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Abstract: Higher titers of autoantibodies have been reported in recent studies of depressed patients. In an attempt to investigate the presence of antiphospholipid autoantibodies in patients with depression, sera from both patients and healthy controls were tested for immunoglobulin G and M anticardiolipin and antiphosphatidylserine autoantibodies. We tested positive sera for antiphosphatidylserine (APSA) and anticardiolipin autoantibody (ACA) in 10 dysthymic, 19 major depressive, and 20 healthy subjects. Tests for ACA-IgM were found to be positive in 1 of the dysthymic patients, in 1 of the major depressives and 1 member of the control group. Positive ACA-IgG was found in 1 of the dysthymic patients, 1 of the major depressives and 1 member of the control group. Positive APSA-IgM was found in 3 of the dysthymic patients, 3 of the major depressives and 4 members of the control group. Positive APSA-IgG was found in 2 of the dysthymic patients, 2 of the major depressives and 3 members of the control group. There were no significant differences in IgG, IgM-ACA and APSA between the dysthymic and major depressive groups and the control group. After categorizing both groups for age and sex, no difference was found in the frequency of ACA and APSA positive sera between both groups, indicating that on the basis of serology, no evidence exists that antiphospholipid autoantibodies might be the etiological factor for dysthymic or major depressive disorders.

Key Words: depressive disorders, antiphospholipid, anticardiolipin, antiphosphatidylserine

Introduction

Antibodies against phospholipids are autoantibodies with high affinity for 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 they play an important role in the coagulation process (2). Antiphospholipid groups react with negatively charged phospholipids via phospholipid binding proteins. The most commonly reported antiphospholipids are anticardiolipin (ACA), antiphosphatidylserine antibodies (APSA) and the lupus anticoagulant (LA) (3,4). These autoantibodies, ACA and LA, mainly the Ig G isotype of anticardiolipin, have been associated with thrombotic vascular events in autoimmune-related disorders, as well as with recurrent fetal loss (5), dementia (6,7), migraine, chorea (8) and epilepsy (9). Maes et al. (1991) have reported higher titers of these autoantibodies in depressed subjects. They measured antiphospholipid (anticardiolipin, antiphosphatidylserine), antinuclear antibodies in healthy controls, minor, simple major and melancholic patients and found that anticardiolipin antibody titers were higher in melancholics than in healthy controls and minor depressives, that antinuclear antibodies were found more frequently in depressed patients than in normal volunteers, and that there was a positive correlation between anticardiolipin and antinuclear antibody titers (10). In another study, Maes et al. (1992) measured the binding index of APSA, ACA and antipartial thromboplastin (APTA) in 22 minor, 23 simple major and

20 melancholic depressives. They found a higher expression of antiphospholipid antibodies during depression but a much lower incidence of antibody-positive patients than in classical autoimmune disorders (11). The aim of the present study was to clarify the possible relationship between the presence of antiphospholipid autoantibodies (i.e., anticardiolipin and antiphosphatidylserine) and various depression categories.

Material and Methods

Subjects

Twenty-nine consecutive patients with depressive disorder and 20 normal controls were included in the study. The patients were categorized according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (12).

Their condition was diagnosed with the aid of the Structured Clinical Interview for DSM-IV, clinical version (13). Depression severity was measured using the Hamilton Depression Rating Scale (Ham-D) (14). None of the subjects had evidence of SLE or other autoimmune-related disorders. Exclusion criteria for the study included epilepsy, history of thrombosis or other vascular events, fetal loss, or chronic medication of any type. Eighteen depressed patients were free of psychotropic drugs for at least one month prior to hospital admission. The others (n=11) had been taking antidepressants. These drugs were discontinued upon admission, and consequently these subjects underwent a washout period of 7 days before blood samples were collected as also done in the study of Maes et al. (11).

Twenty voluntary healthy donors, with no history of psychiatric or vascular events or fetal loss and with no history of chronic medication, were age matched and served as the control group.

Serum samples

Ten milliliters of nonheparinized venous blood was drawn and allowed to clot at room temperature. The sera were separated on the same day and stored at –20°C until use.

Detection of antiphosphatidylserine and anticardiolipin IgG and IgM

Antiphosphatidylserine antibodies were detected by using the micro-ELISA technique and a Clark Laboratories Inc. test kit. The assay wells were coated with phosphatidylserine purified from bovine spinal cord. The positive control, the negative control, the cut-off control and all the samples were diluted 1:100 with sample diluent. 100µl of diluted controls and samples were pipetted into the wells of microtiter strips. The plates were incubated at room temperature (18-25°C) for 30 minutes, and then were washed four times with washing buffer. After this treatment, 100µl of enzyme conjugate (horseradish peroxidase conjugated anti-IgG or anti-IgM) was added to the wells. The plates were incubated at room temperature (18-25°C) for 15 minutes. The washing procedure was repeated as described previously. 100µl of substrate solution (tetramethyl benzidine) was added to the wells, which were then incubated at room temperature (18-25°C) for 15 minutes. 50µl of stopping solution (1N H_2SO_4) was added to the wells. The optical density (OD) of the controls, calibrator and samples was read on a multiscan spectrophotometer (multiplate autoreader EL-309) at 450nm.

The results for IgG and IgM antiphosphatidylserine antibodies were calculated separately. A positive value was defined as an OD sample difference higher than the calibrator (OD calibrator for IgG: 60 arb u/ml, OD calibrator for IgM: 60 arb u/ml).

The anticardiolipin IgG and IgM antibodies assays were performed by substituting phosphatidylserine with cardiolipin.

The results for IgG and IgM cardiolipin antibodies were calculated separately. A positive value was defined as an OD sample difference greater than the index value (0.90: negative, 1.10: positive).

Statistical Analysis

All statistical analysis was performed using the SPSS 7.0 statistical program (14). Comparisons were carried out by means of the χ^2 test.

Results

The depressed patients consisted of 10 dysthymic disorder patients, 19 major depressive disorder patients, 10 of them with a single episode (7 with psychotic features) and 9 of them recurrent. There were no significant differences (χ^2 =7.05; df: 5; p< 0.217) in age between the study groups; mean (±SEM) of the control group was 33.3(±2.57), that of the dysthymic disorder group years was 43.38(±7.13), and that of the major depressive disorder group was 30.00(±6.87), with 35.14(±5.68) for a single episode and 41.17(±6.51) years for recurrent episodes. There were no significant differences in the male-to-female ratios between these groups, which were as follows: controls, 10/10; dysthymic disorder, 6/4; major depressive disorder, 9/10.

There were no significant differences in APSA and IgG and IgM cardiolipin antibodies between the depressive group and the control group. The data in the Table show that APSA and IgG and IgM group cardiolipin antibodies were not significantly more common in either the depressive patient group or its subgroups compared with the control subjects. Fifteen patients had mild depressive symptoms, 10 had moderate symptoms and 5 had severe depressive symptoms. There was no significant difference between the groups in terms of positive sera for APSA and ACA. There was no significant relationship between age and positive ACA and APSA. There was no difference in positive ACA and APSA between subjects who were drug-free and those who were on psychotropic drugs prior to admission.

Discussion

The last decade has produced a series of studies documenting that depression may be associated with impairment of the immune function (16). Some authors have reported the presence of antinuclear antibodies in subjects with major depression compared with normal volunteers (10,17-19). There is a parallel between the clinical, biochemical and immunological features of depression and classical autoimmune disorders: (i) both depression and autoimmune disorders tend to be recurrent and may follow a course of alternating exacerbations and remissions (20); (ii) autoimmune disorders such as systemic lupus erythematosus (SLE) show a high rate of mental manifestation and brain reactive autoantibodies are pathogenetically relevant for these symptoms (21), (iii) both disorders occur frequently in females (20,22,23); (iv) the status of sex hormones (such as estrogens) may be linked to exacerbations in both depression (24) and SLE (25); (v) the incidence of autoimmunity tends to increase in aged populations (23), and the frequency and intensity of severe depression increases with age (26,27).

In our study, we could not find any significant relationship between the severity of illness (HDRS) and any of the antiphospholipid autoantibody titers. There were no significant relationships between age and positive ACA and APSA. There were no differences in positive ACA and APSA between subjects who were drug-free and those who were on psychotropic drugs prior to admission. A limited number of studies have reported that depressive patients have higher APSA and ACA titers. In one study, higher ACA titers were found in depressive disorders (10). In another study, Maes et al. found a higher binding index in depressives than in controls but there were no meaningful positive values when compared with SLE (11).

We assessed the sera of donors, identifying them as negative or positive and we used an index value which is

Table . Frequency and statistical comparison of ACA-IgM, ACA-IgG, APSA-IgM, APSA-IgG in depressive patients and control subjects.

	ACA-IgM	ACA-IgG	APSA-IgM	APSA-IgG
Dysthymics	10	10	10	10
No. tested	1	1	3	2
No. positive	1	1	3	2
Major depressives				
single episode				
No. tested	10	10	10	10
No. positive	1	-	2	2
recurrent				
No. tested	9	9	9	9
No. positive	-	1	1	-
Healthy controls				
No. tested	20	20	20	20
No. positive	1	1	4	3
Dysthymics vs. major depressives				
χ^2	9.740	7.232	3.052	2.701
p value	.284	.512	.549	.609
dysthymics vs. control				
χ^2	1.170	.709	1.038	.532
p value	.279	.400	.845	.466
major depressive vs. controls				
χ^2	.498	.042	.714	.480
p value	.480	.837	.398	.488

ACA-IgM: Anticardiolipin Immunoglobulin M, ACA-IgG: Anticardiolipin Immunoglobulin G,

APSA-IgM: Antiphosphatidylserine Immunoglobulin M, APSA-IgG: Antiphosphatidylserine Immunoglobulin p values<0.05 were considered significant.

used for autoimmune disorders. The differing results might be due to this assessment method.

In conclusion, although there are a lot of similarities in terms of clinical and laboratory findings, we do not think there is a causal relationship between systemic immune activation and the pathogenesis of depression. However, studies using a larger sample should be carried out.

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