SHORT COMMUNICATION

DISSOCIATION AND IMMUNE DYSREGULATION: A PRELIMINARY REPORT

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Abstract

Recent evidence indicates that various types of interactions between nervous and immune system are important in pathogenesis of depression. These findings show that a significant role in developing depression play proinflammatory cytokines that may mediate its psychological and neurobiological manifestations. Great importance among these cytokines plays tumor necrosis factor alpha (TNF- α) and there is growing evidence that inflammatory processes related to depression may be influenced by psychological stress as well as organic inflammatory conditions. These findings suggest that specific influences related to traumatic stress and dissociation could be found in close relationship to increased level of cytokine TNF- α . In the present study we have performed psychometric measurement of depression (BDI-II), traumatic stress symptoms (TSC-40) and dissociation (DES), and immunochemical measure of serum TNF- α in 40 inpatients with unipolar depression (mean age 38.4 $\pm$ 8.2). The results show that TNF- α is significantly related to DES (Spearman R= -0.36, $p < 0.05$), but not to BDI-II and TSC-40. Results of the present study suggest that TNF- α alterations related to dissociation could present a specific process of immunomodulation that may be explained by mutual influences between stress and neuroimmune system.

Key words: *depression; dissociation; TNF-alpha; traumatic stress*

1. INTRODUCTION

Recent evidence indicates that proinflammatory cytokines such as TNF- α , IL-6 and IL-1, play a significant role in developing depression and can mediate its psychological, behavioral and neurobiological manifestations (Bizik, 2010; Schiepers et al.; 2005, Wichers & Maes, 2002). In addition, these reciprocal interactions between nervous and immune system are likely important in the pathophysiology of depression and this inflammatory process may be induced by psychological stressors and also organic inflammatory diseases or conditions (Maes et al., 2009; Schiepers, Wichers & Maes, 2005; Wichers & Maes, 2002).

Moreover, there is evidence that psychological stress may induce an inflammatory response with increased production of pro-inflammatory cytokines in humans (Altemus et al., 2001; Maes et al., 1998; Maes et al., 2009) and may also induce a sensitization effect with increased inflammatory responses to stressors (Maes et al., 2001) which may influence an increased probability of relapses, recurrences, residual symptomatology, symptoms of

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Received June 20, 2011; accepted July 11, 2011; *Act Nerv Super (Praha)* 53(3-4), 141-5.

traumatic stress and dissociative symptoms (Bob et al., 2008, 2009; Patel et al.; 2007; Post, 1992, 2007).

These findings suggest a hypothesis that specific influences related to traumatic stress and dissociation in depressive patients could be in close relationship to increased level of cytokine TNF- α . The aim of the present study is to test the hypothesis that serum TNF- α levels could be closely related to symptoms of traumatic stress and dissociation in patients with unipolar depression.

2. METHOD

2.1. Participants

In order to examine the above hypothesis, assessment of basal serum TNF- α levels during rest conditions and psychometric measures were performed in 40 inpatients with unipolar depression. The patients were at the time of recruitment treated at the Department of Psychiatry and the clinical assessments were performed within two weeks from the beginning of hospitalization. The patients had diagnosis of unipolar depressive disorder (i.e. patients with recurrent depression or depressive period) without posttraumatic stress disorder (PTSD) and other comorbid diagnoses confirmed according to DSM IV criteria by clinical interview (American Psychiatric Association, 1994). In order to re-examine diagnosis and to exclude patients with PTSD or other comorbidities all patients were also screened using structured psychiatric interview M.I.N.I. version 5.0.0. (Sheehan et al., 1998). The patients were treated only by SSRI antidepressants in usual recommended doses according psychiatric guidelines (Raboch et al., 2006). Exclusion criteria were organic illnesses involving the central nervous system, psychotic disorders, PTSD, bipolar disorder, alcohol and/or drug abuse, any form of epilepsy and mental retardation, inflammatory, neuroendocrine and metabolic disorders, any hormonal or antipsychotic medication, tricyclic antidepressants, methyldopa, prednisolone and cimetidine medication, ECT or rTMS therapy and pregnancy or lactation in women. The patients were 16 males and 24 females in average age 38.4 years (age range 21-58) predominantly with high-school education, non-smokers with adequate nutritional status and body mass index. All the patients gave written informed consent and the clinical study was approved by university ethical committee.

2.2. Psychometric measures

For the assessment of depressive symptoms was used Beck depression inventory BDI-II (Beck et al., 1996) that represents 21-items questionnaire for assessing depression (Cronbach's alpha 0.89, test-retest reliability after week 0.85). Subjects indicate degree of their experience of depressive symptoms on 4-point Likert scale.

Psychic dissociative symptoms were assessed by Dissociative Experiences Scale (DES) (Bernstein & Putnam, 1986). DES represents 28 items self-reported questionnaire examining main dissociative phenomena such as absorption, amnesia, depersonalization, derealization, reality distortion, and others. Subjects indicate a degree of their experience on the continuum from 0% to 100%. In the present study we have used the Czech version of the DES that similarly as original English version displays high reliability and internal consistency (Cronbach's alpha 0.92, test-retest reliability after week 0.91).

For investigation of traumatic symptoms, Trauma Symptom Checklist (TSC-40) (Briere, 1996) was used. TSC-40 is a self-reported 40-item questionnaire done on a 4-point Likert scale. TSC-40 evaluates symptomatology in adults associated with childhood or adult traumatic experiences and measures aspects of posttraumatic stress and other symptom clusters found in some traumatized individuals. The Czech version of the TSC-40 has high

reliability and internal consistency (Cronbach's alpha 0.91, test-retest reliability after week 0.88).

2.3. Immunochemical measures

For biochemical assessment, the blood samples of 5 ml volumes were collected in rest conditions according to common procedures at the time from 7:30 to 8 a.m. in a laboratory of Psychiatry department. The blood samples were carefully transferred (about 10 minutes) in icebox at the temperature of 4°C to university biochemical department and immediately centrifuged at the temperature of 4°C. After that TNF- α serum levels have been assessed in biochemical laboratory according to common analytical procedures. TNF- α serum levels were measured using a immunoradiometric assay (IRMA) with intrassay coefficients of variation 2.2 – 6.0%.

2.4. Statistical methods

Statistical evaluation for results of serum TNF- α and psychometric measures included means, standard deviations, Mann-Whitney test for independent samples and Spearman correlation coefficients. All the methods of statistical evaluation were performed using the software package Statistica version 6.

3. RESULTS

Because data did not show presence of significant clusters the patients were divided into two groups according to values of TNF- α , i.e. higher (N=20, TNF- α >12.9 pg/ ml) and lower (N=20; TNF- α <12.9 pg/ ml) than median. The results show that statistical comparison using Mann-Whitney test between groups of depressive patients with values of TNF- α higher and lower than median distinguishes the groups of individuals with higher and lower psychic dissociation (Table 1). Worthy of attention is that the statistical comparison using Mann-Whitney test between the groups did not show differences in depression severity measured by BDI-II.

Table 1. Between group comparison for depressive patients with higher and lower TNF- α than median.

	Mean lower	Mean higher	MW-test	
	TNF- α $\pm$ S.D.	TNF- α $\pm$ S.D.	Z	p
TNF-α	7.94 $\pm$ 2.93	20.80 $\pm$ 7.29	5.410	0.000
DES	17.25 $\pm$ 13.24	7.60 $\pm$ 5.78	-2.455	0.014
BDI-II	16.60 $\pm$ 9.06	20.70 $\pm$ 8.80	0.557	0.119
TSC-40	42.55 $\pm$ 19.12	41.00 $\pm$ 15.94	-0.460	0.645

Note. DES- Dissociative Experiences Scale; BDI-II- Beck Depression Inventory; TSC-40- Trauma Symptom Checklist; Higher TNF- α (N=20, TNF- α >12.9); Lower TNF- α (N=20, TNF- α <12.9); df=38.

The results also indicate that TNF- α is significantly correlated to DES (Spearman R= -0.36, p<0.05), but not to BDI-II and TSC-40. This correlation shows that TNF- α exhibits significant

relationship to psychic dissociation. Statistical comparison between men and women did not show significant differences in TNF- α or psychometric measures.

4. DISCUSSION

The relationship between TNF- α alteration and dissociation is likely mediated by feelings and mental processes such as memory and cognitive distortion representing various components of psychic dissociation related to passive coping strategies and defensive reactions (Nijenhuis et al., 1998; Schore, 1994, 2001; van der Kolk et al., 1985). Several findings also indicate that there is close relationship between inflammatory cytokines and hypothalamic neurons that usually induce passive behavior (Song, 2000). In this context, results of the present study suggest that TNF- α alterations related to dissociation could present a specific process of immunomodulation that may be explained by mutual influences between stress and neuroimmune system. On the other hand, the present study has not shown significant relationships of TNF- α levels with and symptoms of traumatic stress and depression indicating specific relationship between immune dysregulation and psychological experience related to dissociative symptoms.

ACKNOWLEDGEMENT

The research was supported by the project of Center for Neuropsychiatric Research of Traumatic Stress 1M06039.

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