High Association of Anticardiolipin Antibodies With Psychosis

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Background: Lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) are autoantibodies that can be detected in plasma or serum of patients with autoimmune-related diseases. The presence of these autoantibodies has been associated with recurrent arterial and/or venous thromboembolism as well as with recurrent fetal loss and thrombocytopenia. In recent years, other medical conditions such as dementia, chorea, psychosis, migraine, and peripheral neuropathy have been associated with these autoantibodies. An adverse response to neuroleptic treatment was reported to be associated with the presence of autoantibodies, but these patients rarely developed clinical vascular manifestations.

Method: We conducted a study of 34 unmedicated patients admitted to the hospital with acute psychosis in whom aCL and LA were examined before and after neuroleptic treatment to determine the presence of antibodies relative to the treatment condition.

Results: 32% (11/34) of the unmedicated psychotic patients had antiphospholipid antibodies: we detected elevated titers of IgG-aCL isotype in 24% (8/34) of unmedicated patients ($p < .02$ compared with 20 normal controls, none of whom tested positive), and 9% (3/34) had LA. Twenty-two patients were followed up after medication; 31.8% (7/22) of these patients showed moderate titers of IgG-aCL ($p < .28$), and 18.2% (4/22) were LA positive. Altogether, antiphospholipid antibodies were detected in 40.9% (9/22) of the medicated patients.

Conclusion: This study shows the increased incidence of LA and aCL antibodies in neuroleptic-treated psychotic patients and the possible association between psychosis and antiphospholipid antibodies.

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Antibodies against phospholipids are autoantibodies with high affinity to negatively charged phospholipids in the inner surface of the cell membrane.[1,2] Phospholipids are also present in the serum, bound to proteins (lipoproteins), and play an important role in the coagulation process.[2] The lupus anticoagulant (LA) was first described in 1952[3] in some patients with systemic lupus erythematosus (SLE). This clotting inhibitor factor was associated with false tests for syphilis.[4] Later, additional studies showed that the lupus anticoagulant activity is caused by antiphospholipid antibodies. Its prevalence in the general population ranges from 1.8% to 9.4%.[5] Other antiphospholipid antibodies have also been described, namely anticardiolipin antibodies (aCL). These autoantibodies (aCL and LA), mainly the IgG isotype of aCL, have been associated with thrombotic vascular events in autoimmune-related disorders, as well as with recurrent fetal loss,[6] dementia,[7,8] migraine, and chorea.[9] Prolonged medication with neuroleptic agents can be associated with the presence of autoantibodies in the serum, mainly IgM-aCL and LA,[10,11] but patients with neuroleptic-induced autoantibodies rarely develop thrombotic events or autoimmune-related disorders.

The aim of our study is to clarify the possible relationship between the occurrence of LA/aCL in psychotic patients and the effect of neuroleptic treatment on that incidence.

PATIENTS AND METHOD

Thirty-four consecutive unmedicated patients with an episode of acute psychosis were included in the study. They fulfilled the DSM-III-R diagnostic criteria for acute psychiatric episode. None had evidence of SLE or other autoimmune-related disorders. Exclusion criteria for the study included patients with epilepsy, history of thrombosis or other vascular events, fetal loss, or chronic medication of any type. The first blood sample was drawn at admission; a second sample was obtained at the end of follow-up (3–9 months) after study entry. The plasma was anticoagulated by adding one part of 3.8% sodium citrate to nine parts of venous blood. All samples were tested for

prothrombin time and partial thromboplastin time. The presence of LA was estimated by two different methods: (1) diluted Russell's viper venom time and (2) tissue thromboplastin inhibition test.[12]

Anticardiolipin antibodies were measured in plasma stored at –20°C by an enzyme-linked immunosorbent assay (ELISA), a technique described by Gharavi et al.,[13] using a modification of the original radioimmunoassay developed by Harris et al.[14] The aCL IgG or IgM was calibrated using samples from Harris's Antiphospholipid Standardization Laboratory, University of Louisville, Ky. Results were calibrated against a standard curve in γ-aCL U/mL and μ-aCL U/mL. Values greater than two standard deviations above the mean values of 100 sera samples from healthy subjects were considered abnormal, with the cutoff of 10 γ-aCL U/mL for IgG and 8 μ-aCL U/mL for IgM anticardiolipin. Titers from 12 to ≤ 20 γ-aCL U/mL for IgG and 10 to ≤ 20 μ-aCL U/mL for IgM were considered low positive; from > 20 to ≤ 60 γ-aCL or μ-aCL U/mL, moderately positive; and > 60 γ-aCL or μ-aCL U/mL, high positive.

Antinuclear antibodies were determined by indirect immunofluorescence on Hep-2 cells serving as substrate. The results were analyzed using the chi-square test. Twenty voluntary healthy donors, without history of psychiatric or vascular events or fetal loss and without history of chronic medication, were age matched and served as the control group.

RESULTS

Thirty-four consecutively admitted patients (17 men, 17 women) with a first episode of acute psychosis were included in the study; they received no neuroleptics prior to admission. Twenty-two of these patients completed the follow-up period; 12 did not return for clinical checkup, and their follow-up blood samples were not obtained. The final DSM-III-R diagnosis in the remaining 22 patients was brief reactive psychosis. The mean age of the 34 patients was 33.5 years (range, 18–57). Among the 34 unmedicated patients, positive titers of IgG-aCL were detected in 8 patients (23.5%) ($p < .02$ compared with normal controls), whereas 3 patients (8.8%) were LA positive. IgM-aCL titers were within normal limits (Table 1). After initiation of treatment with phenothiazines and/or butyrophenones, 22 patients completed the follow-up. Another blood sample was obtained at the end of the follow-up (3 to 9 months). In 9 of these patients (40.9%) anticardiolipin antibodies were detected, 7 of whom (31.8%) had moderate titers of IgG-aCL ($p < .28$ compared with the unmedicated group), including 1 that also had moderate titers of IgM-aCL, and 4 (18.2%) that showed LA activity (2 of whom also showed IgG-aCL activity) (Table 1). In 3 of the patients, titers of IgG-aCL decreased after initiation of the treatment (Patients 4, 6, and 7). Antinuclear antibodies were negative in the sera of all 34 unmedicated patients. Table 2 shows the treatment of all patients who were aCL and/or LA positive and who completed the follow-up period. No significant correlation could be detected relating the specific neuroleptic treatment of the patients and the detection of aCL or LA. All control subjects were negative to both aCL and LA. The mean time to follow-up of the 22 patients was 6.9 months (range, 3–9). In addition, during the follow-up period, no episodes of thrombosis or other clinical vascular events were recorded in any of the LA/aCL positive patients.

Table 1. Psychotic Patients With Anticardiolipin Antibodies in Plasma Before and After Neuroleptic Medication*†

	Unmedicated			Medicated		
Patient	IgG-aCL	IgM-aCL	LA	IgG-aCL	IgM-aCL	LA
1	19	–	–	38	37	+
2	20	–	–	30	–	–
3	20	–	–	n/a	n/a	n/a
4	28	–	–	22	–	–
5	24	–	–	n/a	n/a	n/a
6	17	–	–	11	–	–
7	19	–	–	12	–	–
8	18	–	–	n/a	n/a	n/a
9	–	–	–	20	–	–
10	–	–	–	24	–	–
11	–	–	–	20	–	+
12	–	–	–	21	–	–
13	–	–	+	n/a	n/a	n/a
14	–	–	+	n/a	n/a	n/a
15	–	–	+	n/a	n/a	n/a
16	–	–	–	–	–	+
17	–	–	–	–	–	+

*Abbreviations: + = positive, – = negative, aCL = anticardiolipin antibodies, LA = lupus anticoagulant, n/a = not available. Five patients who completed follow-up are omitted from the table because all values were negative.
†aCL determinations were considered positive when higher than mean ± 2 SD values calculated from healthy subjects (IgG > 12 units, IgM > 10 units). Comparison of IgG-aCL levels between normal controls and unmedicated patients was significant ($p < .02$). Comparison of IgG-aCL levels between unmedicated and medicated patients was nonsignificant ($p < .28$).

DISCUSSION

The association between neuroleptic treatment and antiphospholipid antibodies is well known and has been reported in the past.[10,11,15–17] Despite detection of aCL and/or LA, SLE or vascular manifestations are usually absent in these patients. The aim of our study was to determine the chronological appearance of these autoantibodies in patients that started treatment with neuroleptics. To our surprise, we detected antiphospholipid antibodies in a high percentage of the unmedicated patients. In 24% of our patients, IgG-aCL was detected ($p < .02$), and 9% had LA. In all, 32% of the 34 patients evidenced serum antiphospholipid antibodies previous to any antipsychotic medication. The titers of IgM-aCL were within normal limits in our unmedicated patients, and antinuclear anti-

Table 2. Neuroleptic Treatment of the Patients Who Completed Follow-Up Who Had Antiphospholipid Antibodies or Changes in the Values of IgG-aCL After Treatment

Patient/Sex	Age (y)	IgG-aCL	IgM-aCL	LA	Treatment
1/F	40	38	37	+	Chlorpromazine, haloperidol
2/M	26	30	–	–	Haloperidol
4/F	29	22	–	–	Fluphenazine, haloperidol
6/M	24	11	–	–	Chlorpromazine, haloperidol
7/F	37	12	–	–	Chlorpromazine
9/F	36	20	–	–	Chlorpromazine, haloperidol
10/M	31	24	–	–	Perphenazine
11/F	30	20	–	+	Perphenazine, fluphenazine
12/M	25	21	–	–	Fluphenazine, haloperidol, levomepromazine
16/F	32	–	–	+	Fluphenazine, levomepromazine
17/F	31	–	–	+	Levomepromazine, perphenazine

bodies were not detected. The presence of autoantibodies in unmedicated psychotic patients has been reported in the past, but in only a few cases, and the reasons are not well understood. Chengappa et al.[18] reported the presence of IgG-aCL and IgM-aCL in 3 (16.7%) of 18 schizophrenic patients who were in the first episode and drug-naive, while IgM-aCL (but not IgG-aCL) was associated with neuroleptic treatment. In the present study, a high percentage (32%) of the unmedicated psychotic patients had antiphospholipid antibodies in the plasma, mainly IgG-aCL isotype, while after treatment with neuroleptics, that percentage rose to 40.9%. In 4 patients, IgG-aCL were undetected before the medication but were detected after neuroleptic treatment, and in 3 other patients, the titer of IgG-aCL of the first sample decreased during the treatment.

This is the first report of the dynamic changes in the value of IgG-aCL, and we have no explanation for them. In the follow-up, we could detect no clinically significant differences in the psychotic episode or differences related to the various neuroleptic medications. Further investigations are necessary to try and clarify the connection between these antibodies and psychosis. In contrast with previously reported studies, we did not detect IgM-aCL isotype in the unmedicated patients. IgM-aCL was found in only 1 patient under neuroleptic treatment. We found no type of IgA-aCL autoantibodies or antinuclear antibodies.

During the follow-up, no clinical vascular events were reported. However, we are unable to exclude events in the microcirculation. Brain image studies such as positron emission tomography, single photon emission computed tomography, and others were not done in our study. We have no satisfactory explanation about the role of antiphospholipid antibodies in psychotic patients. Cortical atrophy, ventricular dilatation, and ischemic lesions have been reported in the follow-up of patients with dementia and antiphospholipid antibodies.[8] It can be postulated that aCL are involved in the pathogenesis of such ischemic lesions of psychotic patients, although such a relationship needs to be demonstrated.

Another explanation could be the role of the antibodies on the cell surface in the central nervous system. The antiphospholipid antibodies that can be detected in the patients are specific to the phospholipids present in the central nervous system, mainly to the phosphatidylserine and phosphatidylinositol, and less specific to the lipoproteins in the serum. These phospholipids have been implicated in schizophrenia.[19] It could be—and it is only a speculation—that the presence of IgG-aCL in the plasma of some patients may play a role in the etiology of the psychotic episode. IgG-aCL and LA have been found in a high percentage in our unmedicated patients; perhaps the presence of these antibodies suggests that the etiology may be related to some autoimmune disorder, and the antiphospholipid antibodies may serve as a marker of the psychosis and are not related to the neuroleptic treatment.

The role of genetic factors in the development of these antibodies cannot be excluded. Hereditary factors in schizophrenia are well known[20,21]; Sirota et al.[22] reported the presence of high titers of antiphospholipid antibodies in healthy first-degree relatives of schizophrenic patients. In our study, we did not examine the relatives of the patients.

In light of our findings, we suggest that the antiphospholipid antibodies may have a role in the development of the psychotic episode and are not related to only the neuroleptic treatment. Further investigations are necessary to clarify the understanding of the autoantibodies and their possible role in psychosis.

Drug names: chlorpromazine (Thorazine and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), levomepromazine (Levoprome), perphenazine (Trilafon).

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