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Antiphospholipid Antibodies: Findings at Arteriography

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PURPOSE: The purpose of this study was to determine the frequency and types of abnormalities at arteriography in patients with antiphospholipid antibodies (APA) and ischemic cerebrovascular events.

METHODS: Twenty-three patients with APA and ischemic cerebrovascular events who underwent arteriography were identified. Patients over the age of 65 years were excluded. No patients met diagnostic criteria for systemic lupus erythematosus. All angiograms were reviewed by two neuroradiologists.

RESULTS: Seventeen patients (74%) between the ages of 28 and 64 years (average age, 40 years) had abnormal angiograms. Sixteen patients had arterial abnormalities and one had dural sinus thrombosis. Ten had solely intracranial abnormalities (nine arterial and one venous), six had solely extracranial arterial abnormalities, and one had both intracranial and extracranial arterial abnormalities. Intracranial arterial abnormalities included stem or branch occlusions of the cerebral or basilar arteries, which were generally solitary (six patients), and findings suggestive of vasculitis (four patients). Four patients had stenoses of the origins of two or more great vessels. Two patients had extracranial internal carotid artery stenoses or occlusions that were not typical of atheromatous disease, considered to be embolic in one patient. In another patient, a stenosis of the origin of the internal carotid artery was present that appeared typical of atheromatous disease. Infarctions were seen on CT or MR studies in 13 of 17 patients with abnormal angiograms.

CONCLUSION: In our group of patients, typical atheromatous lesions at the common carotid artery bifurcation were rare. Some lesions that are infrequent in the general stroke population (eg, vasculitis-like findings and stenoses at the origin of great vessels) were common. Patients with APA and cerebrovascular events appear to differ from the general stroke population with regard to types of arterial abnormalities seen at arteriography.

Antiphospholipid antibodies (APA) are circulating immunoglobulins that have been associated with a hypercoagulable state, of which one manifestation is ischemic cerebrovascular disease (1, 2). Some patients with these antibodies can be classified as having the so-called "antiphospholipid syndrome," characterized by early stroke, recurrent arterial or venous thromboses, spontaneous fetal loss, and thrombocytopenia (3, 4). Many recent studies have suggested that APAs are a risk factor for stroke, especially in young and middle-aged adults (1, 5–7). Reports of imaging findings in patients with APA and cerebrovascular disease have emphasized CT and MR imaging findings (8, 9) or only briefly outlined arteriographic findings (2, 8). We examined the arteriographic findings in a series of patients with APA to determine whether a typical disease pattern was present and whether angiographic findings differed from those in the general stroke population.

Methods

The files of the coagulation laboratories at a tertiary care university-based teaching hospital during the period January 1992 to August 1996 were reviewed for patients with elevated titers of anticardiolipin antibody or lupus anticoagulant. This search revealed 621 patients. All patients with elevated antiphospholipid titers were included, not just those who had evidence of a systemic process that could be categorized as antiphospholipid syndrome. The latter group consisted of only a minority of our study population. Laboratory studies were typically drawn for the presence of a prolonged partial thromboplastin time (PTT), a hypercoagulable state (cerebrovascular or systemic arterial or venous thrombosis of unexplained cause), or to screen women with a history of recurrent fetal

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 F_{IG} 2. 56-year-old woman with a mixed connective tissue disorder and transient ischemic attacks who was treated with immunosuppressive therapy for presumed CNS vasculitis with no progression of symptoms thereafter.

A, Left common carotid artery catheter angiogram, lateral view, shows sites of arterial occlusion (*solid arrow*) and alternating segments of dilatation and narrowing (*open arrows*). Similar findings were seen in the vertebrobasilar circulation (not shown).

B, Axial T2-weighted MR image (2200/80/1) shows left-sided thalamic infarction (arrow).

loss. The lupus anticoagulant panel consisted of a prothrombin time (PT), activated partial thromboplastin time (aPTT), tissue thromboplastin inhibition test (TTIT), thrombin clot time (TCT), and a dilute Russell's viper venom time (DRVVT). A lupus anticoagulant was identified on the basis of the presence of the following: a prolonged aPTT that did not correct with mix, a TTIT ratio of more than 1.3, or an abnormal DRVVT with a positive DVV confirmatory test (American Diagnostica, Inc), or a combination of these results. An enzyme-linked immunosorbent assay (ELISA) was used to detect anticardiolipin antibodies (IgG or IgM).

Patients older than the age of 65 years were excluded from analysis because of the possibility that angiographic abnormalities were related primarily to age rather than to a hypercoagulable state associated with APA. It was recognized that atheromatous lesions in the remaining patients would not be excluded. Patients with other causes of a hypercoagulable state (eg, tumor or a clotting factor abnormality) were also excluded. In addition, patients with systemic lupus erythematosus (SLE) were excluded because of the possibility that complications of SLE accounted for their neuroradiologic findings rather than a hypercoagulable state associated with APA. Patients with specific vascular risk factors, such as cigarette use, were not excluded.

The computer-based files of radiologic examinations of all patients with positive titers were searched for those with a history of arteriography of the cerebral vasculature. Twentythree patients (17 women; average age 41 years) with APA and ischemic cerebrovascular events who underwent arteriography were identified. No patients met diagnostic criteria for SLE. All angiograms were reviewed independently by two neuroradiologists who were blinded to the arteriographic interpretations. When opinions differed between the two interpreters, agreement was reached by consensus.

Results

Seventeen patients (74%; 12 women, average age 40 years) had abnormal catheter angiograms. Ten

patients (43%) had solely intracranial abnormalities, of which nine were arterial and one was venous (dural sinus thrombosis). Six patients (26%) had solely extracranial arterial abnormalities, and one patient (4%) had both intracranial and extracranial arterial abnormalities. Infarctions were seen on CT or MR examinations in 13 patients, all arterial events. Of the remaining four patients, dural sinus thrombosis was seen on MR images in one and the other three had normal CT or MR imaging studies and a clinical course compatible with transient ischemic attack. The one dural sinus thrombosis occurred in the right transverse sinus without evidence of associated infarction. Four patients in this study were reported previously in a series in which the focus was general neuroradiologic findings rather than primarily angiographic findings (8).

Two major types of intracranial arterial abnormalities were seen: stem occlusions of major arteries or branch occlusions (Fig 1), which were usually solitary, and multifocal sites of arterial narrowing and widening suggestive of (but not proved to be) vasculitis (Fig 2). Intracranial arterial occlusions were present in six patients, occurring in the basilar (two patients), middle cerebral (two patients), and anterior cerebral (one patient) arteries, and in branches of the middle cerebral artery (one patient).

Four patients had multiple sites of arterial narrowing and dilatation, suggestive of vasculitis. Erythrocyte sedimentation rate (ESR) was normal in three of these patients and elevated in one patient. CSF analysis was normal in all four. None of these patients underwent leptomeningeal or brain biopsy to prove the diagnosis of vasculitis. One patient underwent



Fig 3. 26-year-old woman with a 3-week history of sudden onset of left-sided monocular blindness. Transesophageal echocardiogram showed a hypokinetic left ventricle but no evidence of mural thrombus, valvular vegetations, or right-to-left cardiac shunt by microcavitation study.

A, Aortic arch catheter angiogram, left anterior oblique view, shows occlusion of the left common carotid artery (*arrow*) a few centimeters above its origin. The remainder of the brachiocephalic arteries are normal in appearance. (Image provided courtesy of Leroy Roberts, Chapel Hill, NC.)

B, Long-TR/short-TE proton density-weighted MR image (2500/30/2) shows a small cortical infarction (*arrow*) within the left frontal lobe.

Fig 4. 64-year-old woman with sudden onset of right hemiparesis and history of deep venous thrombosis of the leg a year earlier, indicative of hypercoagulable state. Left common carotid catheter angiogram, anteroposterior view, shows a smoothly contoured intraluminal filling defect (arrow) in the origin of the left ICA, consistent with a thrombus. Thrombus was seen in the aortic arch (not shown). The patient underwent successful ICA thrombectomy and was started on warfarin therapy. The aortic thrombus resolved over the next 3 months but recurred soon after warfarin therapy was discontinued. Fig 5. 22-year-old woman with multiple bilateral transient ischemic attacks and Takayasu-like syndrome. Arch aortogram, left anterior oblique projection, shows severe stenoses of the innominate artery (solid arrow), left subclavian artery, and left ICA (open arrows).

biopsy of the superficial temporal artery, which did not show findings indicative of vasculitis. Among these four patients, one had a clinical course that was thought to clearly reflect CNS vasculitis. This patient was treated with long-term immunosuppressive therapy and subsequently improved clinically. In the remaining three patients, the long-term clinical course did not clearly indicate that CNS vasculitis was the most likely cause of abnormalities seen at arteriography. Instead, a noninflammatory vasculopathy was considered to be the probable cause of the angiographic findings. One of these patients (who had a normal ESR) was treated with immunosuppressive therapy for a period of a few months but continued to have transient ischemic attacks. This patient showed clinical stabilization after long-term anticoagulant therapy was begun. Neither of the remaining two patients (one of whom had an elevated ESR) was treated with immunosuppressive therapy, and both had a stable long-term clinical course, suggesting that vasculitis was unlikely.

Extracranial arterial abnormalities, present in seven patients (32%), could be classified into three types: common carotid or internal carotid artery (ICA) stenosis or occlusion (two patients; Figs 3 and 4), stenoses or occlusions of the origin of two or more great vessels (Takayasu-like pattern, four patients; Fig 5), and narrowing of the ICA in a pattern typical of atheromatous disease (one patient, age 53 years). In one of the patients with stenoses at the origins of multiple great vessels, occlusion of the left common carotid artery extending to involve the intracranial portion of the ICA was seen (on MR images). This patient was classified as having both intracranial and extracranial arterial abnormalities.

Transesophageal echocardiography was performed in eight patients (five with intracranial arterial abnormalities and three with extracranial arterial abnormalities). In one patient, a hypokinetic left ventricle was found (Fig 3), and in another patient, mitral insufficiency was seen. In none of the patients were intracardiac thrombi, vegetations, or other valvular abnormalities seen. One of the patients with extracranial carotid artery occlusion (Fig 4) was found by transesophageal echocardiography and thoracic MR imaging to have aortic thrombus, which was presumed to be the source of an embolus to the ICA. This patient underwent ICA thrombectomy with complete removal of thrombus; the appearance of the artery was normal at follow-up imaging 2 weeks later.

Discussion

Patients above the age of 65 years were excluded from our study in order to focus on the role (if any) that APA might have in the pathogenesis of stroke in young and middle-aged patients and lower the likelihood that strokes in our population were due to more common, age-related factors, such as atheromatous carotid artery disease or cardiogenic embolism related to ischemic heart disease. However, we recognize that by excluding patients over the age of 65 years from our study the mean age of our patients is lower than the mean age of all patients with APA and stroke identified in our review of laboratory and radiologic data. Therefore, our data cannot be taken as evidence that stroke in patients with APA occurs at a younger age than it does in the general population. However, in other studies, APAs have been increasingly recognized as a risk factor for stroke in young and middle-aged adults (1, 5-7, 10). As a group, patients with APA and ischemic cerebrovascular events have been reported to be younger than patients without APA (1). APAs have been reported in 18% to 45% of patients under the age of 50 years with cerebral ischemia (5–7). The increased risk for stroke is thought to be related to a hypercoagulable state associated with APAs (3). An increased frequency of thrombosis or embolism, presumably related to a hypercoagulable state, has also been noted in autopsy studies. In one study, 68% of APA-positive patients were found at autopsy to have thrombosis or embolism (frequently unrecognized in life) compared with 17% of APA-negative patients (11).

Venous thrombosis is recognized as being more common in systemic (i.e. non-CNS) thromboses in patients with APA (12). Therefore, venous thromboses and, in particular, dural sinus thrombosis might be expected to be common in our patient population. However, the majority of arteriographic abnormalities in this series were arterial rather than venous in origin. This finding might be expected in a series based on arteriographic findings, since dural sinus thrombosis is more typically diagnosed by cross-sectional imaging studies (especially MR imaging) than by arteriography. Thus, patients with dural sinus thrombosis might be expected to be underrepresented in a series of patients undergoing arteriography. Nonetheless, the preponderance of arterial abnormalities in this study group is consistent with the findings in a larger series of patients with APA undergoing any form of neuroimaging study previously reported by us, in which arterial strokes were much more common than venous strokes (13).

Embolism from an aortic thrombus was presumed to be the cause of extracranial ICA occlusion in one of our patients. Embolism is believed to be a major cause of stroke in patients with APA, and is usually thought to be due to a cardiac source (14, 15). Cardiac valve abnormalities are common in patients with antiphospholipid syndrome, although they were not found in any of the eight patients in our study who underwent echocardiography. Valve deformities due to fibroelastic thickening in association with plateletfibrin thrombi have been reported (16). In one series of 21 patients with APA and ischemic cerebrovascular events, 15 had echocardiographic evidence of valvular abnormality (usually valvular thickening or vegetations, or regurgitant lesions) (15). At times, the valvular masses, which can attain large size, have been noted to resolve after anticoagulation therapy (17). In one of the few series reporting angiographic findings in patients with APA, about 50% of patients (mean age, 46 years) who underwent cerebral angiography had intracranial lesions, and about half of these had branch occlusions, suggesting an embolic origin (2). In another study of six patients with APA and cerebral infarction, cerebral angiography showed findings that were thought consistent with embolism in three patients and, in another two patients, emboli due to nonbacterial thrombotic endocarditis were thought to be the most likely cause of stroke (14). The cause of occlusion of intracranial arteries in six of our patients is not known with certainty but the evidence does not favor cardiogenic embolism. Among the four patients with such occlusions who underwent transesophageal echocardiography, there was no evidence of a cardiac source of embolism. Nonetheless, this pathogenesis cannot be absolutely excluded in those four patients. It is possible that a source of embolus below the threshold of detection by echocardiography could have been present. Alternatively, an embolus could have migrated from the heart at the time of stroke leaving no evidence of the embolic source on subsequent echocardiography.

In the absence of demonstration of a cardiogenic source of embolus, in situ thrombosis appears to be the most likely mechanism for arterial occlusion in our patients. APAs are postulated to have a procoagulant effect on platelets and endothelial cells, which could cause in situ thrombosis (3). A disorder of fibrinolysis has also been implicated as a potential cause of arterial thrombosis (18). Supporting evidence for thrombosis as the mechanism of arterial occlusion comes from reports of bland thrombi within the lumen of medium-sized and small intracranial arteries (19, 20) as well as in non-CNS vessels (21).

Extracranial arterial disease was common in our patients, but took various forms and occurred primarily in patients much younger than the typical age for atheromatous disease. Extracranial disease has previously been reported in patients with APA, being seen in four of 13 young patients with cerebral ischemia who underwent cerebral angiography (5). Four patients in our series had stenoses or occlusions of the origins of multiple arch vessels in a pattern suggestive of Takayasu vasculitis. An association between a Takayasu-like syndrome and APA has previously been reported (22–24) but it is unclear what relationship (if any) these antibodies might have to Takayasu vasculitis. Stenoses due to intimal connective tissue proliferation, muscular hyperplasia of the media, and fibrosis involving the adventitia have been reported in large and medium-sized arteries of patients with APA (25). In addition, arterial wall hyalinization and thickening have been found in the large and medium-sized arteries within cutaneous ulcers (26). Similar changes could be the cause of the extracranial stenoses in our patients, but in the absence of histologic data, this explanation remains unconfirmed.

The cause of the multiple regions of narrowing within intracranial arteries in four of our patients is uncertain. These findings suggested the diagnosis of vasculitis in each case; however, the diagnosis was not confirmed by leptomeningeal or brain biopsy in any of these cases, and in only one case did the diagnosis appear to be vasculitis after long-term follow-up. We deliberately included these patients in our study population because of the possibility that their angiographic findings represented evidence of an underlying vasculopathy (ie, noninflammatory process) rather than a true vasculitis. It should be noted that several studies of the histopathology of vascular changes in patients with APA have failed to demonstrate vasculitis in the majority of cases (11, 21, 27, 28). In one series of 22 patients with APA and autopsy findings indicative of thrombotic or embolic events, vasculitic features were not seen in any patient (11). Typical features of vasculitis with histologic findings of a transmural lymphocytic infiltrate responsive to corticosteroids have been reported in only a few cases (29, 30), usually in association with an independent underlying disease (31). Instead, almost all cases of large-vessel occlusive disease in patients with APA have been found to be thrombotic in nature (31), often in association with underlying mural abnormalities. In a small number of APA patients undergoing limb amputations for vascular insufficiency, arterial occlusions due to intimal and medial proliferation have been noted (25). Luminal narrowing caused by concentric intimal hyperplasia, fibrous occlusions, and fresh and recanalized thrombi in the absence of vasculitis have been noted in small leptomeningeal arteries in patients with APA and ischemic cerebrovascular events (32, 33). It is possible that similar abnormalities affecting the intracranial arteries were the cause of the arteriographic findings in some or all of our patients with a vasculitis-like pattern. The fact that three of these four patients stabilized without corticosteroid or immunosuppressive therapy (or did not respond to such therapy) may be considered evidence supportive of a noninflammatory vasculopathy causing the arteritis-like angiographic findings.

Patients with APA are reported to have a high rate of recurrence of stroke and other thromboembolic events (1, 34). In one series, the risk of recurrent cerebrovascular events among young patients with APA was reported to be increased eightfold as compared with patients without the antibodies (5). For these reasons, patients with APA are usually treated with long-term anticoagulation (34). However, the hypercoagulable state associated with APA renders many cases refractory to standard doses of anticoagulants, underscoring the importance of identifying these antibodies. Warfarin treatment, which produces high degrees of anticoagulation with an international normalization ration (INR) in the range of 3.0 to 4.0, is often necessary (34) because recurrent thromboses are seen in many patients at standard doses. (The INR is a normalization factor that allows protimes from different laboratories to be compared using a correction factor for different sensitivities of reagents to factor VII. An INR of 2.0 to 3.0 usually proves adequate in healthy persons.)

Conclusion

The sum of evidence from our series and previous studies suggests that the etiology and pathogenesis of stroke in patients with APA fundamentally differ from that in the general stroke population. Typical findings of atheromatous disease were uncommon in our patients, even in those with extracranial disease. We suggest that APA should be considered in young and middle-aged patients when arteriography shows abnormalities other than typical atheromatous lesions. The presence of these antibodies is even more strongly suggested when the following conditions are present: otherwise unexplained prolongation of the activated PTT, unexplained non-CNS thromboses, and a vasculitis-like appearance of the intracranial arteries when clinical or biopsy findings do not strongly indicate a high likelihood of vasculitis.

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