard ELISA, Erkan and coworkers demonstrated a comfortable degree of consistency, even using commercial laboratories.[5]

Thrombotic microangiopathy is an uncommon but devastating manifestation of long-standing APS. It presents as

Michael D. Lockshin, M.D., is Professor of Medicine and Obstetrics-Gynecology, Weill Medical College of Cornell University, and an Attending at the Hospital for Special Surgery and the New York Presbyterian Hospital, New York, New York.

Correspondence: Michael D. Lockshin, M.D., 535 East 70th Street, New York, New York 10021; lockshinm@hss.edu.

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Table 1 Distinctions Between Antiphospholipid Antibody-Associated Multiple Sclerosis-like Syndrome and Multiple Sclerosis*

Item	APS	APL	APS/SLE	Unclassified	Multiple Sclerosis
Number	30	20	20	20	20
Symptoms	Chorea, pseudotumor, migraine, seizure, dysarthria	None	Cognitive dysfunction, numbness	Ataxia, TIA, headache, confusion	Numbness, optic neuritis, bladder and gait disturbance, paresthesias
MRI	Small UBOs, nonenhancing, CVA	None	Like APS	Like APS	Large UBOs, enhancing, confluent
aCL/β2GP1	High	High	High	Variable	Low
Lupus anticoagulant	Present	Present	Present	Present	Absent
Other APS symptoms	Present	Present	Present	Absent	Rare

*Unpublished data from Tenedios F, Apatoff B, and Lockshin M. APS, antiphospholipid syndrome; aPL, antiphospholipid antibody without thrombotic events; SLE, systemic lupus erythematosus; CVA, cerebrovascular accident; UBO "unknown bright object," hyperintense lesion on MRI; TIA, transient ischemic attack.

bland proteinuria with hypertension and progresses slowly, but can lead to renal failure. The multiple sclerosis-like presentation of APS mostly reflects cognitive dysfunction and abnormal MRI. In a cross-sectional study of patients with APS, aPL without syndrome, systemic lupus erythematosus (SLE) and aPL antibody, unclassified autoimmune disease with aPL antibody, and multiple sclerosis patients with aPL antibody, Tenedios found chorea, migraine, seizure, and dysarthria more frequent in APS, while optic neuritis, bowel and bladder abnormalities, and gait disturbances were more common in multiple sclerosis. Distinctions could be made among the MRI abnormalities (in APS, abnormalities are nonenhancing with gadolinium); antibody tests are generally strongly positive in patients with APS and less so, or low-positive in patients with multiple sclerosis (Table 1). Cardiac thrombi and cardiac valve disease both occur in APS and can be responsible for embolic disease. In SLE, Libman-Sacks valvular abnormalities are associated with aPL antibody.[6,7] The catastrophic syndrome remains a rare but highly lethal manifestation of the syndrome.[8,9] In some cases, occlusion of multiple vessels occur, beginning at the microvascular level rather than at the macrovascular one.[10] Surgery and pregnancy appear to trigger thrombotic events; arterial events are more likely in hypertensive patients and in smokers.[11]

Mechanisms of Action

Many hypotheses have been offered to explain how aPL antibody triggers or is associated with thrombotic events. Leading hypotheses include the ability of this antibody (which likely results from cross reactivity with a common viral infection in a genetically prepared host) to induce tissue factor in endothelial cells and monocytes, to induce platelet aggregation, and to induce endothelial cell adhesion receptors, or to activate complement.[11] A particularly compelling hypothesis is supported by animal models in which full anticoagulation with the noncomplement activating anticoagulants hirudin or fondaparinux cannot prevent pregnancy loss or thrombosis; however, sub-anticoagulant doses of heparin, complement deficiency, or complement inactivation by other mechanisms are able to do so. This strongly argues that the first and critical step of aPL antibody-associated thrombosis or fetal loss is complement-mediated and is not a coagulation step.[12,13] New therapies in the future may address this issue.

Treatment in 2008

Warfarin remains the mainstay of treatment for the thrombotic manifestations of the syndrome, and heparin for the pregnancy manifestations. Nonetheless, no data indicate that anticoagulation is beneficial for thrombotic microangiopathy, valvular heart disease, livedo reticularis, leg ulcers, or MRI abnormalities associated with cognitive dysfunction. Two high dose and low dose-controlled clinical trials strongly support the idea that a target international normalized ratio (INR) of 2.5 is sufficient for the treatment of most patients.[14,15] A systematic retrospective review, however, took the position that for secondary prophylaxis a higher dose was both more effective and more likely to lead to hemorrhagic complications.[16] Two reviews reached remarkable consensus on treatment recommendations.[17,18]

Recent data indicate that genetic variation in warfarin metabolism may be important in dose adjustment,[19] and gene expression patterns among bearers of aPL antibody may predict clinical phenotype (specifically, whether or not thrombosis results).[20] Most authorities agree that lifelong anticoagulation is indicated, but questions have arisen whether in patients with triggered thromboses, those antibodies disappear, or for patients who no longer have trigger risks, whether they might eventually, safely be able to discontinue anticoagulation.

With regard to primary prophylaxis, a randomized 3-year prospective controlled trial of aspirin versus placebo indicated there was no benefit of aspirin for persons found

to carry a moderate to high titer aPL antibody but who had no prior thromboses.[21] By contrast, a retrospective 10-year study, using low titer antibody positive persons, but which did not verify dosing, argued that aspirin is beneficial.[22] No definitive statement yet exists regarding the efficacy of other agents such as clopidogrel, low molecular weight heparin, or alternatives for thromboses prevention.

Some investigators advocate the use of hydroxychloroquine and statin drugs; biological theories supporting the recommendations of clinical trials demonstrating efficacy do not exist. Case reports suggest that rituximab may be beneficial, as may intravenous immunoglobulin in the catastrophic syndrome. Trials are underway to examine these possibilities. In particular, a trial is underway at this institution to test whether rituximab could be of benefit in patients with anticoagulant resistant manifestations, including thrombotic microangiopathy, valvular heart disease, thrombocytopenia, and cognitive dysfunction.

Disclosure Statement

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