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Melancholic and atypical major depression — Connection between cytokines, psychopathology and treatment

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ABSTRACT

Background and purpose: Growing scientific evidence indicates that there is a correlation between depression and alternations in the immune system. The main aim of the study was to investigate serum levels of Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α) in melancholic and atypical depressive patients during acute exacerbations of illness, compared to healthy subjects. The secondary aim was to explore a possible association between cytokine levels and clinical characteristics, as well as total duration of prior antidepressant treatment.

Method: We measured serum levels of IL-6 and TNF-α in 47 patients suffering from major depressive disorder (MDD) (29 melancholic and 18 atypical) in exacerbation of illness, compared to 39 healthy controls, matched by sex, body mass index (BMI) and smoking habits. Serum levels of IL-6 and TNF-α were measured by enzyme-linked immunosorbent assay (ELISA). The severity of psychopathology was assessed using the Hamilton Depression Rating Scale (HDRS).

Results: IL-6 was significantly elevated in melancholic depressive patients (MDD-M) compared to healthy controls, while no difference was found between the patients with atypical depression (MDD-A) and the healthy group. Lower TNF-α serum level was found both in melancholic and in patients with atypical depression, compared with healthy subjects. We detected a positive correlation between cytokine levels in atypical, but not in melancholic subjects. Sex, age, smoking habits and BMI were not associated to cytokine levels in neither group. Clinical parameters (duration of illness, current episode, age of onset) were related to cytokine levels in atypical depression, while the duration of lifetime exposure to antidepressant treatment correlated to IL-6 serum levels in both melancholic and atypical depression.

Conclusion: Our results suggest that the difference in pro-inflammatory cytokine levels could reflect a biological difference between melancholic and atypical depression. A positive correlation between the cytokines (TNF-α and IL-6) observed in depressive patients with atypical features, might be influenced by chronic course of illness, while IL-6 elevation could represent a state indicator for acute exacerbation, especially in melancholic patients. Total duration of antidepressant treatment could be a relevant factor influencing the immune status of patients who suffer either from melancholic or atypical depression.

1. Introduction

Extensive research in the field of psychoneuroimmunology has resulted in growing evidence which indicates an interconnection between psychiatric diseases, especially mood disorders, and certain changes in the immune system (Elomaa et al., 2012; Müller and Ackenheil, 1998; Schiepers et al., 2005). According to a recent, cytokine hypothesis, proinflammatory cytokines, (acting as neuromodulators), have a crucial role in differentiating between the behavioural, neuroendocrine and neurochemical characteristics of depression (Schiepers et al., 2005). So far, major depressive disorder (MDD) has been associated with altered levels of various inflammatory cytokines and their

Abbreviations: IL-6, interleukin-6; TNF–α, tumor necrosis factor- alpha; BMI, body mass index; MDD, major depressive disorder; MDD-M, major depressive disorder with melancholic features; MDD-A, major depressive disorder with atypical features; IL-1β, Interleukin-1beta; IL-2, Interleukin-2; INF-γ, interferon-gamma; DSM, Diagnostic and Statistical Manual; HDRS, Hamilton Rating Scale for Depression; EKG, electrocardiogram; EEG, electroencephalogram; ELISA, enzyme-linked immunosorbent assay; cAMP, cyclic adenosine monophosphate; SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic antidepressants; SNRI, Serotonin–norepinephrine reuptake inhibitors; NaSSA, Noradrenergic and specific serotonergic antidepressants.

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soluble receptors, such as Tumour Necrosis Factor alpha (TNFα), Interleukin-6 (IL-6), Interleukin-1beta (IL-1β), Interleukin-2 (IL-2) and INF-γ (Brambilla and Maggioni, 1998; Capuron and Miller, 2004; Carpenter et al., 2004; Dowlati et al., 2010; Howren et al., 2009; Kagaya et al., 2001; Rothermundt et al., 2001a; Ushiroyama et al., 2002). Despite numerous heterogeneous and often inconsistent findings, the most reliable ones convincingly suggest that IL-6 and TNF-α levels are often altered in depressive patients (Dowlati et al., 2010). However, MDD is a chronic, heterogeneous disorder, which includes at least two types of depression (with melancholic and atypical features) (American Psychiatric Association, 2000; Thase, 2009). Not only do these two types of depression differ from the point of clinical phenomenology, but their biological characteristics might vary as well. Very few attempts at elucidating a possible diversity in neuroimmunological basis of depressive illnesses have been made so far. Current research scarcely indicates a possible association between cytokine alterations and melancholic depression. However, there is no data concerning atypical type (Anisman et al., 1999; Karlović et al., 2012). Another question that is sufficiently not addressed is whether the same immunological alterations can be found in all depressive individuals after a certain period time. It is also important to find out if the duration or the course of illness affects the level of inflammatory parameters, or they simply reflect the current depressive episode. Moreover, it seems that the relationship between total duration of antidepressant treatment and cytokines has not been explored so far. Therefore, our study was primarily designed to investigate serum levels of IL-6 and TNF-α in melancholic patients and those with atypical MDD during the acute phase, and compare them with the findings in healthy subjects. Our secondary aim was to explore a possible correlation between the course of illness (age of onset, duration of illness, number of episodes, duration and severity of current episode) and the total duration of antidepressant treatment with serum levels of these immune parameters.

2. Methods

2.1. Subjects and design

Forty-seven MDD inpatients, (29 with melancholic and 18 with atypical features), hospitalized at the Clinic for Psychiatry, Clinical Centre of Serbia, Belgrade, provided informed written consents to participate in the study. The study was approved by the Ethics Committee of School of Medicine in Belgrade and Board of Psychiatric Clinic. The study protocol was in accordance with the Declaration of Helsinki. All depressed patients fulfilled the DSM-IV (American Psychiatric Association, 2000) criteria for major depressive disorder. The 17-item version of Hamilton Rating Scale for Depression (HDRS) (Hamilton, 1960) was used to assess the severity of current episode. Depressed patients were enrolled only if their baseline HDRS was ≥17 points. Clinical subtypes (melancholic or atypical features) were determined according to the DSM-IV criteria (American Psychiatric Association, 2000). Diagnosis and HDRS evaluation were made by two experienced psychiatrists through complete semi-structured interviews in combination with all other available medical records. Only the patients, who had been examined and diagnosed with the same type of depression, were recruited into the study. All clinical data concerning the course of illness and previous antidepressant treatment were obtained by reviewing complete medical records and charts. Total duration of antidepressant treatment was defined as the time (in months) during which a patient was taking an antidepressant at any time in their life. At the time of testing, all subjects were free of major psychotropic drugs for at least 4 weeks. Refractory patients were not included in the study. Our study included only subjects with a history of good response to previous antidepressant treatment (SSRI or other, see Table 1). The patients who had had a history of any other psychiatric illness such as schizophrenia or other psychosis, substance or alcohol abuse, obsessive–compulsive disorder, or

Table 1
Socio-demographic and clinical characteristics of the study subjects.

Socio-demographic variables	MDD-M (n = 29)	MDD-A (n = 18)	Healthy controls (n = 39)	Statistics	p-values
Sex (male/female)	13/16	8/10	17/22	$\chi^2 = 0.546$	0.761[a]
Age (years)	50.28 ± 7.41	52.26 ± 7.29	49.90 ± 4.99	F = 8.415	0.632 [b]
BMI (kg/m^2)	22.25 ± 1.07	22.56 ± 1.19	22.21 ± 0.36	F = 0.352	0.704 [b]
Smoking (cigarettes/day)	12.74 ± 3.71	14.46 ± 3.27	10.62 ± 4.31	F = 0.658	0.871[b]
Marital state (with partner, %)	57.1	60.9	61.1	$\chi^2 = 1.532$	0.232 [a]
Education (%)				$\chi^2 = 48.957$	0.000[a]
Elementary school	35.7	26.1	5.2		
High school	35.7	65.1	17.2		
University	28.6	8.7	77.6		
Employed (%)	28.6	26.1	96.6	$\chi^2 = 32.734$	0.000[a]
Clinical variables					
Age of onset (years)	31.86 ± 11.71	40.65 ± 8.26	–	t = −2.678	0.011[c]
Duration of illness (years)	18.42 ± 10.46	13.39 ± 6.18	–	t = 1.637	0.118[c]
Number of previous episodes	6.71 ± 3.54	4.00 ± 1.93	–	z = −2.566	0.100[d]
Duration of current episode (months)	3.30 ± 1.07	3.94 ± 1.57	–	z = −1.258	0.219[d]
HDRS	25.83 ± 0.51	22.41 ± 0.79	–	z = 0.000	0.000[d]
Total duration of antidepressant treatment (months)	59.14 ± 34.17	37.83 ± 37.62	–	z = −2.355	0.019[d]
Previous antidepressant treatment (%)			–	$\chi^2 = 0.972$	0.914[a]
SSRI	50.0	39.2			
TCA	21.4	26.1			
SNRI	28.6	30.4			
NaSSA	–	4.3			
Heredity (yes/no, N)	111/18	7/11	–	–	1.000[e]
Suicidal risk (yes/no, N)	8/21	1/17	–	–	.258[e]

Values are means ± standard deviations unless otherwise stated.
Abbreviations: BMI = body mass index; MDD-M = major depressive disorder with melancholic features; MDD-A = major depressive disorder with atypical features; HDRS = Hamilton Depression Rating Scale; SSRI = Selective serotonin reuptake inhibitors; TCA = Tricyclic antidepressants; SNRI = Serotonin–norepinephrine reuptake inhibitors; NaSSA = Noradrenergic and specific serotonergic antidepressants.
[a] Chi-squared test.
[b] One-way analyses of variance (ANOVA).
[c] Independent samples *t*-test.
[d] Mann–Whitney *U*-test.
[e] Fisher's exact test.