Anti-ribosomal P antibodies related to depression in early clinical course of systemic lupus erythematosus

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Background: Diagnosis and treatment of neuropsychiatric lupus is still a major challenge in clinical practice. We investigated the association between depression and anti-ribosomal P (anti-P) antibodies in a sample of Iranian patients with systemic lupus erythematosus (SLE). **Materials and Methods:** This cross-sectional study was conducted on adult patients with SLE referring to a referral out-patient clinic of rheumatology. Demographic data and clinical data with regards to measuring disease activity with the systemic lupus erythematosus disease activity index were gathered. Anti-P antibodies were measured with the enzyme-linked immunosorbent assay method. Depression severity was measured by the Beck Depression Inventory-II. **Results:** One hundred patients (80% female and 20% male, age = 34.8 ± 10.9 years) were included. Anti-P antibodies were present more frequently in depressed than non-depressed patients (30% vs. 10%, $P = 0.015$). Depression severity was correlated with anti-P antibodies level only in patients with disease duration of less than 2 years ($r = 0.517$, $P = 0.019$). There was no association between the depression severity and disease activity. Binary logistic regression analysis showed age ($B = 0.953$, CI 95%: 0.914-0.993) and positive anti-P antibodies ($B = 4.30$, CI 95%: 1.18-15.59) as factors that independently associated with depression. **Conclusion:** We found an association between depression and presence of anti-P antibodies, and also strong correlation between depression severity and anti-P antibodies level in newly diagnosed SLE patients. Depression severity in newly diagnosed SLE patients may reflect a neuropsychiatric involvement, and in later phases, it is more affected by the chronicity of the disease as well as other environmental factors.

Key words: Autoantibody, depression, neuropsychiatric, ribosomal proteins, systemic lupus erythematosus

INTRODUCTION

Neuropsychiatric systemic lupus erythematosus (NPSLE) belongs to a number of different focal and general neurologic and psychiatric syndromes that may present in approximately one-half of patients with systemic lupus erythematosus (SLE), commonly at disease onset or within the 1st years after diagnosis. The underlying mechanisms of NPSLE are not clear; however, autoantibody mediated vascular or neuronal injury seems to play a major role.[1] Besides substantial impairment of quality of life and disability, studies have shown association of neuropsychiatric events during the disease with adverse long-term prognosis and even mortality.[2-4]

Common neurologic manifestations of NPSLE include cerebrovascular disease and seizures (5-15%). Severe cognitive dysfunction and peripheral nervous disorders are relatively uncommon (1-5%).[5,6] With regards to psychiatric syndromes, depression is the most common psychological symptom that presents

with various degrees in about 40% of patients with SLE.[7] When begin acutely, depressive symptoms may reflect the patient's reaction to such a chronic illness with significant life-style limitations; however, such symptoms may also reflect an organic brain syndrome in some cases.[7-9] Distinguishing between organic and functional etiologies of the NPSLE is of great importance for prompt and appropriate treatment strategies. However, there is no diagnostic test that can reliably establish a specific diagnosis of NPSLE, yet.[5]

An association between depression and anti-ribosomal P (anti-P) antibodies has been reported in SLE patients.[10] Antibodies to ribosomal P proteins are one of the most studied serological markers in detecting NPSLE. These antibodies are directed mainly against the carboxy 22 amino acids of the three large-subunit ribosomal phosphoproteins, called P0, P1, and P2.[11] Experimental studies showed that anti-P antibodies can induce pure depression-like behaviors in mice, and suggested involvement of olfactory and limbic brain areas in the pathogensis of

depression in this case.[12,13] However, while early studies claimed that serum anti-P antibodies are accurate for the diagnosis of NPSLE,[10] further investigations did not approve it. A recent meta-analysis combined data from 1,537 patients contributed by 14 research teams found that anti-P antibody testing has limited diagnostic value (sensitivity 25-27%, specificity 75-80%) for NPSLE, and it is not helpful in differentiating among various subsets (e.g., psychosis vs. depression).[14]

Diagnosis and treatment of NPSLE is still a major challenge in clinical practice. The pathogenic role of anti-P antibodies in NPSLE is not fully delineated. Considering few data on the association between depressive symptoms and anti-P antibodies in SLE patients, and differences between different populations regarding involvement of anti-P antibodies in SLE, we investigated the association between depression and anti-P antibodies in a heterogeneous sample of Iranian SLE patients.

MATERIALS AND METHODS

Patients and settings
This cross-sectional study was conducted in Isfahan city (central of Iran) from November 2011 to November 2012. For this study, sampling was performed from a referral outpatient clinic of rheumatology in a university hospital, which is specifically belongs to diagnosis and treatment of SLE. Adult patients with SLE, according to the American College of Rheumatology criteria for diagnosis of SLE, were consecutively enrolled.[15] Those who were under pharmacologic and non-pharmacologic treatment for depression were not included in this study. Considering α = 0.05 and study power of 80%, and predicting a difference of at least 10% in positive anti-P antibody between those with and without depression, total sample size was calculated as 100 patients.[14] The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences and informed consent was obtained from all patients.

Data collection and assessment
Each patient was examined independently by a rheumatologist. Data were gathered including demographic data and clinical data with regards to measuring disease activity with the systemic lupus erythematosus disease activity index (SLEDAI-2K).[16] For measurement of anti-P immunoglobin G antibodies, enzyme-linked immunosorbent assay (ELISA) method was applied with a commercial available kit (ALPCO ELISA kit, Italy). The cut-off values are as 1-1.5 Relative unit: Borderline and >1.5: Positive based on the manufacturer advice.

For evaluating depression, patients responded to the Persian version of the Beck Depression Inventory-II (BDI-II), which is 21-item self-report inventory and one of the most widely used instruments for measuring the severity of depression. Each answer is scored on a scale value of 0-3. The cut-offs includes; 0-13: no or minimal depression; 14-19: mild depression; 20-28: moderate depression; and 29-63: severe depression. Higher total scores indicate more severe depressive symptoms.[17] A validated Persian version of the BDI-II was used in this study.[18]

Statistical analyses
Data were analyzed using the SPSS software, version 16.0 (Chicago, IL, USA). Descriptive data are presented by mean ± standard deviation (standard error [SE]) or number (%). Comparisons of quantitative data between patients with and without depression were performed using Independent Sample *t*-test or Mann-Whitney test in the case, which data were not normally distributed. Chi-square test was used for comparison of qualitative data. Examining the correlation between quantitative variables was evaluated by Pearson and Spearman (when data were not normally distributed) tests. Multivariate analysis was also performed for controlling confounding factors. A *P* value of < 0.05 was considered significant in all analyses.

RESULTS

A total of 100 patients (80% female, 20% male) with a mean age of 34.8 ± 10.9 years (ranged: 16-69 years) and disease duration of 4.1 (SE = 0.41) years (ranged: 6 months to 24 years) were included into the study. None of the patients had recent neurologic lupus manifestation including seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, and cerebrovascular attack. The SLEDAI-2K score ranged from 0 to 20; mean = 4.5 (SE = 0.45). Accordingly, 35% and 65% of the patients were categorized to have active and inactive SLE, respectively. With regards to the anti-P antibodies, 22% and 18% of the patients had positive and borderline anti-P antibody test. The BDI-II scores ranged from 3 to 44, mean = 18.5 ± 10.5. Accordingly, 20%, 19%, and 21% of the patients were categorized to have mild, moderate, and severe depression (40% had no or minimal depressive symptoms). Comparisons between patients with (BDI-II≥14) and without depression with regards to demographic and clinical data are presented in Table 1. Compared with non-depressed patients, depressed patients were younger (32.9 vs. 37.8 years, *P* = 0.027) and had more frequent active disease (40% vs. 27.5%, *P* = 0.142); though, it did not reach statistical significance. Also, depressed patients had more frequent positive anti-P antibody (30% vs. 10%, *P* = 0.015). The frequency of positive anti-P antibody in patients with minimal, mild, moderate, and severe depression was 10% (4/40), 30% (6/20), 15.7% (3/19), and 42.8% (9/21), respectively (*P* = 0.020). However, antibody mean levels were the same

Table 1: Association of anti-P antibody levels with demographic and clinical characteristics

Variable	BDI-II score <14 *n*=40	BDI-II score ≥14 *n*=60	*P*
Age (year)	37.8±12.8	32.9±9.1	0.027*
Female/male	31 (77.5)/9 (22.5)	49 (81.6)/11 (18.3)	0.396**
Disease duration (year)	3.9 (0.5)	4.2 (0.5)	0.496***
SLEDAI-2K	3.9 (0.7)	4.8 (0.5)	0.143***
Active disease	11 (27.5)	24 (40)	0.142**
Anti-dsDNA (U/mL)	88.6 (26.1)	68.9 (11.9)	0.131***
Anti-P antibody (RU)	1.24 (0.39)	1.99 (0.49)	0.213***
Positive anti-P antibody	4 (10)	18 (30)	0.015**

Data are shown ad mean±SD (SE) or *n* (%); BDI-II=Beck Depression Inventory-II; SLEDAI-2K=Systemic lupus erythematosus disease activity index-2k; Anti-dsDNA=anti-double stranded DNA; Anti-P=anti-ribosomal P; RU=Relative unit; *Independent sample *t*-test; **Chi-square test; ***Mann-Whitney U Test

Table 2:Association of demographic and clinical characteristics

Variable	Anti-dsDNA	SLEDAI-2K	BDI-II score	Anti-P antibody
Age	−0.098	−0.038	−0.098	−0.194
Disease duration	−0.005	0.075	0.227*	−0.188
Anti-dsDNA		0.465**	0.118	0.286**
SLEDAI-2K			0.119	0.263**
BDI-II score				0.100

Data are shown as Spearman correlation coefficients; BDI-II=Beck Depression Inventory-II; SLEDAI-2K=Systemic lupus erythematosus disease activity index 2000; AntidsDNA=anti-double stranded DNA; Anti-P=anti-ribosomal P; *P<0.05; **P<0.01

Table 3: Binary logistic analysis on possible predictors of depression

Variable	*P*	*B*	BDI-II score	95% CI for B
Age	0.023	0.953	−0.098	0.914-0.993
Gender	0.316	0.573	0.227*	0.193-1.703
Disease duration	0.255	1.069	0.118	0.953-1.199
SLEDAI-2K	0.887	1.008	0.119	0.905-1.122
Positive anti-P antibody	0.026	4.304		1.188-15.591

BDI-II=Beck Depression Inventory-II; SLEDAI-2K=Systemic lupus erythematosus disease activity index 2000; Anti-P=anti-ribosomal P; CI=Confidence interval

Figure 1: Correlation between anti-P antibody and Beck Depression Inventory-II score in patients with <2 years (*r*=0.517, *P*=0.019) and those with ≥2 years (*r*=0.009, *P*=0.934) duration of the disease

CI95%: 0.91-0.99) and largely positive anti-P antibody (*B* = 4.3, CI95%: 1.1-15.5) were found as independently associated with depression.

Considering possible different pathophysiology of depression in various disease duration states, we categorized patients to those with <2 years and ≥2 years of disease duration. In separate analyses of these two groups, a linear strong correlation was found between BDI-II score and anti-P antibody level only in patients with disease duration of less than 2 years (*r* = 0.517, *P* = 0.019), but not in those with disease duration of ≥2 years (*r* = 0.009, *P* = 0.934), Figure 1.

DISCUSSION

Differentiating organic from non-organic psychiatric symptoms in patients with SLE is of great importance; but, no specific serological or imaging marker has been introduced yet for this challenge. We investigated the association between depression and anti-P antibody in a heterogeneous sample of Iranian patients with SLE. The results of our study showed an association between depression and

between those with and without depression (*P* = 0.213), and among patients with minimal, mild, moderate, and severe depression (Kruskal-Wallis test, *P* = 0.464).

Linear correlations among different demographic and clinical variables are presented in Table 2. Anti-P antibody level was positively correlated with disease activity and anti-double stranded DNA antibody level. Also, BDI-II score was positively correlated with disease duration, but not with disease activity or anti-P antibody level.

Considering some associations between depression, age, and disease duration, and also between anti-P antibody level and disease severity, and not expecting a linear association, we conducted a binary logistic regression analysis on possible predictors of depression while controlling confounding factors. As presented in Table 3, minimally age (*B* = 0.95,
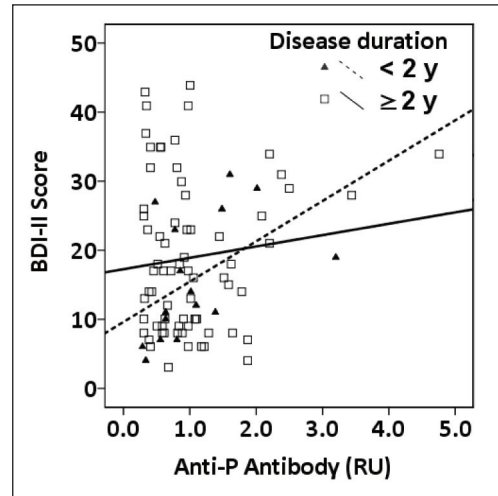
presence of anti-P antibodies. However, without considering disease duration, there was no linear correlation between depression severity and anti-P antibody level. However, in newly diagnosed SLE patients (<2 years disease duration), depression severity was linearly and strongly correlated with anti-P antibody level. This is while depression severity increased by increasing disease duration. These findings suggest that in newly diagnosed SLE patients, depression severity may reflect a neuropsychiatric involvement while in later phases of SLE; depression severity is more affected by the chronicity of the disease as well as other factors. Also, we found mild to severe depression in more than half of our patients, similar to other study from Iran.[19] Although previous studies in different populations have shown different frequencies of psychiatric syndromes almost all revealed that depression is the most common psychiatric symptoms in SLE patients with prevalence of about 40%. Differences in assessment techniques and definitions are the main sources of the variability in findings.[7] Moreover, results of previous studies on the association between the depression severity and disease activity have been controversial.[2,20-22] In our study, though active SLE was non-significantly more frequent in depressed patients, multivariate analysis did not confirmed such association. These results accompanying with previous studies highlight the fact that the pathophysiology of depressive symptoms in patients with SLE is multifactorial.[7]

Experimental studies showed that anti-P antibodies can induce depression-like behaviors in animal models. Interestingly, depressive behaviors could be reversed by specific therapy with monoclonal anti-idiopathic antibody to anti-P, intravenous immunoglobulin, and anti-depressant drugs.[12,13] With regards to human studies, previous investigations on the association between depressive symptoms and anti-P antibodies often included relatively small sample of patients and their results have been controversial. Schneebaum *et al.* in a large sample of SLE patients (*n* = 269) reported the presence of anti-P antibody in 19% of the patients and also a higher frequency in those with severe depression (88%) and psychosis (45%).[23] Higher frequency of anti-P in those with severe depression in the mentioned study is relatively similar to our findings, but still a linear correlation could not be found from current data. In a recent report from 50 patients with childhood-onset SLE, Aldar *et al.* found an association between anti-P and anxiety, but not depression in these patients. However, depression was still two times more frequent in those with positive anti-P and the study sample size has limited the analysis.[24] In contrast to these studies, Teh *et al.* in a relatively large sample of SLE patients (*n* = 116) found anti-P antibodies in 16% of their studied patients, but there was no association between the presence of anti-P

antibodies and depression.[25] Furthermore, Nery *et al.* in investigating 71 SLE patients found no difference between lupus psychiatric manifestations in the presence of anti-P or disease activity.[26] With regard to including patients without neurological manifestations this study is similar to ours, but our results are against it which might be due to the difference in the method for diagnosing psychiatric disorders. Finally, Jarpa *et al.* in a sample of Chilean patients with SLE (*n* = 83) found psychiatric disorders in 44.6% of patients, mostly mood and anxiety disorders, but authors found no association between any psychiatric disorder and anti-P or with disease activity.[20] However, authors in this study found anti-P in 94.4% (17/18) of those with a major depressive episode, compared with an overall frequency of 13.3%. The meta-analysis by Karassa *et al.*, which combined data from 1,537 patients showed limited diagnostic value of testing for anti-P antibody for NPSLE, though it did not provide particular information on depression.[14] Differences among these studies can be mainly attributed to different psychiatric diagnostic methods. Some studies, such as ours, have used standard patients-administered questionnaires like BDI, which also provide data on the severity of depression while others have used structured psychiatric interview, which provide more accurate diagnosis and also diagnosis of other disorders. Different ethnic (genetic) backgrounds, accuracy of the assays employed for autoantibody detection, and multiplicity of autoantibodies causing NPSLE are also key factors in this regard. Arnett *et al.* in a large sample of SLE patients (*n* = 394) from different ethnic groups showed an association between certain major histocompatibility complex class II alleles and presence of anti-P antibodies, highlighting the role of genetic factors. Authors also reported a significant association of NPSLE (psychosis and/or depression) with the presence of anti-P antibodies.[27,28]

There are some limitations in our study. For example, diagnosis of depression in our study was based on a self-reported questionnaire. Although BDI-II is highly accurate for diagnosing depression, additional structured psychiatric interview could provide more accurate diagnosis as well as information on other psychiatric disorders and also determine if depressive symptoms were acute or chronic. Second, depression symptoms in SLE patients wax and wane[28] and so and the use of corticosteroids in the treatment of disease impact on symptoms.

CONCLUSIONS

In this study, which was carried out on a heterogeneous sample of Iranian patients with SLE, we found an association between depression and presence of anti-P antibodies. When we considered disease duration, also we found a

linear and strong correlation between depression severity and anti-P antibody level in newly diagnosed SLE patients (<2 years disease duration). According to these results, depression severity in newly diagnosed SLE patients may reflect a neuropsychiatric involvement, and in later phases, it is more affected by the chronicity of the disease as well as other environmental factors. Anyway, we believe that assay for anti-P antibodies is just helpful in diagnostic approach to SLE patients with depressive symptoms particularly if depressive symptoms present early after SLE diagnosis. Further studies, especially cohort studies, with larger sample of patients are required for better understanding the accuracy of autoantibodies in the differential diagnosis of psychiatric manifestation of lupus.

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