Anticardiolipin Antibodies Are Frequently Present in Patients With Idiopathic Intracranial Hypertension

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Background: Anticardiolipin antibodies (ACL-Ab) are associated with various neurologic syndromes, but idiopathic intracranial hypertension (IIH) has only rarely been reported in this context.

Objectives: To delineate the frequency and clinical and radiological features of, as well as the cause-and-effect relationship between, ACL-Ab and IIH.

Methods: We analyzed the medical records of patients with IIH hospitalized between January 1989 and September 1995. All patients underwent magnetic resonance imaging or magnetic resonance venography or angiography. Excluded were patients with intracranial hypertension due to dural sinus thrombosis or traumatic, structural, neoplastic, or infectious disorders. Patients who were found on at least 2 separate occasions to have increased IgG titers of ACL-Ab were identified and compared with patients without ACL-Ab.

Results: Six (43%) of 14 patients with IIH had ACL-Ab. No differences in clinical, laboratory, or radiological variables could be found between patients with and without ACL-Ab. Only 3 of the 11 ACL-Ab–positive patients had previous systemic or neurologic abnormalities associated with ACL-Ab.

Conclusions: Anticardiolipin antibodies may cause IIH through mechanisms unrelated to major venous thrombosis. Idiopathic intracranial hypertension is frequently associated with ACL-Ab and can be the presenting symptom of the antiphospholipid syndrome. There are no major clinical, laboratory, or radiological features that distinguish between patients with IIH with and without ACL-Ab.

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PATIENTS AND METHODS

PATIENTS

We analyzed the medical records of patients diagnosed as having IIH in the Hadassah University Medical Center, Jerusalem, Israel, from January 1989 to September 1995. During this time, it was our practice to examine the cerebral blood vessels in every patient presenting with intracranial hypertension (IH). Thus, all included patients underwent magnetic resonance imaging (MRI), including magnetic resonance (MR) angiography and MR venography or standard angiography. All patients were screened for the presence of ACL-Ab, according to our routine policy. Included in the IIH group were patients with headaches with or without minor focal symptoms of transient visual obscurations, tinnitus, and diplopia. Patients with minor neurologic signs such as asymmetry of deep tendon reflexes or pronation of a limb were not excluded from the IIH group because these most probably do not represent focal brain dysfunction in the absence of radiological evidence of focal lesions. All patients with IIH had an initial cerebrospinal fluid pressure above 25 cm H2O and no evidence of dural sinus thrombosis or cortical vein thrombosis on neuroimaging. Excluded from the study were patients with dural sinus or cortical vein thrombosis and patients with traumatic, neoplastic, infectious, structural, or congenital causes of IIH. Patients with IIH who did not have an adequate neuroimaging study (eg, patients who underwent only MRI without the completion of MR venography) were also not included in this study. The study group was further divided into subgroups of patients with and without ACL-Ab.

METHODS

The presence of ACL-Ab was determined by a commercial enzyme-linked immunosorbent assay kit (before July 1995, Disse, Rome, Italy; afterward, Cambridge Life Sciences, Cambridge, England). Values above 20 U/mL for the first kit (reference value, <10 U/mL) and above 15 U/mL for the second kit (reference value, <7.5 U/mL) were considered significantly abnormal. At least 2 assays more than 14 days apart that demonstrated elevated IgG levels of ACL-Ab were required to consider the test positive for ACL-Ab.

Statistical analysis was performed by the Student t test and χ² test. We used commercially available statistical software (Sigma Stat, Jandel Scientific, San Rafael, Calif) for the analyses.

CLINICAL FEATURES

Common symptoms included transient visual obscurations in 4 patients (2 with and 2 without ACL-Ab), minor lateralizing signs in 2 (1 in each subgroup), and diplopia in 2 (both without ACL-Ab) (Table). No clinical variable could differentiate between patients with and without ACL-Ab. The time from the onset of symptoms to diagnosis tended to be shorter in patients with ACL-Ab, but this difference did not reach statistical significance.

AUXILIARY EXAMINATIONS AND LABORATORY FINDINGS

The mean initial cerebrospinal fluid pressure and constituents did not differ between patients with and without ACL-Ab (Table). Three ACL-Ab–positive patients had moderately increased serum antinuclear factor titers (+2-3/4). Serum antinuclear factor was also identified in a single patient without ACL-Ab. Anti-DNA antibodies were identified in one ACL-Ab–positive patient with a history of systemic lupus erythematous.

None of the ACL-Ab–positive patients had protein C or S deficiency. One ACL-Ab–negative patient had protein C deficiency. Because activated protein C resistance was not tested during this study, we do not have results of this test in our patients.

NEURORADIOLOGICAL FINDINGS

Thirteen of the patients had MRI with MR angiography and venography, and 1 patient had angiography as the inclusion neuroradiological procedure. A few non-
specific periventricular hyperintense T2-weighted lesions were seen on MRI in 2 patients with (1 with systemic lupus erythematosus) and 1 patient without ACL-Ab. No other radiological abnormalities were detected.

TREATMENT AND OUTCOME

None of the patients, whether with or without ACL-Ab, received anticoagulant medication. Patients who had ACL-Ab were treated with aspirin. All patients with and without ACL-Ab were treated with acetazolamide with or without furosemide, with the subsequent reduction of cerebrospinal pressure from a mean (± SD) of 37.3 (± 11.0) cm H2O to 21.7 (± 2.0) cm H2O in ACL-Ab-negative patients and from 44.5 (± 13.0) cm H2O to 23.0 (± 5.0) cm H2O in ACL-Ab-positive patients.

None of the patients died during the acute episode of IH or during a follow-up period of a mean of 26 months (range, 3–63 months). Despite residual chronic papilledema in 3 of the patients, no significant visual loss occurred in any of our patients.

COMMENT

Following a few anecdotal reports of a possible association between ACL-Ab and IH,11,12 our study is the first to evaluate systematically the clinical, laboratory, and radiological findings of patients with IH and ACL-Ab and to compare them with those of similar patients without ACL-Ab.

A substantial number of our patients with IH (6 of 14) had persistently elevated titers of ACL-Ab. Although some of these patients had other potential risk factors for IH, the absence of such risk factors in most of our patients and the much higher rate of ACL-Ab in these patients than in the general population lend support to the important role of ACL-Ab in this disorder.

Most patients (4 of 6) with serum ACL-Ab had ACL-Ab without evidence of systemic lupus erythematosus. Furthermore, only one patient with ACL-Ab was known to have the antiphospholipid syndrome (APS) before the current hospital admission for IH. During the follow-up period, none of the patients had a thrombotic event that could be indicative of APS. The absence of further thrombotic events in most of our patients may be due to effective preventive therapy (eg, aspirin). It is also possible that IH may represent a restricted form of APS limited to the central nervous system. Another possibility is that the moderately elevated titer of antibodies present during the acute event represents a nonspecific finding and that APS will never develop in these patients. Yet, the presence of elevated antibody titers on repeated examinations and the frequency with which they were noted are not in favor of the latter hypothesis. Thus, it appears that APS can present as IH in a substantial number of patients.

With the exception of the time between the onset of symptoms and diagnosis, which tended to be shorter in patients with than in those without ACL-Ab, no clinical, laboratory, or neuroradiological variable examined differed between patients with and without ACL-Ab. Likewise, all our patients had the benign course typical of IH.13,14

The pathogenesis of the vascular events associated with ACL-Ab is not clear. It was suggested that alterations of the natural balance between the coagulation and the fibrinolytic systems favor thrombosis. Several possible targets for ACL-Ab action in thrombosis have been implicated, including endothelial cells,15 apoprotein H,16,17 naturally occurring anticoagulants,18 and proteins C and S.19 The moderately elevated ACL-Ab IgG titers in our patients, and the association of such titers with vascular thrombosis in the antiphospholipid syndrome,20,21 could implicate thrombosis as a plausible mechanism for the development of IH in our patients. None of the patients, however, had evidence for thrombosis or received anticoagulants, and yet, all recovered completely under therapy aimed at lowering the intracranial pressure. This suggests either that ACL-Ab has no role in the formation of IH or that the increased intracranial pressure was not mediated by evident vascular thrombosis. The mechanism for IH in these patients, however, might still be partial dural sinus obstruction missed by MRI or angiography. Indeed, cases of partial venous obstructions causing IH have been recently demonstrated.22,23 Intracranial hypertension may also be due to increased blood viscosity induced by ACL-Ab without actual thrombosis. Although this was not directly studied in the present study, hyperviscosity may elevate the intracranial pressure similarly to the case in polycythemia vera.24 Another possibility might be that the presence of ACL-Ab predisposes patients with other risk factors such as endocrine abnormalities or dysimmune disorders to the development of IH. In such a context, minimal changes in the venous drainage of brain parenchyma may suffice to elevate the intracranial pressure. Finally, apoprotein H has been demonstrated in brain tissue (Y. Chapman, MD, PhD, oral communication, November 1996). Thus, ACL-Ab may be directed against specific brain antigens and cause IH by interaction with these antigens and by blocking cerebrospinal fluid drainage.

CONCLUSIONS

Anticardiolipin antibodies are frequently associated with IH. The exact pathogenesis of IH in IH patients with ACL-Ab is unclear. It may be impossible to distinguish clinically and radiologically between patients with and without ACL-Ab in this syndrome. Future research to corroborate our findings is needed before a firm recommendation can be made to screen all patients with IH for the presence of ACL-Ab and to treat patients with IH and ACL-Ab.

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REFERENCES


