Is Serum TWEAK a Useful Biomarker of Neuropsychiatric Systemic Lupus Erythematosus?

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Summary

The aim of this study was to determine the role of the tumor necrosis factor like weak inducer of apoptosis (TWEAK) as a serum biomarker of neuropsychiatric involvement in systemic lupus erythematosus (NPSLE). Levels of TWEAK levels were measured in sera of 92 patients with systemic lupus erythematosus (SLE), including 28 patients with neuropsychiatric lupus, and in 59 healthy controls using ELISA. All SLE patients underwent rheumatological, neurological and psychiatric assessments. We found no significant differences in TWEAK levels, between SLE patients and the healthy controls (p=0.2411). Similarly, no difference was observed between the subgroup of NPSLE and healthy controls (p=0.7658). The mean SLE disease activity (SLEDAI) was 13.25. No correlations between TWEAK levels with disease activity (SLEDAI, r=0.2113, p= 0.2805) or the most common NPSLE manifestations such as headache (r=0.2079), seizures (r=0.1101), cerebrovascular disease (r=- 0.2347), cognitive dysfunction (r=0.1597) and anxiety (r=0.1397) were observed. Our data do not support the use of serum TWEAK as a discriminating biomarker for NPSLE. The role of the TWEAK in NPSLE remains to be investigated.

Key words

TWEAK • NPSLE • Systemic lupus erythematosus • Neuropsychiatric lupus

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Introduction

The systemic lupus erythematosus (SLE) is a chronic multiorgan autoimmune disease with a broad spectrum of clinical manifestations, affecting particularly women of child-bearing age (Frieri 2013). Neuropsychiatric manifestations include a heterogenous variety of neurological and psychiatric syndromes involving the central, peripheral and autonomic nervous system (Bortoluzzi *et al.* 2015, Magro-Checa, Zirkzee, Huizinga, and Steup-Beekman, 2016). The prevalence of neuropsychiatric systemic lupus erythematosus (NPSLE) differs significantly among studies and ranges from 11 % to 95 % of SLE patients (Bortoluzzi *et al.* 2015, Hanly *et al.* 2010, Joseph and Scolding 2010, Kasama *et al.* 2016, Sibbitt *et al.* 2002). This broad span of the prevalence of NPSLE depends largely on the use of a different diagnostic and classification criteria, differences in cohort characteristics that may represent important confounders (e.g., age, ethnicity, gender), period of observation, and sometimes, by different clinical focus of clinicians (Perricone *et al.* 2015, Sarbu *et al.* 2015). Importantly, NPSLE is associated with increased morbidity and mortality and has a tremendously negative impact on the health-related quality-of-life of these patients (Hanly *et al.* 2010, Yazdany 2011).

In 1999, the American College of Rheumatology (ACR) developed nomenclature and definitions of 19 neuropsychiatric manifestations associated with SLE. ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999). The most common presentations of NPSLE include headache, cognitive dysfunction, cerebrovascular disease, seizures and mood disorders (Bortoluzzi *et al.* 2015, Hanly *et al.* 2004, Jeong *et al.* 2015, Pamfil *et al.* 2015, Popescu and Kao 2011, Sarbu

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et al. 2015). Despite the ACR criteria, there is no unified diagnostic test sensitive or specific enough for NPSLE. Therefore, assessment of NPSLE still remains a clinical challenge and the diagnosis is based on physical examination, neuroimaging methods (MRI), psychiatric and neuropsychological tests and immunological tests.

The pathogenesis of NPSLE is multifactorial and not completely understood. There are two main pathophysiological mechanisms involved in the formation of a neuropsychiatric disability (Hanly 2014, Zirkzee *et al.* 2012): Inflammatory mechanisms characterized by the presence of autoantibodies, inflammatory mediators (tumor necrosis factor, cytokines, or immune complex deposits) and non-inflammatory mechanisms including thrombotic or ischemic mechanisms (antiphospholipid antibodies, complement activation) (Belmont *et al.* 1996, Magro-Checa *et al.* 2016).

A variety of autoantibodies play a significant role in the pathogenesis of NPSLE and their detection may support the diagnosis of NPSLE. Anti- ribosomal P protein antibodies, were significantly associated with psychiatric disorders, especially psychosis and depression (Briani *et al.* 2009, Isshi and Hirohata 1998). Some studies described the association between the anti-neuronal antibody (anti-NA) and psychosis (Kang *et al.* 2008, Wilson *et al.* 1979). Anti-phospholipid antibodies, particularly anti-cardiolipin antibodies have been reported in cognitive dysfunction and in reduction of psychomotor speed in SLE patients (Menon *et al.* 1999). Anti-NR-2 antibodies directed against NR2a and NR2b subtypes of the N-methyl-D-aspartate (NMDA) receptor are being investigated for cognitive dysfunction. (Kozora *et al.* 2008). Elevated levels of anti-NR-2 antibodies in cerebrospinal fluid in patients with diffuse NPSLE were observed, whereas there were no differences in serum anti-NR2 levels between NPSLE and healthy groups (Arinuma *et al.* 2008). The recent study shows the same association of antibodies to the NR1 subunit of NMDA receptors with NPSLE (Ogawa *et al.* 2016). One of the inflammatory mediators that contribute to cognitive dysfunction by disruption of the blood-brain barrier is metalloproteinase 9 (MMP-9) (Kozora *et al.* 2008).

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) plays an important role in the pathogenesis of SLE. TWEAK, a member of tumor necrosis factor superfamily, is a multifunctional, pleiotropic and proinflammatory cytokine, which is synthesized as a type II transmembrane protein (Bertin *et al.* 2013). Through the activation of its receptor - fibroblast growth factor-inducible molecule 14 (Fn14), TWEAK regulates multiple cellular functions such as cell differentiation, proliferation, migration, angiogenesis, apoptosis or induction of inflammatory cytokines and chemokines (Winkles 2008, Xu *et al.* 2016). In addition, it has been demonstrated that TWEAK is significantly increased in urine and correlate with renal disease activity of patients with lupus nephritis (Liu *et al.* 2011, Ruiz-Ortega *et al.* 2014, Xuejing *et al.* 2012).

There are several studies reporting that in animal models TWEAK/Fn14 pathway causes disruption of the blood-brain barrier (Wen *et al.* 2015). In animal models, MRL/lpr Fn14 wild type had impaired cognition increased immobility (depression-like behavior) in comparison to Fn14 knockout mice (Polavarapu *et al.* 2005, Wen *et al.* 2013, Winkles, 2008).

Based on these data, we aimed to determine the levels of serum TWEAK in patients with SLE, NPSLE and healthy controls to explore the value of serum TWEAK as a biomarker for neuropsychiatric lupus.

Methods

Patients

Patients fulfilling the revised ACR classification criteria for the diagnosis of SLE (Font and Cervera 1993) were recruited from the outpatient and inpatient clinic at the Institute of Rheumatology, Prague. Age- and sex-matched healthy controls were included. A signed consent form was obtained from each subject prior to initiation of the study. All patients were examined by experienced rheumatologists, neurologists, psychiatrists, and clinical psychologist. SLE activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Patients were classified as inactive if the SLEDAI score was < 4. Patients with low active disease had SLEDAI score $\geq 5 < 10$. Active disease was characterized as SLEDAI score ≥ 10. After exclusion of the other causes (neuroinfections, tumors, etc.), the diagnosis of NPSLE was based on neuropsychiatric symptoms, serological tests and brain MRI abnormalities according to the ACR nomenclature ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999).

Laboratory analysis

Blood samples were collected from all SLE patients and healthy controls and were immediately

centrifuged at 3500 g for 10 min and stored at -80 °C until analysis. The values of C3, C4 complement components were detected by immunoturbidimetric assays and the anti-dsDNA levels by immunofluorescence technique. The levels of TWEAK were measured by commercially available ELISA (RayBiotech, Inc., Norcross, USA) according to the manufacturers' instructions. Absorbance was detected using the Sunrise ELISA reader (Tecan Group Ltd., Salzburg, Austria) with 450 nm as the primary wavelength. Interassay and intraassay reliability of the Tweak ELISA were CV <10 % and <12 % respectively. The minimum detectable concentration of TWEAK was 40 pg/ml.

Blood-brain barrier evaluation

The function of the blood-brain barrier was evaluated by magnetic resonance on the T1 weight image after intravenous gadolinium application. If the native and post-contrast image was the same, then we assessed the barrier as unimpaired.

Statistical analysis

TWEAK levels were presented as median (±SD). The distribution of data was verified by D´Agostino and Pearson omnibus and the Shapiro-Wilk normality test and Mann-Whitney U test was used. A p value < 0.05 was considered statistically significant. The correlation coefficients (r) were calculated using Pearson´s correlation. All statistical analyses were performed using GraphPad Prism software.

Results

Ninety-two patients with SLE and 53 age- and sex-adjusted healthy controls were enrolled into this study. Demographics and clinical characteristics of the patients and healthy controls are shown in Table 1.

Neuropsychiatric manifestation occurred in 28 SLE patients (25.76 %) meeting the 1999 ACR criteria. SLEDAI score of the NPSLE patients was significantly higher than in remaining SLE patients (13.3±9.16 vs. 5.55±4.74, p<0.001). The NPSLE group contained 14 patients with a high SLEDAI score and 7 patients with low disease activity.

The levels of TWEAK in sera were comparable between patients with SLE and healthy controls (2554±695 vs. 2366±750 pg/ml, p=0.241). In addition, the levels of TWEAK did not differ in patients with NPSLE compared to either SLE patients without neuropsychiatric involvement or healthy controls (2425 vs. 2554 vs. 2366 pg/ml respectively, p=0.7658, p=0.5922) (Fig. 1).

Table 1. Demographics and clinical characteristics and characteristics of SLE patients, NPSLE subgroup and healthy controls.

	SLE, n = 64	**NPSLE, n = 28**	**Healthy Controls, n = 53**
Age[a]	41.62±13.25	44.92±13.80	45±14.17
Female/male	58/6	26/2	44/9
SLE disease duration (years)[a]	3.93±10.03	1.92±2.96	
Cumulative disease involvement			
Neuropsychiatric	0	28	
Cutaneous	41 (64.06 %)	19 (67.85 %)	
Renal	34 (53.12 %)	10 (35.71 %)	
Articular	56 (87.5 %)	25 (89.28 %)	
Hematologic	52 (81.25 %)	22 (78.57 %)	
Serositis	24 (37.5 %)	13 (46.42 %)	
Disease parameters at the time of study			
anti ds-DNA positivity	38 (59.37 %)	10 (35.71 %)	
C3[a,b]	0.90±0.26	0.95±0.29	
C4[a,c]	0.17±0.09	0.19±0.10	
SLEDAI index[a]	5.55±4.74	13.3±9.16	
High >14	8 (12.5 %)	14 (50.0 %)	
Low <7	41 (64.06 %)	7 (25.0 %)	

[a] mean ± standard deviation, [b] normal value 0,90-1,80 g/l, c normal value 0,10-0,40 g/l

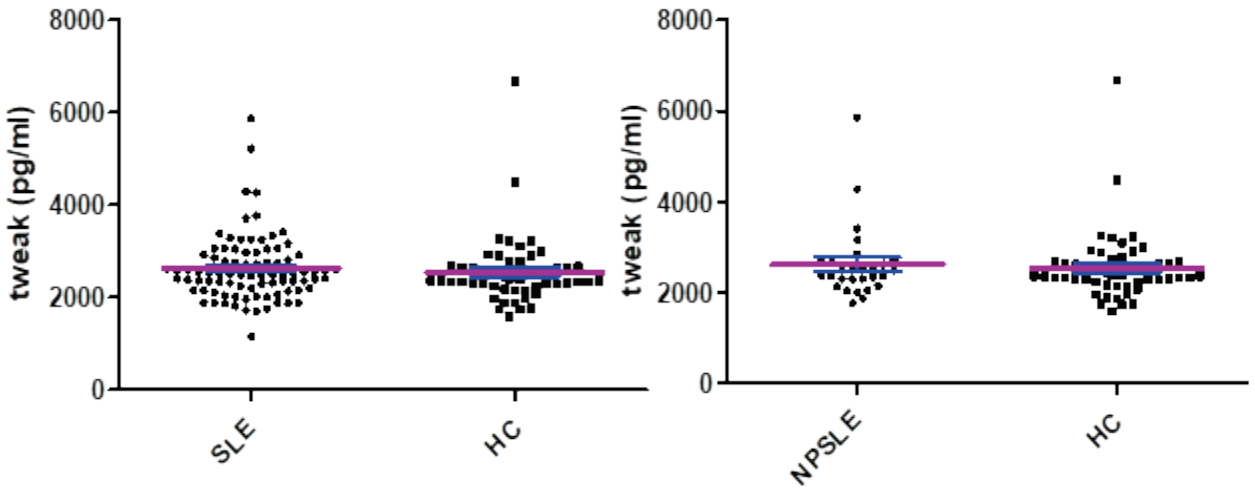

Fig. 1. Comparison of the serum TWEAK levels between SLE, NPSLE patients and healthy control group (HC)

Table 2. Comparison of the serum TWEAK levels of the most common NPSLE.

NPSLE syndrome	Headache	CVD[b]	Seizures	CD[c]	Anxiety
positive	18 (64.28 %)	6 (21.42 %)	12 (42.85 %)	15 (53.57 %)	14 (50 %)
TWEAK[a]	2711 (±956.4)	2253 (±338.9)	2695 (±1027)	2755 (±1025)	2625 (±859.2)
p value (two-tailed)	0.3081	0.2484	0.5922	0.5012	0.4871

a - TWEAK serum level is reported as mean± standard deviation in pg/ml, b - Cerebrovascular disease c - Cognitive dysfunction. The patients might have had > 1 manifestation

Additionally, the levels of serum TWEAK in NPSLE patients with and without the most common NPSLE syndromes (headache, seizures, cerebrovascular disease, cognitive dysfunction and anxiety) did not differ (Table 2), either. There was also no correlation between TWEAK serum levels and SLEDAI score in all SLE patients or in NPSLE patients (Table 3). Similarly, no difference of TWEAK level in NPSLE patients with high and low SLEDAI score was observed. Moreover, no patient had disruption of the blood-brain barrier evaluated by MRI.

Table 3. Correlation NPSLE TWEAK level with disease activity (SLEDAI index).

	TWEAK[a] 2425 (±810)	
SLEDAI index[b] *13.3 (± 9.16)*	r	P
	0.2113	0.2805

r = correlation coefficient p = p value (two tailed) a - TWEAK serum level is reported as mean± standard deviation in pg/ml, b - mean ± standard deviation

Discussion

SLE is a chronic autoimmune disease with multiorgan involvement. Although neuropsychiatric impairment is one of the most common manifestations of SLE, the mechanism of pathogenesis remains unclear and a specific biomarker for diagnosis is still missing. Few studies have shown a potential involvement of TWEAK in the pathogenesis of the disease [30,32,40]. It has been shown that urinary TWEAK is a useful biomarker in lupus nephritis and correlates with renal disease activity (El-Shehaby *et al.* 2011, Gao *et al.* 2009, Liu *et al.* 2011, Ruiz-Ortega *et al.* 2014, Schwartz *et al.* 2009, Schwartz *et al.* 2006, Xuejing *et al.* 2012). More recently TWEAK has become a point of interest in neuropsychiatric involvement.

In our study, we examined serum TWEAK levels in patients with SLE including NPSLE and healthy controls. We showed no significant differences in TWEAK levels among these groups. Our data support previous findings of comparable serum TWEAK levels in NPSLE and SLE patients and the non-autoimmune disease group (Fragoso-Loyo *et al.* 2016). However, in this study the authors did not compare the association of

TWEAK with specific neuropsychiatric manifestations. Our study analyzed TWEAK levels in patients in the most common NPSLE syndromes but no associations were demonstrated, either.

However, there are few studies demonstrating elevated TWEAK serum levels in SLE patients compared to healthy controls (ElGendi and El-Sherif, 2009, Wang *et al.* 2012). In addition, serum TWEAK levels were also higher in SLE patients with vasculitis than those without vasculitis, and so were in the comparison between patients with and without headache. Additionally, Wang *et al.* (2012) examined the expression of TWEAK mRNA in peripheral blood mononuclear cells from patients with SLE and healthy controls, and they found the TWEAK mRNA expression decreased in SLE patients. In addition, El Gendi *et al.* described elevated TWEAK levels in SLE patients with lupus nephritis than in patients without renal involvement (ElGendi and El-Sherif 2009).

The study by Fragoso-Loyo *et al.* examined the levels of TWEAK in cerebrospinal fluid in NPSLE patients, non-NPSLE patients and controls, where TWEAK levels were only slightly elevated in SLE patients compared with non-autoimmune controls. There was no difference between SLE with and without NPSLE group. The major limitation of their study, despite the large number of patients with NPSLE, was the evaluation of the NPSLE group only as a whole with no regard to the particular clinical NPSLE form.

Another study failed to find any differences in TWEAK levels in the cerebrospinal fluid of multiple sclerosis patients versus patients with non-multiple sclerosis inflammatory diseases. However, these data indicated a potential role of TWEAK in inflammatory disorders, including NPSLE (Desplat-Jego *et al.* 2009).

In our study, we did not find any correlations between serum TWEAK levels and activity of the disease in the whole group as well as in the NPSLE subgroup. In NPSLE patients this might be due to the fact, that this was the prevalent study, where only a fraction of patients had acute problems. In acute patients the activity of the disease may be certainly high, but in our group there were mostly patients with chronic long-standing problems or neuropsychiatric manifestation in history, so the disease activity was not so high at the NPSLE group generally. Our data are in keeping with a lack of differences between active and inactive disease SLE patients demonstrated previously. Similarly, no correlations of serum TWEAK levels and the SLEDAI-2K score at the onset of neuropsychiatric manifestation were shown (Fragoso-Loyo *et al.* 2016).

It was demonstrated, that the major function of TWEAK is a modulation of blood-brain barrier permeability (Winkles 2008). However, none of the NPSLE patients in our study suffered from the blood-brain barrier damage evaluated by MRI. This may also, at least, partially explain the lack of differences and associations demonstrated in our study.

The main limitation of our study is the small group of NPSLE patients and the use of serum samples only with no matching cerebrospinal fluid samples. The cytology analysis of cerebrospinal fluid as a basic neurological examination was not available as well.

Despite the fact that our study did not support the hypothesis of that TWEAK is involved in development of NPSLE, there exist data about TWEAK/Fn14 axis (Xu *et al.* 2016) and other findings (Desplat-Jego *et al.* 2009, ElGendi and El-Sherif 2009, Fragoso-Loyo *et al.* 2016, Wang *et al.* 2012) indicating its possible role in the pathogenesis of neuropsychiatric lupus. It seems to be ineffective to measure the serum levels of any biomarker of neuropsychiatric lupus as the levels in CSF are often completely different in majority of biomarkers tested in previous studies. As demonstrated for anti-NMDA antibodies, their correlation with NPSLE was observed in CSF only, not in serum (Arinuma *et al.* 2008). Similarly, levels of certain cytokines were also found to be elevated in NPSLE patients only in the CSF (Yoshio *et al.* 2016), TWEAK may be the same example. And as mentioned above, the presence of TWEAK in CSF might represent a potential discriminating marker for NPSLE but with low specificity. So there is still a need for more clinical trials and arguments, including paired (serum and CSF) samples in this issue which may be potential goal of our future studies.

Conflict of Interest

There is no conflict of interest.

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