Study of brain-derived neurotrophic factor in the serum of patients with systemic lupus erythematosus

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Received 19 February 2016
Accepted 16 June 2016

Egyptian Rheumatology & Rehabilitation
2017, 44:52–57

Objectives
Brain-derived neurotrophic factor (BDNF) is an important mediator of neuronal development, survival, and function. It is related to the pathogenesis of several neuropsychiatric disorders. The aim of this study was to determine the relationship between serum BDNF (sBDNF) level and neuropsychiatric status in systemic lupus erythematosus (SLE) patients.

Patients and methods
This study included the following groups: group I included 35 SLE patients with neuropsychiatric systemic lupus erythematosus (NPSLE) manifestations, group II included 30 SLE patients without neuropsychiatric manifestations, group III included 15 patients with neuropsychiatric disorders due to causes other than SLE, and group IV included 15 apparently healthy volunteers. All groups were matched for age and sex. SLE disease activity was assessed using the SLE Disease Activity Index. A Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Axis I was used for the assessment of psychiatric disorders, whereas neurological disorders were assessed by an expert neurologist. sBDNF was measured by the enzyme-linked immunosorbent assay.

Results
There was a statistically significant increase ($P<0.05$) in the mean titer of sBDNF in group I compared with other groups (314.9±162.1, 151.1±188.2, 218.1±198.4, and 141.9±130.2 ng/ml in groups I, II, III, and IV, respectively), as well as in group III compared with groups II ($P<0.05$) and IV ($P<0.05$). The mean serum titer of BDNF was statistically significantly elevated in active NPSLE patients (320.7±156.2 ng/ml, $P<0.05$) compared with inactive NPSLE (210.6±141.89.6 ng/ml, $P<0.05$), active SLE (142.8±162.7 ng/ml, $P<0.05$), and inactive SLE (139.8±174.8 ng/ml, $P<0.05$) without neuropsychiatric manifestations.

Conclusion
Variation in sBDNF level between SLE patients with and without neuropsychiatric manifestations indicates that it has a particular role in NPSLE disease process. Likely, it could be used as a biological marker for determining NPSLE disease activity.

Keywords:
brain-derived neurotrophic factor, neuropsychiatric systemic lupus erythematosus, structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, axis I disorders, Systemic Lupus Erythematosus Disease Activity Index

Egypt Rheumatol Rehabil 44:52–57

1110-161X

Introduction

Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious organ disorder. Its prevalence varies from 20 to 97%, causing considerable morbidity and mortality in SLE patients and is considered the third cause of death in SLE [1]. It includes a heterogeneous set of diffuse or focal, peripheral, or central psychiatric, complex, isolated, coincident, and/or sequential symptoms and signs, which might characterize both active and inactive disease states [2]. In 1999, a classification was published by the American College of Rheumatology (ACR) research committee, which described 12 central nervous system (CNS) syndromes and seven peripheral neurologic syndromes that were attributed to NPSLE [3].

The brain-derived neurotrophic factor (BDNF), a member of neurotrophines, is the most common growth factor in the CNS associated with neuroplasticity and neuronal repair [4]. It supports both the neurons already present and encourages the

growth and differentiation of new neurons and synapses through axonal and dendritic sprouting. It is active in the hippocampus, cortex, cerebellum, and basal forebrain – areas in the brain that are responsible for learning, memory, and higher thinking [5]. In addition to the nervous system, BDNF is present in a range of tissues, including the retina, the kidneys, and the prostate. In addition, it is secreted by Th1 and Th2 lymphocytes and macrophages and is stored mainly in platelets/thrombocytes; thus, it takes part in the regulation of homeostasis and is later released during increased demand [6].

Prepro-BDNF is a precursor protein that is converted to pro-BDNF, which could then be further converted to mature BDNF [7]. It is released from the postsynaptic membrane and binds to receptors on the surface of cells, tropomyosin-related kinase B receptor, resulting in its dimerization with autophosphorylation of the receptor tyrosine kinase and subsequent activation of intracellular signaling cascades, in addition to augmentation of *N*-methyl-d-aspartate receptor [8].

Patients and methods

Study approval

The aim of the study was explained to all participants. Written informed consents were obtained from all patients before being enrolled into this study, which was approved according to the Research Ethics Committee, Faculty of Medicine, Benha University, Egypt.

Patients

Group I included 35 patients with NPSLE; all of them met the revised criteria of the ACR nomenclature and case definitions for NPSLE (1999) [3].

Group II included 30 SLE patients without neuropsychiatric involvement who met the Systemic Lupus International Collaborating Clinic (SLICC) SLE Criteria [9].

Control groups

Group III included 15 patients with neuropsychiatric disorders due to causes other than SLE diagnosed according to the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Clinical Version [10], and group IV included 15 apparently healthy volunteers. All patients and healthy volunteers were not receiving any psychotrophic drugs at the time of blood sample collection for at least 24 h to 3 weeks according to the drug used.

All patients were recruited from the inpatient and the outpatient clinics of the *Rheumatology & Rehabilitation*, Internal Medicine and Neuropsychiatry Departments of Benha University Hospitals and Benha Teaching Hospitals between February 2014 and March 2015. The control groups were chosen matched for age and sex with SLE patients.

Exclusion criteria

Patients were excluded from this study if they had infections, endocrine and metabolic disorders, and/or drug abuse.

Methods

All patients were subjected to full history taking, thorough clinical examination, and assessment using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) [11]. Patients were classified as active if they had a SLEDAI-2K score equal to or greater than 5, and inactive if SLEDAI-2K score was less than 5. Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Axis I Disorders was used for assessment of psychiatric disorders [10]. Neurological disorders were assessed by an expert neurologist.

Diagnosis of NPSLE needed the presence of at least one item from the first group of criteria (seizures, psychiatric symptoms, cerebrovascular event, lesion of cranial nerves, motor disturbances, quantitative alterations of consciousness) and at least two items from the second group of criteria (cognitive dysfunction, headache due to lupus, peripheral neuropathy, MRI changes, EEG changes) after excluding other causes (except for SLE) [3].

Laboratory procedures

The following investigations were carried out: complete blood count, erythrocyte sedimentation rate (ESR) by the Westergren method recorded in millimeter per first hour, serum glutamate–pyruvate transaminase, kidney function tests, and 24-h urinary protein. Antinuclear antibodies and anti-double-stranded DNA were detected by the indirect immunofluorescence method, whereas the anti-ribosomal-P antibody and antiphospholipid antibodies were tested by enzyme-linked immunosorbent assay. sBDNF was measured by enzyme-linked immunosorbent assay for all subjects involved in this study according to the commercial enzyme immunoassay kit (R&D System GmbH, Wiesbaden, Germany). Samples were stored at 20°C until analysis. When the stop solution changes the color from blue to yellow, the intensity of the color is measured at 450 nm.

Active NPSLE patients included patients who displayed symptoms such as acute stroke, acute psychotic state, acute depression, and others at the time of blood sample collection in group I. In addition, blood samples were collected from group III during the acute episodes.

Statistical analysis

The statistical analysis was performed using SPSS program (statistical package for the social science), version 16 (SPSS Inc., Chicago, Illinois, USA).

Descriptive data

Descriptive data were given in the form of mean±SD, number, and percentage.

Analytical statistics

Using Kruskal–Wallis test, intergroup comparison of categorical data was performed using χ^2-test; Pearson's correlation coefficient (r) test was used to correlate different parameters. P-value more than 0.05 was considered statistically insignificant, P-value up to 0.05 was considered statistically significant, and P-value up to 0.001 was considered highly significant.

Results

Characteristics of the studied groups

There were no statistically significant differences among the studied groups ($P>0.05$) as regards age, sex distribution, and disease duration (Table 1).

The mean serum titer of BDNF was statistically significantly elevated ($P<0.05$) in SLE patients with neuropsychiatric manifestations (group I) compared with other groups (II, III, IV), and it was statistically significantly elevated ($P<0.05$) in group III than in groups II and IV.

Comparison between mean serum brain-derived neurotrophic factor among groups I and II regarding systemic lupus erythematosus disease activity score

The mean serum titer of BDNF was statistically significantly elevated in active NPSLE patients (320.7±156.2 ng/ml, $P<0.05$) compared with inactive NPSLE (210.6±141.89.6 ng/ml, $P<0.05$), active SLE (142.8±162.7 ng/ml, $P<0.05$), and inactive SLE (139.8±174.8 ng/ml, $P<0.05$) patients without neuropsychiatric manifestations (Table 2).

Comparisons of the mean serum level of brain-derived neurotrophic factor regarding the most common neuropsychiatric symptoms between systemic lupus erythematosus patients (group I) and neuropsychiatric patients (group III)

Regarding neuropsychiatric manifestations in group I, psychosis was the most frequent symptom (60%) followed by lupus headache (53.4%), depression (46.7%), and anxiety disorders (26.7%), whereas epilepsy (6.6%) and transverse myelitis (3.3%) were the least frequent symptoms. There was a statistically significant elevation ($P<0.05$) of the mean serum titer of BDNF in psychosis, stroke, epilepsy, depression, lupus headache, and chorea in group I compared with group III (Table 3).

In group I, there were significant positive correlations of serum levels of BDNF with ESR, SLEDAI-2K score of disease activity, SLICC/ACR damage index score, and CNS SLEDAI score, and insignificant correlations with age, hemoglobin, red blood cells, and platelet count. In addition, there were insignificant correlations of serum level of BDNF with white blood cell count, 24-h urinary protein, serum urea, and serum creatinine ($P>0.05$) (Fig. 1).

In group II, there were insignificant correlations of serum levels of BDNF with age, SLEDAI score, SLICC score, white blood cell count, platelets, 24-h urinary protein, serum urea, and serum creatinine. In addition, there were insignificant correlations of serum levels of BDNF with hemoglobin percentage, red blood cell count, and ESR ($P>0.05$) (Fig. 2).

All SLE patients were receiving a low dose of corticosteroids (mean±SD of 24.4±8.55 mg/day); other medications included hydroxychloroquine, azathioprine, and mycophenolate mofetil.

Discussion

BDNF was reported to play a role in the pathogenesis of different neuropsychiatric disorders; for example,

Table 1 Characteristics of the studied groups

Variables	Group I (N=35)	Group II (N=30)	Group III (N=15)	Group IV (N=15)	P-value
Age (years)	30.4±8.26	29.1±7.21	36.4±7.19	32.53±10.11	>0.05
Sex (male/female)	4/26	6/24	3/12	5/15	>0.05
Disease duration (mean±SD) (years)	4.88±4.19	4.5±3.14	4.2±2.18	–	>0.05
sBDNF (mean±SD) (ng/ml)	314.9±162.1	151.3±188.2	218.7±198.4	141.9±130.1	<0.05*

sBDNF, serum brain-derived neurotrophic factor. $P>0.05$, insignificant. *$P<0.05$, significant. **$P<0.001$, highly significant.

Table 2 Comparison between mean serum brain-derived neurotrophic factor among groups I and II regarding systemic lupus erythematosus disease activity score

Variables	Group I (NPSLE) (*N*=35)		Group II (SLE without neuropsychiatric symptoms) (*N*=30)		*P*-value
	Active (20)	Inactive (15)	Active (15)	Inactive (15)	
SLEDAI score	19.6	3.4	12.8	2.3	<0.0001**
sBDNF (ng/ml)	320.7±156.2	210.6±141.89.6	142.8±162.7	139.8±174.8	<0.05*

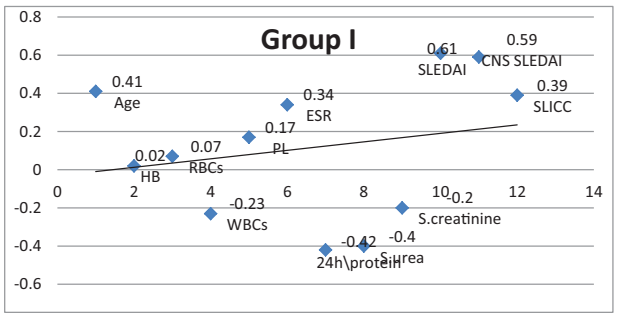
NPSLE, neuropsychiatric systemic lupus erythematosus; sBDNF, serum brain-derived neurotrophic factor; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus. *P*>0.05, insignificant. *P<0.05, significant. **P<0.001, highly significant.

Table 3 Comparisons of the mean serum level of serum brain-derived neurotrophic factor regarding the most common neuropsychiatric manifestations between systemic lupus erythematosus patients (group I) and neuropsychiatric patients (group III)

Neuropsychiatric manifestations	sBDNF (ng/ml)				*P*-value
	SLE patients with neuropsychiatric symptoms (group I) (*N*=35)		Neuropsychiatric patients (group III) (*N*=15)		
	n (%)	Mean±SD	*n* (%)	Mean±SD	
Stroke	4 (13.3)	241.72±39.06	3 (20)	175.89±27.9	<0.05*
Epilepsy	2 (6.6)	297.62±26.05	2 (13.3)	203.76±13.43	<0.05*
Psychosis	18 (60)	407.02±82.87	1 (6.7)	320.24	<0.05*
Depression	14 (46.7)	390.65±53.3	6 (40)	317.98±23.05	<0.05*
Anxiety disorder	8 (26.7)	367.87±37.8	2 (13.3)	297.34±17.98	>0.05
Transverse myelitis	1 (3.3)	311.64	1 (6.7)	275.09	>0.05
Lupus headache	16 (53.4)	453.01±15.45	9 (60)	347.07±48.15	<0.05*
Chorea	4 (13.3)	234.56±7.04	1 (6.7)	169.34	<0.05*

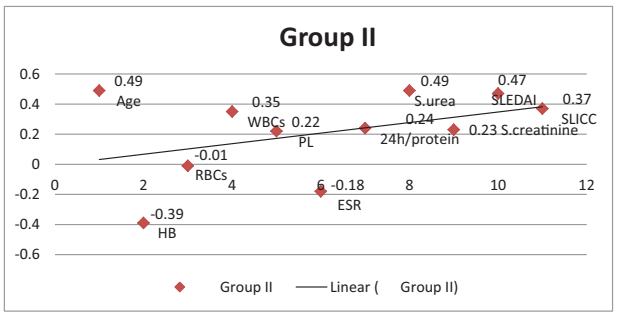
SLE, systemic lupus erythematosus; sBDNF, serum brain-derived neurotrophic factor. *P*>0.05, insignificant. *P<0.05, significant. **P<0.001, highly significant.

Figure 1



Correlations between sBDNF and different variables in group I. CNS, central nervous system; ESR, erythrocyte sedimentation rate; HB, hemoglobin; PL, platelet; RBC, red blood cell; sBDNF, serum brain-derived neurotrophic factor; S. creatinine, serum creatinine; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinic; WBC, white blood cell

Figure 2



Correlations between sBDNF and different variables in group II. ESR, erythrocyte sedimentation rate; HB, hemoglobin; PL, platelet; RBC, red blood cell; sBDNF, serum brain-derived neurotrophic factor; S. creatinine, serum creatinine; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinic; S. urea, serum urea; WBC, white blood cell

Hori *et al.* [12] reported that there was a relation between BDNF and schizophrenia, Yoshimura *et al.* [13] reported a relation with depression, Weinstock-Guttman *et al.* [14] reported a relation with multiple sclerosis, Laske *et al.* [15] reported a relation with Alzheimer's disease, and Berger *et al.* [16] reported a relation with cerebral ischemia.

The relation between neurotrophin (NT)-secreting immune cells and the resultant tissue injury was evaluated in some chronic inflammatory-autoimmune diseases. In rheumatoid or psoriasis arthritis, synovial CD3+ T lymphocytes and monocytes/macrophages generate elevated levels of nerve growth factors (NGFs), which augment both fibroblast-like cell proliferation and synovial T-cell activation via tropomyosin-related kinase A ligation and Akt phosphorylation [17,18].

In sarcoidosis, epithelioid and multinucleated giant cells of the granuloma, alveolar macrophages, and

T-cells produce NGF, BDNF, and NT-3 [19,20]. Expression of CD4 and CD8 NT correlates with sarcoidosis radiological damage index [20].

Increased BDNF levels in sera have also been reported in primary Sjögren's syndrome, which correlates with systemic activity and B cell and T-cell activation [21]. In contrast, sBDNF levels are decreased in systemic sclerosis, reflecting the vascular aspect of the disease [22].

These findings suggest that NT, markedly formed by immune cells in autoimmune diseases, might contribute to disease progression through modulating both immune cell function and tissue lesions [21].

In this study, we found a statistically significant increase in the mean titer of sBDNF in SLE patients with neuropsychiatric manifestations (group I) compared with other groups (II, III , IV) ($P<0.05$).

These results were in agreement with those of Ikenouch-Sugita *et al.* [23] and Tamashiro *et al.* [24] studies. Fauchais *et al.* [21] showed that levels of both NGF and BDNF in both serum and B cells were increased in SLE patients compared with healthy controls, independently of Th1 or Th2 profiles, suggesting that the neurotrophin production pathway is deregulated in SLE.

In 2006, Ikenouchi *et al.* [25] reported a case of SLE with CNS involvement (CNS lupus) and longitudinally investigated plasma levels of BDNF in the patient, and found that plasma levels of BDNF were raised in accordance with the severity of psychotic symptoms in this case of CNS lupus. These results suggest that it is useful to measure plasma levels of BDNF to predict the severity of psychotic symptoms in CNS lupus.

Rage *et al.* [26] reported that numerous cytokines – for instance, tumor necrosis factor-α, interleukin-6, and interleukin-1β – upregulate BDNF, which is also known to have an important role in the development of B cell linked to SLE pathophysiology. Therefore, elevated BDNF serum levels are a consequence of the increased activity of immune systems both in the brain and peripheral organs.

In this study, the mean serum titer of BDNF was statistically significantly elevated in active NPSLE patients (320.7±156.2 ng/ml, $P<0.05$) compared with inactive NPSLE (210.6±141.89.6 ng/ml, $P<0.05$), active SLE (142.8±162.7 ng/ml, $P<0.05$), and inactive SLE (139.8±174.8 ng/ml, $P<0.05$) patients without neuropsychiatric manifestations. This could be explained by the fact that activated B and T lymphocytes induce neurotrophin secretion, BDNF in particular [27]. Moreover, neurotrophins have been shown to act as survival factors for memory B cells [28] and may enhance proliferation of lymphocytes [29]. Thus, BDNF is not a nervous-system-exclusive neurotrophin and instead promotes cross talk between the immune system and the nervous system [30–31], which suggests that these factors play a role in the inflammatory response, as well as in the physiopathology of autoimmune diseases [32].

However, Ikenouchi-Sugita and colleagues [23–25] investigated sBDNF levels in individuals with SLE and did not find any correlation with the SLEDAI score. In addition, in a study conducted by Tamashiro *et al.* [24] it was reported that BDNF levels were increased in inactive NPSLE when compared with active SLE and controls ($P<0.0001$), and there was an inverse correlation between plasma BDNF levels and the SLEDAI score ($r=-0.54$, $P<0.0001$).

Regarding neuropsychiatric manifestations in group I, depression affects about 46.7% of cases, and there was a statistically significant elevation ($P<0.05$) of the mean serum titer of BDNF in depression, in group I compared with group III. In a study conducted by Chang *et al.* [33], depression was observed in 22.8% of 180 SLE patients and BDNF levels were not associated with depression ($P=0.75$) but associated with SLE disease activity index (SLEDAI; $r=-0.21$, $P<0.05$).

Conclusion

Variation in sBDNF level between SLE patients with and without neuropsychiatric manifestations indicates that it has a particular role in the NPSLE disease process. Likely, it could be used as a biological marker for determining NPSLE disease activity.

Financial support and sponsorship

Nil.

Conflicts of interest

There is no conflict of interest.

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