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The relationship between inflammatory state and quantity of affective episodes in bipolar disorder

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ABSTRACT

Objectives: Immunological/inflammatory processes have been proposed to play an important role in the pathophysiology of mood disorders, including bipolar disorder (BD). The present study aimed to examine the influence of immune activation, measured on the basis of inflammatory markers, on the course of illness, proxied by the number of affective episodes, in patients with BD.

Methods: We investigated the relationship between high-sensitive CRP (hsCRP) and Interleukin 6 (IL-6), two inflammatory markers and characteristics of course of illness (e.g. number of affective episodes, depressive and manic symptoms) amongst a group of 190 individuals with BD.

Results: Among females with BD, there was a positive correlation between levels of hsCRP and the number of manic and depressive episodes. Moreover, levels of hsCRP and IL-6 were positively correlated with current manic symptoms, as measured by Young-Mania-Rating-Scale. There were no significant correlations between levels of the foregoing inflammatory markers, and manic and depressive symptoms in male individuals with BD. Furthermore, compared to their untreated counterparts, female patients treated with lithium demonstrated higher levels of hsCRP and male patients treated with atypical antipsychotics lower levels of hsCRP, respectively.

Conclusions: Our results are suggesting that the association between inflammatory state and affective response in patients with BD may be gender-dependent. A future research would be to evaluate whether or not these gender differences can be observed in other inflammatory pathways associated with BD.

1. Introduction

Bipolar disorder (BD) is a complex psychiatric disorder with a wide range of clinical symptoms. Several different biological mechanisms have been proposed to contribute to the pathophysiology of BD. One major area of investigation involves the immune/inflammatory system. In particular, it concerns the effect of increased immune-inflammatory activity on various clinical manifestations of BD (Anderson and Maes, 2015). Many studies have demonstrated that individuals with BD have altered levels of pro-inflammatory cytokines and positive acute-phase proteins. Some of these inflammatory changes appear to be stage-dependent, while others appear to be trait-dependent (Maes et al., 1995b; Maes et al., 1995a; Maes et al., 1997; Wadee et al., 2002). It has been suggested that this may be due to a dysfunctional reciprocal relationship between the immune system and the hypothalamic-pituitary-adrenal axis (HPA) that defines a central stress reactivity network (Maes, 2015). Based on these findings, recent work has been directed towards identifying whether these immunological variables may be used as biological markers to guide the development of more efficacious treatment strategies for patients suffering from BD (Berk et al., 2009; Frey et al., 2013). Recently, several different inflammatory and acute-phase protein markers, including pro-inflammatory cytokine IL-6 and its soluble receptor sIL-6R, have been investigated. Levels of both inflammatory markers were found to be elevated in individuals with BD and major depressive disorder (MDD) compared to healthy controls (Munkholm et al., 2013; Maes et al., 1995b; Maes et al., 1995a).

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Elevated levels of these markers have also been reported for patients in both acute manic and acute depressive states (Maes et al., 1995b; Maes et al., 1995a; Maes et al., 1997; Wadee et al., 2002; Anderson, 2013). However, there is a distinction between BD and MDD in the level of these inflammatory markers. It has been demonstrated that patients with BD present higher levels of certain inflammatory markers, including sIL-6R, compared to patients with unipolar depression (Bai et al., 2015). Other studies have underlined increased levels of IL-6 on the one hand and decreased levels of brain-derived neurotrophic factor on the other in patients with BD (Goldstein et al., 2011). This association with BDNF may mediate the effect of increased IL-6 on neuroprogression of BD (Berk et al., 2014).

Another important inflammatory marker that is widely used in clinical practice is C-reactive protein (CRP). C-reactive protein is an acute-phase protein that plays an important role in inflammatory processes and is a reliable marker for the general inflammatory state of the body. A high-sensitivity-CRP (hsCRP) assay, as we used in our study, can accurately detect low-grade inflammation in a range of 1–5 mg/l (Musunuru, 2008) and is commonly used to stratify cardiovascular risk. Chronic mild inflammation has been reported to be one of the most important pathophysiological abnormalities in BD (Anderson, 2013; Anderson and Maes, 2015; Maes et al., 1995b; Maes et al., 1997; Berk et al., 2014). It has been repeatedly demonstrated that pro-inflammatory cytokines (e.g. TNF-α, IL-1β, IFN-γ, IL-6) exert effects on key processes that are considered to play a central role in the development of mood disorders including neuroplasticity, neurotransmission, oxidative stress and neuroendocrine functions. However, the directionality of the relationship between inflammatory state and mood disturbances remains elusive. So far, it is not known whether an altered inflammatory state causes or is caused by mood disturbances. On the one hand, stress-induced inflammation appears to be augmented by MDD and early life stress (Haroon et al., 2012). On the other hand, studies have also demonstrated that individuals with increased levels of inflammatory markers due to infection or autoimmunity have an increased risk of developing mood disorders (Benros et al., 2013).

Generally, CRP seems to be increased in individuals with BD during all clinical states (Bai et al., 2015). Other data, however, suggest that elevated levels of CRP in a depressed state may increase the risk of a switch to a manic episode within a short time range (Becking et al., 2013). There is also evidence that elevated CRP may be associated with the severity of cognitive dysfunction in BD and schizophrenia (Dickerson et al., 2007, 2004).

The present study is focused on measuring the association between levels of various inflammatory markers and the clinical course of BD. Specifically, we investigated the association between elevated serum levels of hsCRP and IL-6, and clinical outcome measures of BD (e.g. number of illness episodes, illness duration). The foregoing inflammatory markers were selected because they have been widely used in clinical practice and are easy to detect. Furthermore, since gender differences appear to play a significant role in determining outcome measures in patients with BD, the analysis was carried out separately for males and females. To our knowledge, there are currently no published studies that have explored the relationship between levels of hsCRP and IL-6, and the clinical course of illness in patients with BD.

2. Participants and methods

The study was conducted at the Department of Psychiatry and Psychotherapeutic Medicine at Medical University of Graz in Austria. All patients included were former in- or out-patients of the department and had received a diagnosis of BD according to DSM-4 criteria. All patients were participants in the BIPFAT study, which included a complete psychiatric examination and history (Structured Clinical Interview for DSM-IV Disorders, HAM-D, BDI, YMRS), blood samples, cognitive testing, magnetic resonance imaging, electroencephalography, and various lifestyle and personality questionnaires. A detailed description of the BIPFAT study, as well as the results from the study, can be obtained from recent publications from our study group (Reininghaus et al., 2014; Bengesser et al., 2014; Birner et al., 2015; Lackner et al., 2015). For the current study, individuals with BD were asked about their number of lifetime depressive and manic episodes during a structured clinical interview (SKID-I). Additionally, objective data were obtained by going through all available Medical System data and medical reports provided by the patients. A total of 190 individuals with BD were included.

Patients with severe acute somatic illnesses e.g. infections or chronic inflammatory diseases were not included in the study.

3. Biological essays and statistical analysis

Levels of hsCRP and IL-6 were analyzed using a Tina-quant C-reactive protein latex ultrasensitive assay and an electrochemiluminescence immunoassay, respectively. Both assays were purchased from Roche Diagnostics (South San Francisco, California) and measured on a Cobas 8000 modular analyser from Roche Diagnostics.

All analyses were calculated separately for men and women. Mann-Whitney-*U* Test was selected to compare any differences between the male and female subgroup because of non-given normal distribution of data. For the analyses of possible covariates, differences in levels of IL-6 and hsCRP were computed using Mann-Whtiney-*U* Test for the following parameters: smoking, cardiovascular disease, and current medication intake of atypical antipsychotics, lithium, antidepressants and antiepileptics. Partial correlation analyses were performed to test associations between IL-6 and hsCRP levels and the number of depressive/manic episodes, illness duration, global assessment of function and affective symptoms (as measured by BDI, HAM-D, YMRS), and Body-Mass Index (BMI). Error probabilities < 0.05 were accepted to denote statistical significance.

4. Results

Basic descriptive statistics (i.e. mean and standard deviation) for various parameters in males and females with BD can be obtained from Table 1.

4.1. Analyses of possible covariates

Among the male individuals with BD, there was a significant

Table 1
Descriptive statistics of the study sample.

	female 92 (48,4%)		male 98 (51,6%)		
N	M	SD	M	SD	Statistical significance[1]
Age	43.09	12.61	44.89	14.71	n.s.
High-sensitive-CRP mg/dl	3.41	4.03	2.68	4.13	n.s.
Interleukin-6 mg/dl	3.22	4.84	3.10	2.64	n.s.
Number of depressive episodes	18.51	25.03	12.94	11.32	n.s.
Number of manic episodes	11.96	21.12	11.12	17.60	n.s.
BMI	27.59	6.00	25.59	5.78	n.s.
BDI	17.77	11.87	13.02	9.99	n.s.
HAMD	6.61	5.11	5.38	4.41	n.s.
YMRS	1.74	3.77	2.35	4.00	$p < .05$
Smoker	49%		48%		
Vascular disease	9%		15%		
Substance use	12%		13%		
Alcohol use	11%		18%		
Lithium	31%		40%		
Atypical antipsychotics	73%		57%		
Antidepressants	62%		63%		