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Childhood trauma and increased peripheral cytokines in young adults with major depressive: Population-based study

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ABSTRACT

Objective: The aim of this study was to evaluate the effect of childhood trauma in cytokine serum levels of individuals with MDD.
Methods: This was a cross-sectional study population-based, with people aged 18 to 35. The Mini International Neuropsychiatric Interview (M.I.N.I) measured to current major depressive disorder (MDD). To evaluate traumatic experiences during childhood, the Childhood Trauma Questionnaire (CTQ) was applied. Serum TNF- α, IL-6 and IL-10 levels were measured by ELISA using a commercial kit.
Results: The total sample comprised 166 young adults, of these: 40.4% were subjects with MDD and childhood trauma and 59.6% were diagnosed with MDD without childhood trauma. In relation to serum interleukin levels, subjects with childhood trauma showed a significantly higher serum IL-6 ($p = 0.013$) and IL-10 levels ($p = 0.022$) to compare no childhood trauma. Subjects with childhood trauma was observed positive correlation between serum IL-6 and physical abuse ($r = 0.232$, $p = 0.035$) and emotional abuse ($r = 0.460$, $p \leq 0.001$). Moreover, IL-10 were positive correlation with physical abuse ($r = 0.258$, $p = 0.013$). TNF- α was not associated with childhood trauma.
Conclusion: Childhood maltreatment may result higher inflammation dysregulation in individuals with depression than individuals that no has childhood maltreatment.

1. Introduction

Childhood abuse may have long-term effects on health and may represent risk factors for poor mental and physical health outcomes across the lifetime. Previous research has established associations which psychiatric diseases, included major depressive disorder (MDD) (Kessler et al., 2010; Poole et al., 2017). Individuals who have experienced abuse or neglect in childhood are 1.3 to 3.1 times more likely to experience lifetime major depressive disorder or dysthymia, depending on the type, severity, and frequency of the trauma (Poole et al., 2017; Kendler et al., 2000; Widom et al., 2007).

MDD has been frequently linked to dysregulation of the immune system (Schneider and Prvulovic, 2013; Vogelzangs et al., 2016). Cytokines mediate signaling between immune cells, and are mainly secreted from monocytes (or macrophages) or lymphocytes (Schneider and Prvulovic, 2013; Vogelzangs et al., 2016). Cytokines are key role in the control and modulation of inflammatory responses, with a constant balance between proinflammatory and anti-inflammatory cytokines (Vogelzangs et al., 2016). Interleukin-6 (IL-6) is the main proinflammatory cytokine activated in the innate immune process, resulting from microglial activation (Vogelzangs et al., 2016). Interleukin- 10 (IL-10) is recognized as a factor that suppresses the synthesis of cytokines, being one of the most important endogenous anti-inflammatory agents produced by the body (Bromander et al., 2012; Krishnadas and Depression, 2012).

Stress early in life has been evidenced to be associated with a several mental disorders occurring in later life, such as depression, and this disorder is strongly associated with inflammation (Kessler et al., 2010; Carpenter et al., 2010; Danese et al., 2009). Previous studies found that the accumulation of childhood social adversity was associated with

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higher levels of C-reactive protein (CRP) (Slopen et al., 2015), and children who were exposed to adverse psychosocial experiences were at elevated risk of higher CRP levels (Danese et al., 2009). In addition, to the direct physiological effects of early stress on inflammation, stress to be associated with other in later life, such as metabolic syndrome, type 2 diabetes, and cardiovascular disease, which has been shown to be associated with higher levels of pro-inflammatory (Coelho et al., 2014; Baumeister et al., 2016). In MDD patients, higher levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, were associated with depressed mood (Krishnadas and Depression, 2012; Dantzer, 2012; Dowlati et al., 2010), and lower levels of the anti-inflammatory cytokine IL-10 were reported in this disorder (Dhabhar et al., 2009). Moreover, a meta-analysis study, was confirmed that IL-6 and TNF-α levels are elevated in MDD patients (Muller, 2014). Previous study shown to reduce levels of IL-10 contributed to an increase in the expression of IL-6 in the brains of aged mice, moreover, was demonstrated that early life stress induces an increase in IL-6 levels and a decrease in IL-10 levels in a rat model of early-life stress (Reus et al., 2017). Thus, changes in inflammatory mediators in the periphery could increase inflammation in the CNS.

Substantial evidence suggests that childhood maltreatment is associated with increased risk of depression development and anxiety disorders. Moreover, studies point to early-life stress can have deleterious effects on the activity of the HPA axis and the immune system (Levandowski et al., 2016). Studies in literature have suggested changes in serum levels of proinflamatory cytokine levels, such as interleukin-6 (IL-6), and antiinflamatory cytokine levels, such as interleukin-10 (IL-10) among patients with MDD (Vogelzangs et al., 2016; Dowlati et al., 2010). However, the results still have been controversial and some individuals with MDD did not change in cytokine levels. The immune system in MDD may vary with heterogeneity of clinical features, included severity of the disorder and presence of childhood trauma. Carpenter et al. (2010) in a study with individuals without depression, sought to clarify the use of early-life stress regarding IL-6 response. Individuals with maltreatment in childhood had increased IL-6 during a standard stress challenge compared to the control group, suggested that inflammation may be an important developmental mediator linking adverse experiences in early life to poor adult physical and mental health (Carpenter et al., 2010; Grosse et al., 2016). Measuring cytokine changes in people with depression and childhood traumas may be useful in further explaining the underlying pathogenic mechanisms of depression. Thus, to further elucidate the role that childhood trauma exposure has on the cytokine response in individuals with depression, the objective of this study was to evaluate the effect of childhood trauma in cytokine serum levels of individuals with MDD.

2. Methods

2.1. Subjects

This was a cross-sectional study population-based, involving 1380 people aged 18 to 35, living in the city of Pelotas (Brazil), in the period from June 2011 to October 2012.The study was 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 socio-demographic, The National Economic Indicator – IEN (Barros and Victora, 2005), tobacco use and psychopharmacological drugs data. To evaluate alcohol use disorder, the participants also responded to the CAGE questionnaire (Buchsbaum et al., 1992). Height was measured without shoes to the nearest 0.1 cm. Weight was measured in kilograms to the nearest 0.1 kg. Body Mass Index (BMI) was calculated as the weight (in kilograms) and height (in meters), according to the formula: Kg/m^2 (WHO-, 2008).

The Mini International Neuropsychiatric Interview (M.I.N.I) measured major depressive disorder (MDD) in the current episode,

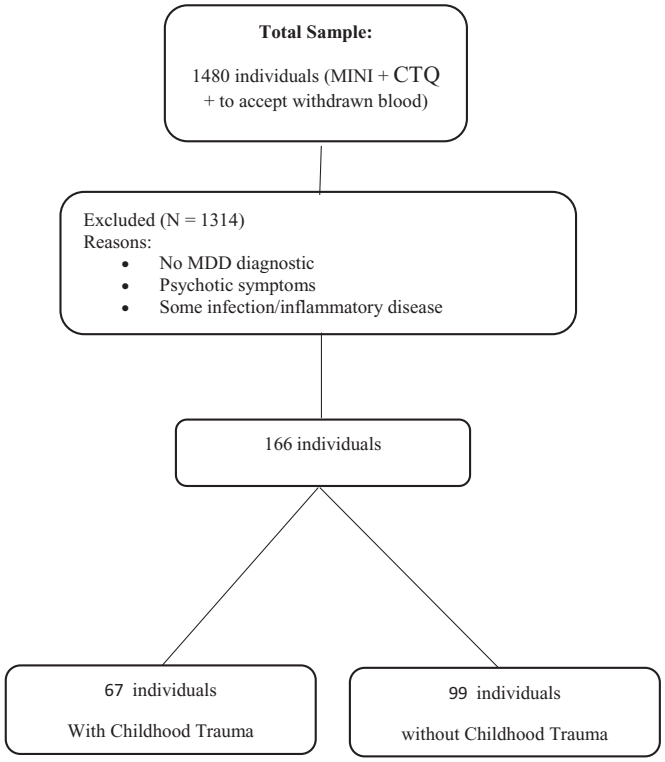

Fig. 1. Flow diagram of the current depressed individuals with and without childhood trauma groups.

administered by well-trained and supervised Psychologists. 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 (Amorim et al., 1998). The questionnaire has 0.92 of both sensitivity and specificity. According to the DSM-IV criteria, the MINI psychometric characteristics for the diagnosis of major depressive episode are: sensitivity of 96%, specificity of 88%, positive predictive value of 87%, negative predictive value of 97%, and efficiency of 91%.

Those individuals who were unable to understand the instruments of evaluation, those who presented with psychotic symptoms or some infection/inflammatory disease, and who did not accept to participate in withdrawn blood were excluded. Moreover, for the purpose of the present study, we included only individuals with MDD diagnosis in current episode, independent of the use of psychiatric medication, resulting in a total of 166 subjects eligible for this study (Fig.1).

To evaluate traumatic experiences during childhood, the Childhood Trauma Questionnaire (CTQ) was applied, adapted for Brazil (Bernstein et al., 2003; Grassi-Oliveira et al., 2006). The original version of the instrument presented good validity and reliability coefficients, with internal consistency medians ranging from $\alpha = 0.66$ to $\alpha = 0.92$ (Bernstein et al., 2003). The Brazilian translated and adjusted version is appropriate for evaluating people older than 12 years of age (Grassi-Oliveira et al., 2006). The Childhood Trauma Questionnaire (CTQ) is a reliable and valid self-reporting questionnaire with 28 items (Grassi-Oliveira et al., 2006). It can yield five sub-scales which evaluate five aspects of CTE, emotional abuse, emotional neglect, sexual abuse, physical abuse, and physical neglect, respectively. The CTQ is an easily understandable 5-item Likert scale on which the individual rates the frequency of 28 sentences related to traumatic situations during childhood.

2.2. Blood sample collection and cytokines assessment

For the biochemical analyses, 10 ml of blood was withdrawn from

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