Antiphospholipid Antibodies in Cerebral Ischemia

J. Montalbán, MD; A. Codina, MD; J. Ordi, MD; M. Vilardell, MD; M.A. Khamashta, MD; and G.R.V. Hughes, MD, FRCP

In a 2-year prospective study of 146 patients with cerebral ischemia, we compared vascular risk factors for stroke with clinical and laboratory findings, particularly antiphospholipid antibodies. Ten patients (6.8%) were positive for at least one antiphospholipid antibody; one patient had systemic lupus erythematosus, one had rheumatoid arthritis, and the remaining eight fulfilled criteria for the diagnosis of primary antiphospholipid syndrome. These patients were predominantly male, not necessarily young, and 50% of them did not have any other vascular risk factors; there were no significant clinical or paraclinical differences between these patients and those without antiphospholipid antibodies. Outcome in the 10 patients was good, and platelet antiaggregating drugs proved to be useful in preventing further cerebrovascular ischemic events in our patients. (Stroke 1991;22:750-753)

In 1983, Hart and Miller1 listed almost 100 potential causes of stroke in young adults. Using an aggressive evaluation a few years later, Adams et al2 were able to suggest a likely cause of stroke in approximately 90% of their patients. It is now 7 years since detailed description of the antiphospholipid antibodies first appeared.3 Clinically, one of the most prominent as well as the gravest feature associated with these antibodies is cerebral ischemia.4 Nevertheless, this association has often been reported in patients with autoimmune disorders such as systemic lupus erythematosus (SLE) and the recently described “primary” antiphospholipid syndrome,5 but there are few studies based on a general population with thrombotic stroke.

How important are antiphospholipid antibodies in the causation of stroke? To answer this question we performed a 2-year prospective study of 146 patients with cerebral ischemia, investigating different antiphospholipid antibodies and comparing vascular risk factors with clinical and laboratory findings.

Subjects and Methods

Over 2 years we collected plasma from 146 consecutive patients (107 men and 39 women; mean age 51.4 [range 14–88] years) with cerebral ischemia attending Hospital General “Vall d’Hebron,” Barcelona, during the first week after the event. Embolism and hemorrhage had reasonably been excluded in all cases. The inclusion criteria were 1) the presence of a focal neurological deficit, 2) the absence of a hemorrhagic infarct or hematoma on the cerebral computed tomogram (CT scan), 3) the absence of a potential source of emboli, 4) the absence of embolism to other organs, and 5) the presence of atherosclerotic vascular disease by angiography. We also collected plasma from 100 healthy blood donors. Ten milliliters blood was drawn from each subject into a citrated glass tube; plasma was obtained immediately by centrifugation and stored frozen at −70°C until use.

Clinical data were obtained at the time of plasma collection from the patients by interview and from chart review. The data collection form was designed to provide a complete record of the clinical, biochemical, and radiological manifestations of disease for each patient. Hypertension (blood pressure of ≥160/90 mm Hg), diabetes, hyperlipidemia (total cholesterol concentration of ≥250 mg/dl), cigarette smoking (>10 cigarettes/day), alcohol intake (>60 g/day), oral contraceptive use, previous transient ischemic attacks (focal deficit lasting <24 hours), stroke or other thrombotic episodes, and previous miscarriages were included on the data form.

Full medical and past histories were obtained from all patients, and all underwent complete physical examination. Full hematologic and biochemical investigations were carried out according to standard procedures. These included a full blood count; glu-
TABLE 1. Correlations Between Different Antiphospholipid Antibodies in Patients With Cerebral Ischemia

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LA, lupus anticoagulant; ACA, anticardiolipin antibodies; APAA, antiphosphatidic acid antibodies; ASA, antiphosphatidylethanolamine antibodies; APEA, antiphosphatidylyceroglycan antibodies; AVDRL, antivenereal disease research laboratory antibodies; RPR, rapid plasma reagin test.

Concentration of the lupus anticoagulant was measured in the plasma. Concentrations of anticardiolipin antibody and antibodies to phosphatidylethanolamine, sphingomyelin, phosphatidic acid, and the Venereal Disease Research Laboratory antigen were measured at room temperature in normal (not heat-treated) plasma by a standardized enzyme-linked immunosorbent assay as devised by Gharavi et al. Results of the anticardiolipin antibody assay were expressed according to the standardization workshop and results of the other antiphospholipid antibody assays were considered positive when the optical densities were >4 standard deviations above the mean for the 100 healthy blood donors. All tests were performed in a blinded fashion at the Lupus Research Laboratory, St. Thomas’ Hospital, London. All positive results were repeated at least once, and a second blood sample was checked 2 months later.

The patients with a positive antiphospholipid antibody test were clinically evaluated again before discharge from the hospital. The deficit was considered mild when the individual was able to return to work or usual levels of daily activity; moderate when the individual was not able to return to work or usual levels of daily activity but did not require chronic institutional care or assistance with dressing, feeding, or personal toilet; and severe when the individual required chronic institutional care and assistance with dressing, feeding, or personal toilet. Patients were reevaluated at 6-month intervals.

The groups with and without antiphospholipid antibodies were compared using univariate analysis, using a t test for continuous variables and the \( \chi^2 \) test for categorical variables.

Results

Of the 146 patients, 10 (6.8%; nine men and one woman; mean age 49.4 [range 27-59] years) were positive for at least one antiphospholipid antibody (Table 1). No healthy blood donor was positive. In two of the 10 patients there were associated immunologic disorders (SLE or rheumatoid arthritis). The remaining eight patients fulfilled criteria for the diagnosis of primary antiphospholipid syndrome. Cases 1, 8, and 10 had a history of thrombosis (stroke, pulmonary embolism, and myocardial infarction, respectively). Only one patient had thrombocytopenia.

Five of the 10 patients were smokers, three had hypertension, two suffered from diabetes, and two had high levels of total cholesterol. The concentration of antithrombin III and the prothrombin time were within the normal range in all 10 patients. Studies of the supra-aortic vessels showed signs of atheroma in three. Of the 10 patients with positive antiphospholipid antibody assays, six had involvement of the carotid territory and two of the posterior circulation territory; in one case it was not possible to know the exact topography of the cerebral ischemia. Echocardiography was performed in eight of the 10 patients with positive antiphospholipid antibody assays, and was normal in all cases. When we compared antiphospholipid antibody-positive patients with those having negative results, we found no differences between groups for any parameter on the data collection form.

The outcome in all 10 antiphospholipid antibody-positive cases but one (case 8) was good. In five cases there was no deficit at the time of discharge, in three the deficit was mild, and in one the deficit was moderate; one patient died in spite of being treated with immunosuppressive agents and anticoagulants,
thrombosis. A relation between the lupus anticoagulant and a low antithrombin III activity has been suggested. Our findings confirm the data of Hasselaar et al, who also could not show a correlation between a decreased antithrombin III activity and presence of the lupus anticoagulant.

Treatment choices are uncertain. Conventional clinical wisdom suggests platelet antiaggregating drugs for patients with antiphospholipid antibodies and stroke. However, the appropriate therapy for these patients remains controversial.

While thrombosis seems to be the main pathogenesis of cerebral ischemia in patients with antiphospholipid antibodies, other mechanisms, including lacunar infarction and even embolism, may also be involved. Clinical diagnosis of cardiogenic brain embolism is based on a constellation of findings, none of which is individually diagnostic. Clinical studies of embolic stroke are limited by our inability to diagnose cardiogenic embolism with certainty.

Valve lesions in association with antiphospholipid antibodies and cerebral ischemia have been reported in patients with SLE and, perhaps significantly, less frequently in patients with primary antiphospholipid syndrome. In this series, echocardiography was performed in eight of the 10 patients with positive antiphospholipid antibody assays and was normal in all cases. The presence of these antibodies in patients with SLE may predispose those with underlying valve lesions to superimposed thrombus formation, but the low incidence of valve lesions among patients with primary antiphospholipid syndrome may be due to the absence of inflammatory endothelial disease in these patients.

In conclusion, our data indicate that a considerable proportion (6.8%) of patients with cerebral ischemia have antiphospholipid antibodies and that most such patients fulfill criteria for the diagnosis of primary antiphospholipid syndrome. We believe that measurement of the antiphospholipid antibody concentration might be useful in patients with cerebral ischemia since those with such antibodies may have a good prognosis. Furthermore, platelet antiaggregating drugs could prevent further cerebrovascular ischemic events in these patients.

Acknowledgment

We wish to thank Dr. J. Guardia from Universitat de Barcelona for his assistance in the statistical analysis.

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Key Words • anticoagulants, antiphospholipid antibodies • anticoagulants, lupus • risk factors
Antiphospholipid antibodies in cerebral ischemia.
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Stroke. 1991;22:750-753
doi: 10.1161/01.STR.22.6.750

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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