Neurotrophic factors in systemic lupus erythematosus: markers of disease activity

Sirs,

Brain-derived neurotrophic factor (BDNF), neurotrophic factor-3 (NT-3), neurotrophic factor-4 (NT-4), nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) are neurotrophic factors responsible for the growth, development and survival of neurons, being implicated in the pathophysiology of neuropsychiatric disorders (1). Neurotrophic factors also take part in the modulation of immune system functioning (2).

A few studies have evaluated neurotrophic factors in SLE with contradicting results (3, 4). In the current study, our main objective was to investigate whether plasma levels of BDNF, NT-3, NT-4, NGF and GDNF in patients with SLE differed from healthy controls. We also evaluated whether neurotrophic factors were associated with SLE-related parameters and depressive symptoms in patients with SLE.

Thirty-four patients with SLE followed at the Outpatient Rheumatology Clinic, Hospital das Clínicas, Federal University of Minas Gerais (UFMG) were enrolled and compared to 34 age- and sex-matched healthy individuals with no known rheumatic diseases (control group). Inclusion criteria were: age from 18 to 50 years old and diagnosis of SLE according to the American College of Rheumatology revised criteria (ACR/1997) (5). Patients presenting with acute clinical conditions and/or neuropsychiatric diseases (ACR/1999) that compromised psychopathological evaluation were excluded from the study. The study was approved by the Research Ethics Committee of UFMG. SLE activity was evaluated by the modified SLE Disease Activity Index (SLEDAI-2000). Those with an index ≥4 were considered active (6). Depressive symptoms were assessed with the Beck Depression Inventory (BDI). Patients with a score ≥21 were considered as presenting clinically meaningful depression (7). Plasma levels of neurotrophic factors were determined through enzyme-linked immunosorbent assay (DuoSet, R&D Systems, Minneapolis, USA).

Table I. Demographic, clinical and laboratory characteristics of patients with SLE and individuals from the control group.

Characteristics	Patients with SLE (n=34)	Control Group (n=34)	*p*-value
Females*	32 (94.1)	32 (94.1)	1.00
Males*	2 (5.9)	2 (5.9)	1.00
Age (anos)**	33±7 33.85±10.9	0.70	
GDNF (pg/ml)&	51.6 (22-79)	71.5 (39.8-156.8)	**0.031**$
NGF (pg/ml)&	36.8 (10.2-56.3)	66.3 (49.9-136.3)	**<0.001**$
NT-3 (pg/ml)&	35.6 (7.2-107.1)	43.8 (27.2-106.3)	0.185$
NT-4 (pg/ml)&	14.5 (7.4-32.2)	27.9 (18.8-58.5)	**0.002**$
BDNF (pg/ml)&	4804 (4346-6099)	7973 (5557-9785)	**<0.001**$
BDI (score)#	10 (4.8-22.3)	3.5 (1-7.3)	**0.001**$
Mucocutaneous disorders*	6 (17.6)		
Arthritis*	4 (11.7)		
Nephritis*	6 (17.64)		
Aseptic meningitis (ACR)*	1 (2.9)		
Haematological disorders*	18 (52.4)		
Lymphopenia*	12 (35.3)		
Low C3/C4*	16 (47.1)		
Positive double strand antiDNA*	10 (30.3)		
SLEDAI-2K#	2 (0-26)		
Current steroid use*	28 (82.4)		
Current steroid dose (mg)**	11.4 (13)		
Cumulative steroid dose(mg)**	2016 (2140)		
Antimalarial use*	29 (85.3)		
Current immunossupressants use*	20 (58.4)		
azathioprine*	10 (29.4)		
cyclophosphamide*	5 (14.7)		
methotrexate*	3 (8.8)		
cyclosporine*	2 (5.9)		
Thalidomide use*	1 (3.4)		
Antidepressants use*	11 (32.4)		

SLE: systemic lupus erythematosus; GDNF: glial cell line-derived neurotrophic factor; NGF: nerve growth factor; NT-3: neurotrophic factor -3; NT-4: neurotrophic factor -4; BDNF: brain-derived neurotrophic factor; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; BDI: Beck Depression Inventory; ACR: American College of Rheumatology.
*n (%), **Mean (standard deviation), & Median (interquartile range), # Median (minimum and maximum variation), $ Mann-Whitney test.

Plasma levels of GDNF, NGF, NT-4 and BDNF were lower in SLE patients than in controls (Table I). When compared with controls, SLE patients had higher BDI scores. Ten SLE patients (29.4%) had depression.

There was a negative correlation between GDNF and SLEDAI (r=-0.350; *p*=0.042). Patients with reduced levels of complement and positive anti-dsDNA had lower levels of GDNF and NGF when compared to those without laboratory abnormalities (Table II). Plasma levels of GNDF were lower in patients with disease activity when compared to those with inactive disease [36.4 (16.9–56.46) *vs*. 55.4 (24.9–198.4), *p*=0.043]. Plasma levels of GDNF positively correlated with BDI (r=0.353; *p*=0.041).

A previous study reported higher levels of neurotrophic factors in patients with SLE compared with controls (3). However, Tamashiro *et al*. (4) found that only SLE patients with an inactive disease had higher levels of BDNF when compared to controls. In line with our results, patients with active SLE had lower levels of BDNF when compared with patients with inactive

Table II. Plasma levels of neurotrophic factors in patients with SLE with and without laboratory abnormalities (n=34).

Neurotrophic factor (pg/ml)	Reduced C3			Reduced C4			Anti-dsDNA antibody		
	yes	no	*p*	yes	no	*p*	yes	no	*p*
GDNF*	30.7 (20.6-70.2)	54.5 (24.3-85.1)	0.395	22.3 (16.3-50.2)	56.2 (39.9-85.1)	**0.018**	28.6 (16.3-46.3)	56.5 (24.9-86.4)	**0.018**$
NGF*	8.5 (0-36.7)	46.6 (23.2-60.3)	**0.011**	12.6 (0-38.3)	46.6 (30.9-60.3)	**0.016**	7.8 (0-34.7)	44.7 (25.4-60.7)	**0.005**$
BDNF*	4476.9 (3967.5-5536.6)	4990.8 (4407.1-6234.1)	0.121	4895.7 (3967.5-6506)	4803.7 (4407.1-5562.4)	0.649	5831.6 (4528.4-7058.5)	4763 (4353.9-5591.5)	0.170$

SLE: systemic lupus erythematosus; C3/C4: complement; GDNF: glial cell line-derived neurotrophic factor; NGF: nerve growth factor; BDNF: brain-derived neurotrophic factor.
* Median (interquartile range), $ Mann-Whitney test.

disease (4). Zheng *et al*. (8) also showed that BDNF levels decreased with increasing activity of SLE.

Levels of GDNF correlated with disease activity, with lower levels indicating more severe disease. Accordingly, lower plasma levels of GDNF, NGF and BDNF were associated with laboratory changes, *i.e*. reduced levels of complement C3 and C4 and positive anti-dsDNA antibody. Tamashiro *et al*. (4) found similar results with BDNF in SLE: lower plasma levels of BDNF correlated with higher SLEDAI scores.

Increased synthesis of neurotrophic factors seems to occur during inflammatory responses (2). Nevertheless, in conditions with chronic inflammatory responses like SLE (9), there may be an exhaustion of the production of neurotrophic factors during the disease activity, which would explain decreased levels of GDNF, NGF and BDNF in patients with an increased activity of the disease.

Patients with SLE and more depressive symptoms had higher levels of GDNF. In depression, there is large variation of GDNF levels among different studies (10). As GDNF and other neurotrophic factors have been implicated in the physiopathology of mood disorders, comorbidity with psychiatric conditions is a potential confounding factor to be considered in future studies.

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