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Short communication

Inflammatory cytokines and functional impairment in drug-free subjects with mood disorder

Carolina David Wiener [a,b], Fernanda Pedrotti Moreira [a], Taiane Azevedo Cardoso [a], Thaise Campos Mondin [a], Pedro Vieira da Silva Magalhães [c], Flavio Kapczinski [c], Luciano Dias de Mattos Souza [a], Ricardo Azevedo da Silva [a], Jean Pierre Oses [a], Karen Jansen [a,*]

[a] Department of Health and Behavior, Universidade Católica de Pelotas, RS, Brazil
[b] Department of Epidemiology, Universidade Federal de Pelotas, RS, Brazil
[c] Department of Psychiatry and Legal Medicine, Universidade Federal do Rio Grande do Sul, RS, Brazil

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ABSTRACT

Objective: To assess the association between peripheral levels of inflammatory cytokines and functional impairment in subjects with Bipolar Disorder (BD), Major Depressive Disorder (MDD) and population controls.
Methods: This was a cross-sectional study with a matched sample of drug-free young adults with BD ($n = 48$), MDD ($n = 48$) and population controls ($n = 48$). Mood disorder was confirmed by a certified psychologist using the Structured Clinical Interview for DSM-IV (SCID-I). Functional impairment was assessed using the Functional Assessment Short Test (FAST). Serum levels of IL-6 and IL-10 were measured by ELISA.
Results: Peripheral levels of IL-6 and IL-10 were not significantly different between subjects with BD, MDD compared to controls. Higher levels of functional impairment were verified in subjects with BD and MDD compared to population controls ($p \leq 0.001$). In addition, IL-6 and IL-10 levels were positively correlated with functional impairment in subjects with BD (IL-6: $r = 0.349$, $p = 0.016$; and IL-10: $r = 0.351$, $p = 0.016$).
Conclusion: Inflammatory dysregulation was associated with functional impairment among drug-free subjects with BD. This finding suggests that inflammatory dysregulation may be involved in the neuroprogression of BD.

1. Introduction

Bipolar disorder (BD) and major depressive disorder (MDD) are severe, chronic and highly disabling mental conditions that affect 2–21% of the general population (Kessler and Bromet, 2013; Merikangas et al., 2007). Both illnesses have been associated with functional impairment (Birnbaum et al., 2010; Jansen et al., 2012; Jansen et al., 2011). Patients with MDD had higher rates of non-recovery, recurrence, and mortality (Berk et al., 2007; Kapczinski et al., 2009). The staging model proposed by Kapczinski et al. (2009) includes a latent phase: patients at high-risk for developing BD, characterized by a family history of BD, temperament traits, mood, and anxiety symptoms as well as genetic vulnerability for developing the disorder; Stage I: patients who return to their baseline level of functioning when mood episodes resolve; Stage II: biomarkers and functioning impairment are related to comorbidities or rapid-cycling presentations; Stage III: persistent cognitive and functioning impairment in the inter-episode period as well as changes in biomarkers; and Stage IV: same findings as in Stage III associated with extreme cognitive and functioning impairment, to the point that patients are unable to live autonomously. Therefore, it is important to assess functional impairment in subjects with BD, as well as the role the biomarkers play at all stages of the disease (Kapczinski et al., 2009).

A recent study has assessed functional impairment in the four stages of BD and found that the global functioning was similar between healthy controls and subjects with BD in stage I. In addition, subjects with BD in stages II, III and IV demonstrated a higher level of functional impairment when compared to healthy controls. These findings suggest that functional impairment could be considered a marker for neuroprogression in subjects with BD (Rosa et al., 2014). The biochemical changes have been linked to neuroprogression and are generally associated with the severity of symptoms, cognitive impairment and functional impairment (Kauer-Sant'Anna et al., 2009; Larson and Dunn, 2001). The individual burden of MDD is a reflection of the impact of the disorder, i.e., suffering due to symptom severity (intensity, frequency, duration), functioning (occupational, social, and leisure activities), and quality of life (patient's satisfaction with health, occupational, social, and leisure activities (Ishak et al., 2013).

Studies have demonstrated increased levels of inflammatory markers, including IL-6 and IL-10, in the serum of individuals diagnosed with BD and MDD, when compared to healthy controls (Dowlati et al.,

* Corresponding author at: Rua Gonçalves Chaves, 373, sala 424C. Centro, Pelotas, Rio Grande do Sul CEP 96015-560, Brazil.
E-mail address: karen.jansen@pq.cnpq.br (K. Jansen).

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2010; Kim et al., 2007; Munkholm et al., 2013). Different mechanisms are present in the relationship of inflammatory mediators, neuronal function and neurotransmission in mental disorders. However the studies assessing the role of inflammation in the neuroprogression of BD were performed with a sample of outpatients.

Anti-inflammatory agents have become of great interest in the novel treatment of mood disorders. A meta-analysis with 6262 subjects showed that the use of nonsteroidal anti-inflammatory drugs was associated with better antidepressant effects. The treatment, in particular celecoxib, decreased the depressive symptoms without increased risks of adverse effects, with or without concomitant antidepressant medication (Karson et al., 2013; Kohler et al., 2014). The resulting reports on the impact of lithium remain controversial. Kim et al. reported that after the administration of mood stabilizers, the cytokine production increased, while Su et al. did not find any significant changes in bipolar patients (Kim et al., 2007; Su et al., 2002).

To the best of our knowledge, no studies have assessed the association between inflammatory markers and functional impairment in community samples of young adults in the early stage of BD. Thus, the aim of this study was to assess peripheral levels of inflammatory cytokines and functional impairment in subjects with bipolar disorder (BD) and major depressive disorder (MDD) compared to the population control. We also assessed the correlation between inflammatory cytokines and functional impairment.

2. Methods

2.1. Sample and instruments

This was a cross-sectional study with a matched sample of drug-free young adults, nested in a population-based study, including 1560 subjects aged 18 and 24 years. The study was conducted in the urban area of Pelotas, southern Brazil, during 2007–2008. Full details on the original study have been published elsewhere (Jansen et al., 2011).

After an initial psychopathology screen, the whole population was assessed with the Brazilian version of the Mini-International Neuropsychiatric Interview-MINI (Amorim et al., 1998). In order to improve diagnosis reliability, in this subsample, the diagnosis was provided by psychologists using the Brazilian version of Structured Clinical Interview for DSM-IV (SCID) (Del-Ben et al., 1996).

The psychometric characteristics of Brazilian version of the MINI compared to SCID were satisfactory for major depressive episode (Kappa: 0.84, sensibility: 0.96, specificity: 0.88, predictive positive value: 0.87, predictive negative value: 0.97), for current manic episode (Kappa: 0.67, sensibility: 0.82, specificity: 0.95, predictive positive value: 0.63, predictive negative value: 0.98), and for lifetime manic episode (Kappa: 0.73, sensibility: 0.81, specificity: 0.94, predictive positive value: 0.76, predictive negative value: 0.95) (Sheehan et al., 1998). In a test-retest reliability investigation, the Brazilian version of the SCID showed good agreement between interviewers for bipolar disorder (current: $k = 0.84$; lifetime: $k = 0.84$), and fair agreement between interviewers for major depression disorder (current: $k = 0.64$; lifetime: $k = 0.69$) (Del-Ben et al., 1996).

For the purposes of the current study, we recruited all the drug-free subjects with BD from the population-based study. Additionally, two groups of control subjects were recruited. Subjects without any history of mood disorder were randomly selected and matched for sex, age and years of education—i.e. a healthy control sample. We also recruited a second control group, those with major depression disorder. Using this strategy, we were able to obtain data from 144 subjects (48 population controls, 48 subjects with MDD and 48 subjects with BD). All subjects were informed about the study and agreed to participate by providing their free and informed consent, answered the questionnaires and the structured diagnostic interviews. The project was approved by the Ethics Committee of the Catholic University of Pelotas (UCPel), Brazil.

The Hamilton Depression Rating Scale (HDRS) (Fleck et al., 2004) was used for evaluating depressive symptoms. Functional impairment was assessed using the Functional Assessment Short Test (FAST) (Cacilhas et al., 2009). It comprises 24 items, which are divided among 6 specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. The total score ranges from 0 to 72. The higher the score, the more serious the difficulties are.

2.2. Blood sampling

Ten milliliters of blood were withdrawn from each subject by venipuncture and stored in a free-anticoagulant vacuum tube after the interview, between 8 and 11 AM. Serum was separated within 2 h by centrifugation at $4000 \times g$ for 15 min and was kept frozen at −80 °C for biochemical analysis. It is worth mentioning that no significant changes were observed when serum was stored at −80 °C (Zander et al., 2014). Serum IL-6 and IL-10 levels were measured by enzyme linked immunosorbent assay (ELISA) using a commercially available immunoassay kit (DuoSet, R&D Systems, Minneapolis, MN, USA) and were expressed in pg/mL.

2.3. Statistical analysis

Statistical analyzes were performed using the GraphPad Prism 6.0 and the Statistical Program for Social Sciences (SPSS) 22.0. The Chi-Square test was used to determine the consistency of match between groups regarding gender, age, and years of education. The ANOVA test was used to verify differences in severity of depressive symptoms and functional impairment between groups, followed by Bonferroni post hoc test. Cytokine levels had a non-Gaussian distribution and were logarithmically transformed before the Statistical analysis. Comparisons between cytokine levels in MDD, BD, and control group were performed by ANOVA. Correlation between cytokine levels and the Fast score was calculated using Spearman's correlation coefficient. Serum levels of IL-6 and IL-10 were expressed as mean and standard deviation (mean ± S.D.). Results were considered statistically significant when p-value was <0.05.

3. Results

The total sample consisted of 144 individuals: 48 with BD, 48 with MDD and 48 population controls. Each group included 36 women and 12 men, with a mean age of 21.92 ± 2.32, 21.81 ± 2.14, and 21.88 ± 2.31 years, respectively. The average education years for the groups were 8.95 ± 3.58 for BD, 9.07 ± 2.85 for MDD and 9.97 ± 3.31 for controls. The sample was successfully balanced and no differences were found in the BD, MDD and control groups for gender, age and years of education.

There was no significant difference between the diagnosis groups and population controls with regards to serum levels of IL-6 ($p = 0.883$) and IL-10 ($p = 0.443$). However, HDRS scores were higher in the BD (14.00 ± 8.69) and MDD (11.52 ± 7.57) groups compared to population controls (1.08 ± 2.26) ($p \leq 0.001$). FAST scores were higher in BD (19.77 ± 11.85) and MDD (16.83 ± 11.08) groups compared to population controls (7.71 ± 7.37) ($p \leq 0.001$) (Table 1). In addition, there was no significant correlation between HDRS and IL-6 in BD ($r = 0.077$, $p = 0.608$), in MDD ($r = 0.002$, $p = 0.987$), and in control group ($r = 0.127$, $p = 0.402$). Also, there was no significant correlation between HDRS scores and IL-10 in BD ($r = 0.132$, $p = 0.376$), in MDD ($r = 0.104$, $p = 0.481$), and in control group ($r = 0.063$, $p = 0.686$).

In subjects with BD, there was a positive correlation between functional impairment and serum IL-6 levels ($r = 0.349$; $p = 0.016$) and serum IL-10 levels ($r = 0.351$; $p = 0.016$) (Fig. 1). Of note, the statistical analysis was performed on log-transformed data, however,