Higher concentration of interleukin 6 - A possible link between major depressive disorder and childhood abuse

Ana Munjiza[a,*], Milutin Kostic[a,c], Danilo Pesic[a], Milan Gajic[e], Ivanka Markovic[b], Dusica Lecic Tosevski[a,c,d]

[a] Institute of Mental Health, Belgrade, Serbia
[b] Institute for Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia
[c] Department of Psychiatry, School of Medicine, University of Belgrade, Belgrade, Serbia
[d] Serbian Academy of Sciences and Arts, Belgrade, Serbia
[e] Department of Statistics, School of Medicine, University of Belgrade, Belgrade, Serbia

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ABSTRACT

Little is known about the correlation between IL-6 and childhood abuse and neglect which may be risk factors for the development of affective disorders in adulthood. The aim of this study was to analyze differences in serum concentrations of IL-6 between patients with major depressive disorder and healthy controls, and to investigate possible correlations with adverse childhood experiences. Peripheral venous blood samples were obtained from 64 patients who fulfilled DSM-IV-R criteria for a current major depressive episode without psychotic symptoms (MDD) and 53 healthy controls, matched for age and gender. Participants were assessed by the Beck Depression Inventory (BDI), Childhood Trauma Questionnaire (CTQ), Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS). The concentration of IL-6 was significantly higher in patients with major depressive disorder compared to healthy controls. The total score of childhood trauma questionnaire highly statistically significantly correlated with IL-6 levels in patient group. Persons who were physically abused, physically neglected and emotionally abused had higher levels of IL-6. Interleukin 6 as a pro-inflammatory immune marker could be an important developmental mediator linking physical and emotional abuse in early life with the development of depressive disorder in adulthood.

1. Introduction

It has been proposed that interleukin 6 (IL-6), which acts as a pro-inflammatory cytokine, is involved in the pathophysiology of depressive disorder. Inflammatory hypothesis in mood disorders was set more than two decades ago (Maes et al., 1993), but still there are inconsistences in clinical findings regarding cytokine levels in patients with depressive disorders (Valkanova et al., 2013; Cassano et al., 2017). Study results of IL-6 serum levels in patients with depression compared to healthy controls are also inconsistent: findings show either higher concentrations or no change in it (Dunjic-Kostic et al., 2013; Maes et al., 1993; Marques-Deak et al., 2007). Therefore, it is indicated to search for more precise, person orientated reasons for these findings. Possible causes of elevated interleukin 6 concentrations in depression include psychological stress, sensitization of neurons to neurotoxic peptides and oxidative stress (Maes et al., 2014). The theory of glucocorticoid resistance-mediated depression and hyper function of hypothalamic-pituitary-adrenal axis is also connected with gained proinflammatory IL-6

activity (Felger and Lotrich, 2013). Central nervous system cells produce IL-6, and express receptors for it (Dame and Juul, 2000). Interleukin 6 is involved in the regulation of serotonin transporter levels (Kong et al., 2015.), and also modulates synaptic functions including synaptic transmission and synaptic plasticity (Gruol, 2015; Antonioli et al., 2012). It has been shown that long term low grade inflammation induces depression through modification of neural plasticity and that anti-inflammatory drugs reduce symptoms of depression (Miller and Raison, 2016), as well as that central administration of IL-6 induces depressive-like behavior (Sukoff Rizzo et al., 2012). All of the above indicates multiple possible reasons for variable concentration of interleukin 6 in depressive disorder.

Childhood abuse and neglect are predictors for the development of affective disorders in both childhood and adulthood (Mac Millan et al., 2001; Dvir et al., 2014). Many studies have been done in this field, linking emotional abuse and neglect with depressive disorder (O'Mahen et al., 2015), as well as physical and sexual abuse (Lindert et al., 2014). Childhood adversity is associated with treatment

resistance in depressed patients (Kaplan and Klinetob, 2000) and greater risk of suicidality (Tunnard et al., 2014). A recent meta-analysis of Baumeister and colleagues has shown that only a few studies analyzed proinflamatory cytokines in depressed persons who had a history of adverse childhood experiences (Baumeister et al., 2016). The same study demonstrates that childhood trauma contributes to a proinflamatory state in adulthood (higher levels of IL-6, CRP and TNF-α). As interleukin 6 represents a key point in promotion and regulation of acute phase inflammatory response (regulating further production of TNF alpha and IL 1-beta) and also induces the synthesis of acute phase proteins in the liver such as CRP - we decided to explore it in this study (Richard and Galudie, 1995).

The aim of this study was to analyze differences in serum concentrations of IL-6 between patients with major depressive disorder and healthy controls, and to investigate possible correlations with clinical features and adverse childhood experiences.

2. Methodology

2.1. Patients

Our study comprised 64 consecutive inpatients treated for major depressive disorder (MDD) without psychotic symptoms (both first episode and recurrent), recruited at the Institute of Mental Health (Belgrade, Serbia). The diagnosis was established using the Structured Clinical Interview for Axis-I (SCID-I) for DSM-IV (First et al., 2002). Patients were excluded if they were (a) <18 and >65 years old; (b) had any other central nervous system disease or other causes of focal or diffuse brain damage; (c) had any psychiatric comorbidity within the Axis I, except for panic disorder, social anxiety disorder and generalized anxiety disorder (GAD); (d) were diagnosed with any auto-immune disorder. Besides the already mentioned comorbidities of panic disorder, social anxiety disorder and generalized anxiety disorder from Axis I, personality disorders were also allowed (examined by the Structured Clinical Interview for Axis-II (SCID-II) for DSM-IV) (First et al., 1997). All patients were treated with antidepressants and adjunct therapy such as mood stabilizers, antipsychotics, benzodiazepines and/or hypnotic drugs. Fifty three healthy controls (HC) were also included in the study, and they were recruited as a convenience sample of hospital staff and their friends and family members. All healthy controls were matched for age and gender with someone from the patients group. Also the same exclusion criteria were applied for HC and patients.

The study was approved by the Ethics Committee of the Institute of Mental Health. Patients and HC were included in the study after signing an informed written consent.

2.2. Clinical assessment

Detailed interview on socio-demographic and clinical data, including treatment course and family history of mental disorders, was obtained from all patients and HC. Whenever possible patients data were also cross checked with family members and a detailed survey of existing medical charts was taken. Participants fulfilled the Beck Depression Inventory (BDI) (Beck et al., 1961), and interviewers filled in the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959). Measures of reliability (internal consistency coefficients - Cronbach's alpha) in this research for BDI is 0.860; for HAMA and HAMD it is 0.550.

Childhood abuse was assessed by the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) which retrospectively examines five forms of maltreatment – emotional, physical and sexual abuse, and emotional and physical neglect as well as minimization/ denial. The questionnaire is composed of 28 items, each item rated on a 5-point scale. Rating-wise, all questions are grouped in 5 sub-scales, and the sub-scales are summarized in the total CTQ score. Existence of

childhood trauma experience is determined by a cutoff score at each CTQ sub-scale. The cutoffs of each sub-scale for moderate-severe exposure are the following: emotional abuse ≥13; emotional neglect ≥15; physical neglect ≥10; physical abuse ≥10; sexual abuse ≥8. Based on our study, the internal consistency coefficients (Cronbach's alpha) for the CTQ total score is 0.73 and the ranges for subscales are: 0.88 for sexual abuse subscale, 0.82 for emotional neglect, 0.79 for emotional abuse, 0.89 for physical abuse and 0.60 for physical neglect.

2.3. Blood tests

Participants were afebrile, without a history of any recent inflammatory process and did not report any significant stressor at the day peripheral venous blood samples were obtained from all subjects (between 8 and 9 in the morning). Blood was collected in serum separator tubes, and the samples were allowed to clot for 30 min before separating serum by centrifugation (15 min, 3000 rpm). Serum samples were aliquoted and stored at −80 °C. Serum IL-6 concentration was determined by enzyme-linked immunosorbent assay, using commercial kit (e-Biosciences), according to the manufacturer's instructions.

2.4. Statistics

Differences in demographic and clinical characteristics between groups were assessed using analysis of variance for continuous data and non-parametric statistics (Kruskal-Wallis test and Chi square test) for categorical data. Independent sample t test was carried out for parametric data (differences between groups of IL-6 concentration). Bivariate Pearson correlation and linear regression between immune marker and CTQ scores was carried out. Fisher's r-to-z was used to assess whether there is a significant difference in correlation coefficients between the control and patient groups. Results were considered statistically significant at $p \leq 0.05$. Statistical analysis was performed with SPSS (v.20.0 for Windows; SPSS Inc., Chicago, IL).

3. Results

Final analyses included 64 patients and 53 controls. There were no statistically significant differences between these two groups in gender, age, marriage status, having children and place of living, but patients were less educated and more often without a job than the controls (Table 1). Concentrations of IL-6 were significantly higher in patients with major depressive disorder compared to healthy controls ($p = 0.046$).

In our patient group we did not find any statistically significant difference between serum levels of IL-6 by comorbidity on Axis II ($p = 0.195$), comorbidity of anxiety disorders ($p = 0.994$), the first vs.

Table 1
Sociodemographic characteristics.

	Patients	Controls	*p* value
Number of patients	64	53	/
Age (years)[a]	45.98 ± 10.31	46.04 ± 10.15	0.514
Male/female ratio[b]	13/51	10/43	0.864
Married[c]	60.7%	74%	0.336
Having children[c]	77.4%	78%	0.862
Living in city[c]	67.9%	82%	0.131
Employment[c]	48.8%	94%	0. < 001***
Education[a]	3.15 ± 0.82	4.76 ± 1.25	0. < 001***
BDI[a]	31.26 ± 12.87	1.86 ± 3.90	0. < 001***
IL6 (pg/ml)[a]	2.24 ± 3.71	1.25 ± 1.15	0.046*

[a] Values presented as means ± SDe.
[b] Values presented as number of patients; BDI: Beck Depression Inventory.
[c] Values presented as percentage.
* Statistically significant, $p < 0.05$.
*** Highly statistically significant, $p < 0.01$.