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Interleukin-6 and Interleukin-10 in mood disorders: A population-based study

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ABSTRACT

Objective: The aim of this study was to assess if cytokines levels (IL-6 and IL-10) are related to major depressive disorder (MDD) and bipolar disorder (BD), in a population-based study.
Methods: This was a cross-sectional study population-based, involving 1037 people aged 18–35. MDD, BD, anxiety and suicide risk were assessed using the Mini International Neuropsychiatric Interview. Serum IL-6 and IL-10 were measured by ELISA using a commercial kit.
Results: The total sample comprised 1034 young adults, being 14.4% with MDD and 13.7% with BD. MDD and BD groups showed significantly higher serum IL-6 levels ($p \leq 0.001$) and IL-10 levels ($p \leq 0.001$) when compared to healthy control group. No correlation was found between serum IL-6 and IL-10 levels in health control group ($p = 0.830$; $r = {}^{-}0.008$), non-suicide risk ($p = 0.337$; $r = 0.032$) and non-anxiety disorder ($p = 0.375$; $r = 0.031$). Covariance analysis showed that mood disorders alone, increase both interleukin levels (IL-6, $p = 0.019$; and IL-10, $p = 0.026$), whilst the interaction of mood disorders and suicide risk or anxiety disorders did not.
Conclusion: Our results suggest that inflammatory dysregulation may be involved in the physiopathology of mood disorders and serum IL-6 and IL-10 levels are putative biomarkers for these disorders.

1. Introduction

Mental disorders are regarded as major contributors, 12% approximately, of the global burden of disease. (Knudsen et al., 2013; Skapinakis et al., 2013; Vos et al., 2012). Among them are bipolar disorder (BD), major depressive disorder (MDD), and anxiety disorders, that present as debilitating psychiatric morbidities (Schmidt et al., 2011), and are well-documented risk factors for suicide. The etiology of these disorders is not completely understood, however, several studies have demonstrated an association between inflammatory processes and psychiatric disorders (Blume et al., 2011; Dantzer et al., 2008; Dowlati et al., 2010; Neto et al., 2011; Schneider and Prvulovic, 2013). Studies suggest a bidirectional communication between the immune system and the central nervous system (CNS), indicating that brain-immune interactions can be associated with in neuropathological processes (Maes et al., 2012). In this sense, psychiatric disorders can be considered a psychoneuroimmunological disorder, in which peripheral immune activation through the release of proinflammatory cytokines may be responsible for the behavioral, neuroendocrine and neurochemical changes observed in individuals with psychiatric disorders (Schmidt et al., 2011; Schneider and Prvulovic, 2013).

In general, studies provide preliminary evidence that psychiatric disorders, particularly, MDD and BD, may be associated with an increased inflammatory state, evidenced by changes in peripheral concentrations of cytokines IL-6 and IL-10, although, such findings are inconsistent among literature, and often contradictory (Barbosa et al.,

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2014; Dowlati et al., 2010; Haapakoski et al., 2015; Vogelzangs et al., 2016; Wiener et al., 2017). For example, Dowlati et al. (2010) through a meta-analysis showed that pro-inflammatory cytokines, such as IL-6, are consistently increased in depression. However, in this same study, the authors did not detect significant differences in serum IL-10 levels, compared to healthy controls (Dowlati et al., 2010). On the other hand, recent data show that BD does not implicate alterations in serum levels of IL-6 and IL-10 in drug-free patients, when compared to healthy controls (Wiener et al., 2017).

Compared to depression and BD, studies on the role of the immune system in anxiety disorders and suicide risk are scarce. Studies have shown that co-occurrence of both anxiety orders or suicide risk and mood disorders increased proinflammatory cytokines, as compared to individuals suffering from the mood disorders alone (Furtado and Katzman, 2015; Glaus et al., 2018; O'donovan et al., 2013). However, this hypothesis requires further investigation. Thus, the aim of this study was to assess if cytokines levels (IL-6 and IL-10) are related to major depressive disorder (MDD) and bipolar disorder (BD), in a population-based study.

2. Methods

This was a cross-sectional study population-based, involving 1168 people aged 18–35, living in Pelotas (Brazil), in the period from June 2011 to October 2012, approved by the Catholic University of Pelotas Ethics Committee (2010/15).

After the subjects were identified and invited, the volunteers signed an informed consent and answered a questionnaire on sociodemographics, the National Economic Indicator – IEN (Barros and Victora, 2005) and tobacco use data. To evaluate alcohol use disorder, the participants also responded to the CAGE questionnaire (Buchsbaum et al., 1992).

The evaluation of psychiatric disorders was performed by the Mini International Neuropsychiatric Interview (MINI). This is a short structured interview, lasting around 15–30 min, designed to be used in clinical practice and research, with the goal of diagnosing the interviewee according to DSM-IV criteria. In this study, we evaluated mood disorders in current episodes (bipolar disorder and current depression), and in the following anxiety disorders: social phobia, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorders, and generalized anxiety disorder. We introduced the variable 'anxiety disorders' (AD), which is the sum of each current anxiety disorder. All individuals who met diagnostic criteria for at least one anxiety disorder were coded as "1″ and those with no anxiety disorder were coded as "0″. The module on suicide questions several components of suicide risk from the following questions: During the past month - (1) Have you ever thought that it would be better to be dead or wish you were dead? (score: 1 point); (2) Have you ever wanted to hurt yourself (2 points); (3) Have you ever thought about committing suicide? (6 points); (4) Have you ever planned on committing suicide? (10 points); (5) Have you ever tried suicide? (10 points); and (6) Have you ever tried suicide over the course of your life? (4 points). Suicide risk was classified as low (score 1–5), moderate (score 6–9), and high (score > 10). For risk of suicide, scores were dichotomized in absence of risk (low or absent) and presence of risk (moderate or high risk - ≥ 6 points), as recommended by the MINI authors (Sheehan et al., 1998). Moreover, individuals who were taking a psychoactive substance, or in use of psychopharmacological drugs, or who presented any psychotic disorder or those who were unable to understand or answer the questions were excluded from the study.

For the biochemical analyses, 10 mL of blood was withdrawn from each subject by venipuncture, into an anticoagulant-free vacuum tube, after the interview, between the hours of 8:00 AM and 11:00 AM. After blood collection, it was anticipated clot formation (approximately after 30 min) and thus the sample was centrifuged to 4000 x *G* for 10 min, and the resulting serum was aliquoted and frozen at −80 °C for later analysis. Serum cytokines levels were assessed with a sandwich-ELISA immunoassay kit perfomed according to the manufacturer's instructions (DuoSet ELISA Development, R&D Systems, Inc., USA) and expressed in pg/mL.

Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS) 21.0 (IBM Corporation, Armonk, NY) and Graph Pad Prism 6.0 (GraphPad Software Inc., San Diego, USA). The serum levels of cytokines had non-Gaussian distributions and were presented as a median and interquartile range. Wilcoxon and Kruskal–Wallis tests with Bonferroni post hoc test for multiple comparisons were performed were used for comparison of medians of cytokines between mood disorders. Additionally, correlation between serum IL-6 and IL-10 levels and groups diagnose was assessed with Spearman correlation test. Sociodemographic and clinical characteristics regarding mood disorders were evaluated with the chi-squared test. IL-6 and IL-10 levels were logarithmically transformed before the regression analysis. The independent main effects of mood disorders and suicide risk; mood disorders and anxiety, as well as the interaction effects of mood disorders and suicide risk; mood disorders and anxiety with cytokines were analyzed using two-way analysis of covariance (ANCOVA), followed by Sidak post hoc test. IL-6 levels were adjusted for ethnicity, current smoker and alcohol abuse, and IL-10 levels for sex and alcohol abuse. The results with *p*-values of ≤0.05 were considered statistically significant.

3. Results

The total sample comprised 1034 young adults, of these most of the subjects were female (53.3%), age between 18–23 years (37.8%). Regarding mood disorders, 14.4% individuals were diagnosed with MDD, 13.7% with bipolar disorders (Table 1). Moreover, serum levels of cytokines are presented in table 1 according to sociodemographic and clinical characteristics. Serum IL-6 levels were associated with ethnicity ($p = 0.038$), current smoker ($p = 0.001$), alcohol abuse ($p \leq 0.001$), suicide risk ($p = 0.003$). While, serum IL-10 levels were associated with sex ($p = 0.004$), alcohol abuse ($p \leq 0.001$), and suicide risk ($p = 0.032$). We found a significant difference in the median of IL-6 ($p \leq 0.001$) and IL-10 ($p \leq 0.001$), between mood disorders. The Bonferroni post hoc test for multiple comparisons revealed significant differences for higher serum levels of IL-6 and IL-10 in individuals with MDD, as well as BD, when compared to healthy control (Pair-wise IL-6: MDD-Health control, $p = 0.001$. BD-health control, $p = 0.026$) (Pair-wise IL-10: MDD-Health control, $p = 0.038$. BD-health control, $p = 0.002$).

Furthermore, we show in Table 2, significant difference in several socio-demographic characteristics in relation to the diagnostic groups. Furthermore, regarding suicide risk, 40.3% accompanied MDD and 45.1% BD, as well as anxiety disorders were present in 54.4% of MDD and 62.0% of BD.

Serum IL-6 and IL-10 levels were positively correlated in MDD group ($p \leq 0.001$; $r = 0.412$), in BD group ($p = 0.007$; $r = 0.235$), in suicide risk group ($p \leq 0.001$; $r = 0.347$) and anxiety diseases group ($p \leq 0.001$; $r = 0.267$). However, no correlation was found between serum IL-6 and IL-10 levels in health control group ($p = 0.830$; $r = -0.008$), non-suicide risk ($p = 0.337$; $r = 0.032$) and non-anxiety disorder ($p = 0.375$; $r = 0.031$) (data not shown)

In Table 3, the two-way ANCOVA shows mood disorders effect on IL-6 levels ($F = 3.971$, $p = 0.019$) and IL-10 levels ($F = 3.682$, $p = 0.026$) adjusted for confusion variables. Mood disorders may implicate increased serum levels of cytokines, but that effect was not influenced by suicide risk or anxiety disorder. The interaction between mood disorders and suicide risk, and mood disorders and anxiety were not significant on IL-6 and IL-10 levels.

Table 1
Distribution of sample, median with interquartile of IL-6 and IL-10 levels with interquartile according to sociodemographic and clinical characteristics.

Characteristics	Sample distribution *N* (%)	IL-6 level (pg/mL)	IL-10 level (pg/mL)
Sex[a]		$p = 0.808$	$p = 0.004$
Female	551 (53.3)	15.56 (11.50–22.58)	53.62 (37.06–65.57)
Male	483 (46.7)	15.65 (12.05–21.80)	49.18 (25.13–63.85)
Age (years)[b,*]		$p = 0.907$	$p = 0.131$
18–23	391 (37.8)	15.90 (11.55–24.00)	52.88 (36.10–65.13)
25–29	337 (32.6)	15.73 (11.54–22.20)	49.42 (30.85–61.98)
30–35	305 (29.5)	16.64 (11.86–22.21)	53.85 (33.83–68.80)
Ethnicity[a]		$p = 0.038$	$p = 0.292$
Caucasian	784 (75.8)	15.65 (11.20–22.07)	51.87 (32.74–63.99)
No-Caucasian	250 (24.2)	15.85 (11.83–22.20)	52.85 (30.41–66.44)
BMI[a,*]		$p = 0.651$	$p = 0.760$
Normal	487 (47.1)	14.85 (11.31–23.30)	52.06 (30.82–65.17)
Excess weight	504 (48.7)	15.73 (11.83–21.64)	52.60 (33.03–65.13)
Marital status[a,*]		$p = 0.221$	$p = 0.962$
Single or divorced or widowed	647 (62.6)	15.64 (11.57–22.85)	52.02 (32.65–64.63)
Married or living with a partner	385 (37.4)	16.70 (11.97–22.80)	52.73 (30.93–66.25)
Brazilian Economic index[b,*]		$p = 0.367$	$p = 0.079$
1 (minor)	338 (32.8)	16.41 (11.89–22.75)	52.99 (32.29–67.12)
2 (middle)	349 (33.8)	15.75 (12.07–22.81)	51.74 (28.77–65.60)
3 (highest)	345 (33.4)	15.41 (11.55–23.57)	51.62 (31.69–62.84)
Schooling (years)[b]		$p = 0.121$	$p = 0.135$
0–5	60 (5.8)	15.59 (11.56–22.15)	52.57 (40.59–62.96)
6–11	469 (45.4)	16.75 (11.80–23.86)	52.98 (32.60–66.73)
12 or more	505 (48.8)	15.19 (11.75–22.22)	51.33 (29.66- 63.85)
Current smoker[a,*]		$p = 0.001$	$p = 0.857$
No	791 (76.8)	15.49 (11.51–21.99)	52.24 (32.78–63.85)
Yes	239 (23.2)	17.53 (12.49–30.83)	52.60 (29.42–68.16)
Alcohol abuse[a,*]		$p \leq 0.001$	$p \leq 0.001$
No	899 (86.9)	14.85 (10.91–21.01)	53.03 (36.69–65.13)
Yes	124 (12.0)	19.41 (15.67–40.28)	28.36 (19.12–67.37)
Suicide risk[a]		$p = 0.003$	$p = 0.032$
No	910 (88.0)	15.48 (11.42–22.22)	51.85 (31.44–63.74)
Yes	124 (12.0)	18.53 (13.06–29.86)	55.19 (34.90–78.90)
Anxiety disorders[a]		$p = 0.670$	$p = 0.674$
No	865 (83.6)	15.48 (11.51–22.25)	52.25 (31.76–63.85)
Yes	169 (16.4)	17.99 (12.55–27.74)	52.55 (32.61–73.46)
Mood disorders[b]		$p \leq 0.001$	$p = 0.001$
MDD	149 (14.4)	18.44 (12.76–28.70)[1–3]	57.41 (39.87–81.91)[1–3]
BD	142 (13.7)	17.64 (12.27–29.19)[2–3]	54.41 (39.87–71.39)[2–3]
Health control	743 (71.9)	14.97 (11.22–21.27)	52.35 (34.97–63.34)
Total	1034	15.64 (11.83–22.56)	51.23 (39.88–64.63)

MDD = major depression disorder. BD = Bipolar disorder.
Pair-wise differences ($p < 0.005$): 1-individuals with MDD; 2-patients with BD; 3-healthy controls.
[a] Mann-Whitney test
[b] Kruskal–Wallis following Bonferroni post hoc test for multiple comparison.
[*] Variable with missing.

4. Discussion

In this study, we evaluated cytokines levels related to mood disorders, MDD, and BD in young subjects. MDD and BD showed higher serum IL-6 and IL-10 levels when compared to healthy control subjects. In this study, we can also observe a positive correlation between serum levels of IL-6 and IL-10 only in individuals with mood disorders. The main finding of this study was that mood disorders may increase serum levels of cytokines, but that effect is not influenced by suicide risk or anxiety disorder. The interactions between mood disorders and suicide risk, and mood disorders and anxiety were not significant on IL-6 and IL-10 levels.

Regarding mood disorders, MDD and BD, our study observed

Table 2
Socio-demographic and clinical characteristics of the sample according to psychiatric disorders.

	Health control *N* (%)	Major depression disorder *N* (%)	Bipolar disorder *N* (%)	*p*-value
Sex				≤0.001
Female	354 (47.6)	113 (75.8)	84 (59.2)	
Male	389 (52.4)	36 (24.2)	58 (40.8)	
Age (years)				0.289
18–23	290 (39.1)	43 (28.9)	58 (40.8)	
25–29	247 (33.3)	49 (32.9)	41 (28.9)	
30–35	205 (27.6)	57 (38.3)	43 (30.3)	
Ethnicity				0.058
Caucasian	576 (77.5)	111 (74.5)	97 (68.3)	
No-Caucasian	357 (22.5)	38 (25.5)	45 (31.7)	
BMI[*]				0.228
Normal	357 (50.0)	60 (42.6)	70 (51.5)	
Excess weight	431 (50.0)	81 (57.4)	66 (48.5)	
Living with a partner[*]				0.020
No	477 (64.4)	78 (52.3)	92 (64.8)	
Yes	264 (35.6)	71 (47.7)	50 (35.2)	
Brazilian economic index[*]				≤0.001
1 (minor)	212 (28.5)	70 (47.0)	56 (40.0)	
2 (middle)	259 (34.9)	47 (31.5)	43 (30.7)	
3 (highest)	272 (36.6)	32 (21.5)	41 (29.3)	
Schooling (years)				0.001
0–5	36 (4.8)	14 (9.4)	10 (7.0)	
6–11	316 (42.5)	72 (48.3)	81 (57.0)	
12 or more	391 (52.6)	63 (42.3)	51 (35.9)	
Current smoker[*]				≤0.001
No	611 (82.6)	104 (69.8)	76 (53.9)	
Yes	129 (17.4)	45 (30.2)	65 (46.1)	
Alcohol abuse[*]				≤0.001
No	666 (90.9)	127 (85.2)	106 (75.2)	
Yes	67 (9.1)	22 (14.8)	35 (24.8)	
Suicide risk				≤0.001
No	743 (100.0)	89 (59.7)	78 (54.9)	
Yes	0 (0.0)	60 (40.3)	64 (45.1)	
Anxiety disorders				≤0.001
No	743 (100.0)	68 (45.6)	54 (38.0)	
Yes	0 (0.0)	81 (54.4)	88 (62.0)	
Total	743 (71.9)	149 (14.4)	142 (13.7)	

Chi-square test represented by absolute frequency (relative frequency)
[*] Variable with missing.

Table 3
Two-way analysis of covariance: cytokines, mood disorders, suicide risk and anxiety disorder.

	Serum IL-6 levels		Serum IL-10 levels	
	F	*p*-value	*F*	*p*-value
Main effects of mood disorders	3.971	0.019	3.682	0.026
Main effects of suicide risk	0.416	0.519	1.261	0.262
Main effects of anxiety	0.004	0.951	0.061	0.805
Mood disorders X suicide risk interaction	1.261	0.262	0.023	0.879
Mood disorders X anxiety interaction	0.043	0.835	0.000	0.989

Adjusted variables: IL-6 levels: ethnicity, current smoker and alcohol abuse. IL-10 levels: sex and alcohol abuse.

significantly increased serum IL-6 levels. Meta-analyses have confirmed a relationship between circulating inflammatory markers and mood disorders, although this association is not consistent in all studies (Howren et al., 2009; Rozing et al., 2019; Young et al., 2014). Haapakoski et al., (2015) show higher IL-6 levels in MDD, whereas Luo et al., 2016 shown that whilst IL-18 levels were only higher in depressive subjects, serum TNF-α and IL-6 levels were higher in BD (Haapakoski et al., 2015; Luo et al., 2016). Under physiologic conditions, there is a feedforward loop, that is likely to result in an IL-6 driven induction of IL-10 release, which would, in turn, have the potential to dampen or resolve inflammatory processes through its immunoregulatory/anti-inflammatory effects. It is suggested that an impairment of this finely regulated process could occur to contribute to mood disorder development. Actually, in earlier stages, there is an immune response involving an increase in IL-10 levels; however, with the course of the disorder, there is a reduction in IL-10 levels, thus increasing symptoms. In the present study, an increase of IL-6 and IL-10 was observed, which contributes to this hypothesis. Furthermore, studies have shown that depressed patients have indeed an increase in IL-6, but present a decrease in IL-10 (Dhabhar et al., 2009). In the sample from our study, patients were in the early stages of the disease, while in the Dhabhar study, they were patients in more advanced stages, which would justify the contradictive observation regarding IL-10 levels. In addition, a reduction in serotonin levels may contribute to an increase in the ratio of pro-inflammatory and anti-inflammatory cytokines (Dantzer et al., 2008; Miller et al., 2009).

Furthermore, increased cytokines levels may be related to increased HPA axis activity as indexed by higher levels of cortisol, which in turn, generally has anti-inflammatory effects (Stephens and Wand, 2012) Thus, a dysregulated HPA axis could also play a role in the relationship between mood disorders and inflammation. Thus, we suggest that HPA axis dysregulation could have a significant contribution to the observed inflammation in individuals with suicide risk and mood disorder. Also, in our study, we observed higher serum IL-6 and IL-10 levels in subjects presenting suicide risk, as compared to those without suicide risk. Similarly, patients with increased suicidal risk have been shown to have higher IL-6 concentration (Kim et al., 2008). Moreover, in the literature, there is still scarce studies involving IL-10 in suicide risk.

Apparently, IL-6 and IL-10 levels are involved in mood disorders, anxiety disorders, and suicide risk, agreeing with previous studies. Surprisingly, after adjusted covariance analysis, mood disorders alone influence IL-6 and IL-10 levels, whilst the interactions between these factors and suicide risk or anxiety disorders did not. A dysregulated immune system affects monoamine regulation, implicated in several neuropsychiatric disorders, and consequently, related to neuroprogression and degenerative processes that occur in mood disorders (Mina et al., 2015). Studies found increased microgliosis in the postmortem brain of suicide victims with affective disorders and schizophrenia compared with normal control subjects,. Moreover, several studies found in suicidal victims an increase in cytokines levels, including IL-6 and IL-10 (Schizophrenia Working Group of the Psychiatric Genomics, 2014). These data led to the hypothesis of an increase in proinflammatory cytokines in the risk of suicide. Therefore, although here we show that in early stages of psychiatry disorders, IL-6 and IL-10 play a role in the mood disorders, we believe in later stages the global cytokine dysregulation could be a pivotal role in suicide risk. Taken as a whole, we believe that others cytokines may be involved in suicide risk, like IFN-α and IL1-beta, and these cytokines are able to induce IL-6 production (Mina et al., 2015; Monfrim et al., 2014).

The study has the methodological strength of using a large sample size and also the fact that we studied a community-based sample of young and non-medicated experiencing the early stages of this disease. However, a major limitation was that the cross-sectional design did not enable us to make causal inferences between psychiatric disorders and inflammatory process. Our study agreeing to literature, presented an increase in serum IL-6 and IL-10, and the positive correlation between IL-6 and IL-10, which exhibits a predominance of inflammation in the individual with mood disorders. These results suggest that inflammatory dysregulation may be involved in the physiopathology of these disorders. However, further studies should clarify the specific immune mechanisms involved in patients suffering from MDD, BD, anxiety disorders and suicide risk, as well as in the development of anti-inflammatory therapies for these individuals.

Conflict of interest

The authors have no conflict of interest to declare.

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