

## Antiphospholipid Antibodies and Stroke

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The clinical study of stroke is a recent occurrence. The clarion call awakening interest consisted of two reports that appeared during the years following World War II: the detailed description by Kubik and Adams [1] of the clinical and pathologic findings in patients with basilar artery occlusion, and C. Miller Fisher's monograph [2] directing attention to the signs and symptoms found in patients with carotid artery disease in the neck. During the next three decades, pathologists, clinicians, and radiologists worked to clarify the anatomy, pathology, and imaging features of strokes involving the large and small blood vessels of the brain. During the last decade, stroke clinicians have rediscovered that blood flows through the blood vessels.

Diseases of the blood and blood vessels can cause or contribute to thromboembolism and bleeding, with resultant brain damage. Blood disorders in the most general sense are diseases detected or monitored by tests of the blood rather than imaging or sonographic studies of the anatomy and function of the brain and its vascular supply. During the past 5 years, many advances have been made in understanding the complex process of clot formation, clot lysis, and treatment of thrombosis. Table 1 lists broad categories of blood abnormalities that predispose to thrombosis and brain ischemia [3]. In this issue of the *AJNR*, Pulpeiro and colleagues [4] discuss the MR findings in a patient with a syndrome in one of these categories of blood disorders: the antiphospholipid antibody (APLA) syndrome, a type of immunological disorder that has recently received much attention [5–10].

The nomenclature of the APLA syndrome is confusing. Antiphospholipid antibodies are immunoglobulins (IgG, IgM,

IgA classes) directed against anionic and neutral phospholipids [5]. The two most commonly studied and recognized antibodies are the so-called lupus anticoagulant and the anticardiolipin antibodies. Since the VDRL test assays for antibodies directed against a lipid antigen derived from heart tissue, a cardiolipin, it is not surprising that APLA-bearing patients will often show a false-positive serologic test for syphilis. They also often test positively for antinuclear antibodies. The lupus anticoagulant (a misnomer, since it is associated with increased coagulability not bleeding) is a phospholipid antibody that interferes with formation of the prothrombin activator, a complex of Ca<sup>++</sup>, factors V, Xa, and the phospholipid platelet factor 3, in the coagulation cascade

**TABLE 1: Blood Disorders That Predispose to Brain Ischemia**

1. Abnormal amounts of formed blood elements; i.e., too many or too few RBCs, WBCs, platelets.
2. Qualitative abnormalities of formed blood elements; e.g., sickle cell anemia and other hemoglobinopathies; abnormal platelet secretion, adhesion, and aggregation.
3. Increased blood viscosity; e.g., increased fibrinogen, hyperglobulinemias, polycythemia.
4. Coagulation disorders; e.g., congenital and acquired deficiencies of serum protein coagulation inhibitors (protein C, protein S, antithrombin III); abnormalities of coagulation cascade factors (factors V, VIII, antihemophilic globulin); abnormalities of fibrinogen, thrombin, and fibrinolysis.
5. Immunologic abnormalities; e.g., circulating antigen-antibody complexes; antiphospholipid antibodies.

This article is a commentary on the preceding article by Pulpeiro et al.

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[10]. The laboratory sign of the presence of lupus anticoagulant is a prolonged activated partial thromboplastin time that does not correct when normal plasma is added, indicating the presence of a clotting inhibitor rather than a deficiency of a necessary component [3]. Although antibodies are directed against many phospholipids, in practice, cardiolipin is the most widely used antigen, tested by using a commercially prepared enzyme-linked immunoabsorbent assay. About 70% of patients with lupus anticoagulant also have positive anticardiolipin antibodies, and 70% of patients with anticardiolipin antibodies also have positive tests for lupus anticoagulant [3]. Phospholipids are important components of many tissues, including blood platelets, vascular endothelium, myocardium, and heart valves.

APLAs may be found in patients with recognized systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), in which case the clinical findings are those of the primary disease. As Pulpeiro and colleagues [4] point out, most patients with APLAs have no known recognized systemic disorder, in which case the disorder is referred to as the primary APLA syndrome. Patients with either secondary or primary APLA syndromes have an increased frequency of thromboembolism. APLAs have been associated with venous and arterial thromboses, and infarctions have been of the small and large vessel types. Pathologic studies have shown thrombotic occlusion of vessels without evidence of vasculitis or atherosclerotic disease [6]. The most frequent clinical manifestations of thromboembolism are recurrent venous thrombophlebitis in the lower extremities, brain and eye ischemia in the form of TIAs and strokes, and frequent miscarriages in mid-pregnancy. These clinical findings are readily explained by increased blood coagulability. Laboratory testing also frequently shows thrombocytopenia, antinuclear antibodies, and false-positive serologic tests for syphilis. More difficult to explain is the frequent co-occurrence of other disorders. Many patients with APLAs have other stroke risk factors, such as hypercholesterolemia, smoking, hypertension, and so on [5, 7]. Hypercoagulability likely potentiates and adds to these risk factors in causing stroke. Many have cardiac wall and valve abnormalities that could predispose to cardiogenic embolism [5]. In their retrospective study, the Antiphospholipid and Stroke Study Group (APASS) noted predominant involvement of the mitral valve [5]. Others have noted involvement of both the mitral and aortic valves, characterized by valve prolapse or insufficiency, myxomatous degeneration with associated thrombi, or changes resembling verrucous endocarditis [11–13]. The cause of this is unclear; perhaps the valve surface or subjacent endocardial tissue is a site of action of an APLA.

More difficult to explain is the associated high rate of occurrence of other neurologic disorders that are not usually considered to be characterized by thromboembolism. These include migraine, seizures, chorea, Guillain-Barre syndrome, multiple sclerosis, and Degos disease. Some healthy people with no clinical signs of disease have APLAs. Are these other disorders merely the accidental co-occurrence of unrelated conditions? Are the APLAs etiologically related in ways not presently understood? Are some conditions—such as mi-

graine, seizures, and the subacute encephalopathy reported by Sunseri and colleagues [14]—manifestations in some patients of microinfarcts? Are the APLAs merely a marker for many different autoimmune phenomena? Do the immunological reactions cause release of substances such as leukotrienes that have effects on the nervous system? To make matters even more complex, some patients with the typical clinical syndrome found with the primary APLA syndrome do not have lupus anticoagulant or anticardiolipin antibodies. Clearly, these two antibody types do not satisfactorily explain the clinical and pathologic findings but are merely the currently used and available diagnostic markers.

Some of these dilemmas are apparent in the case history presented by Pulpeiro et al. [4]. Their patient had visual, motor, sensory, and ataxic symptoms. Examination showed abnormalities of the optic nerve, pyramidal tract, and cerebellum. Both lupus anticoagulant and anticardiolipin antibodies were present. Tests for SLE were negative. The brain MR studies showed multiple subcortical foci of high signal intensity on T2-weighted images, although the CT scans, even with double-dose delayed contrast enhancement, failed to show white matter lesions. Were these lesions indicative of multiple sclerosis, ischemia, or some other process? Unfortunately, no tests of vascular patency or function such as sonography or angiography were reported, and no pathologic specimens were available.

Ophthalmologic complications in patients with APLAs have included amaurosis fugax, acute ischemic optic neuropathy, and retinal artery and vein occlusions [6, 7]. The patient described by Pulpeiro et al. [4] had total blindness in one eye and only slight pallor of that optic disk, findings more consistent with optic neuritis than anterior ischemic optic neuropathy, although posterior ischemic optic neuropathy is a possibility [15]. Oppenheimer and Hoffbrand [16] reported a patient with optic neuritis associated with SLE and both anticardiolipin antibodies and lupus anticoagulant. SLE-associated optic neuropathy is more likely to cause complete blindness or persistent central scotomas than is optic neuritis due to multiple sclerosis. Circulating antibodies may be a marker for "vasculitic optic neuritis," for example, secondary to SLE.

Transverse myelitis can occur in SLE in association with APLA and is mistaken for multiple sclerosis as well [16–18]. In addition to optic neuropathy, Oppenheimer's patient had myelopathy, adding to the diagnostic confusion [16]. In one patient with SLE and APLA, MR of the spinal cord showed increased signal intensity and diffuse edema but returned to normal after treatment with corticosteroids and cyclophosphamide [19]. However, in another patient with a history of SLE, positive anticardiolipin antibodies and transverse myelitis, the MR studies were normal [20].

The risk of stroke or other neurologic disease in patients harboring APLA is not yet clear. Kushner [8], in a recent prospective study that screened patients with neurologic disease for APLA, found that the presence of anticardiolipin antibodies was significantly more common in the group with brain ischemia than in those with nonischemic neurologic disorders. Brey et al. [9] found a high rate (45.6%) of APLA in young stroke patients. They also found that these antibod-

ies do not appear to be related to "brain disease" per se, as they are found significantly more frequently in stroke/TIA patients than in age- and sex-matched patients with other neurologic diseases, such as vascular headache and epilepsy. Recurrent stroke seems to be more likely in those with APLA and may be better prevented by warfarin than corticosteroids [7], although the numbers are small and results are not entirely conclusive.

The report of Pulpeiro et al. [4], and this brief review, are more likely to raise questions than to provide clear answers. Neuroradiologists are urged to stay abreast of developments in this fast-moving field. Certain neuroimaging findings might allow them to suggest to their less widely read clinical colleagues the need to test for APLAs and blood coagulation components in individual patients. Neuroradiologists have always shown ingenuity and innovative capabilities. Perhaps they will discover a way to image the blood and obviate the present confusing array of blood tests. A picture is worth a thousand words.

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