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Effects of depression on the cytokine profile in drug naïve first-episode psychosis

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ABSTRACT

Schizophrenia is accompanied by alterations in immuno-inflammatory pathways, including abnormalities in cytokine profile. The immune assessment of patients in a first episode of psychosis (FEP) and particularly in drug naïve patients is very important to further elucidate this association.

The objectives of this study are to delineate the cytokine profile (IL-2, IL-10, IL-4, IL-6, IFN γ , TNF α and IL-17) in FEP patients (n = 55) versus healthy controls (n = 57) and to examine whether the presence of depressive symptoms in FEP is accompanied by a specific cytokine profile.

We found increased levels of IL-6, IL-10 and TNF α in FEP patients when compared to healthy controls. FEP patients with depression showed higher IL-4 and TNF α levels versus those without depression. Cytokine levels were not correlated to the total PANSS and the positive or negative subscale scores.

Our results suggest that FEP is accompanied by a cytokine profile indicative of monocytic and T regulatory cell (Treg) activation. Depression in FEP is accompanied by monocytic and Th-2 activation, whereas FEP without depression is characterized by Treg activation only. In conclusion, depression emerged as a key component explaining the cytokines imbalance in FEP that is responsible for a large part of the immune-inflammatory abnormalities described.

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1. Introduction

Psychosis is a core symptom of schizophrenia, a severe neurodevelopmental disorder, with large economical and social impact (Insel, 2010). Abnormal immune-inflammatory responses, including increased levels of pro-inflammatory cytokines are found in patients with schizophrenia (Potvin et al., 2008; Miller et al., 2011). In 1995, the immune-inflammatory theory of schizophrenia proposed that activated immune-inflammatory pathways, particularly activated macrophages and T-lymphocytes, may explain the higher offspring schizophrenia risk associated with gestational infections through the neurotoxic effects of pro-inflammatory cytokines and their detrimental consequences (Smith and Maes, 1995). More recently, several reviews addressed the role of activated immune-inflammatory pathways in

the neurodevelopmental pathophysiology of schizophrenia (Anderson et al., 2013a; Meyer, 2013).

Cytokines are proteins involved in the activation, coordination and suppression of immune responses. Their neuromodulatory actions appear to be critical for the regulation of neuroplasticity, cell resilience and apoptosis (Boulangier and Shatz, 2004; Golan et al., 2004; Bauer et al., 2007). Macrophages are activated during innate immune response in two functional distinct states (M1 and M2), producing different cytokines. M1 macrophages produce pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-12 and tumor necrosis factor (TNF) α , stimulating cell-mediated response. M2 macrophages produce negative immunoregulatory cytokines, such as IL-10 and transforming growth factor (TGF) β (Seruga et al., 2008; Maes et al., 2012b). During the adaptive immune response, T lymphocytes differentiate into T helper (Th)1, Th17, T regulatory (Treg) and Th2 cells. Naïve cells are driven towards Th1 and Th2 phenotypes by M1 and M2 macrophages, respectively (Seruga et al., 2008; Maes et al., 2012b). A Th1-shift cytokine profile indicates immune activation, whereas a Th2-shift may indicate negative immunoregulatory effects and activated humoral immunity

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(Maes et al., 2012b). A recent meta-analysis showed that schizophrenia is accompanied by increased levels of pro-inflammatory cytokines indicating M1 activation and increased levels of Th1-like cytokines, indicating T cell activation (Miller et al., 2011). There are, however, few studies that have examined the associations between psychosis and levels of monocytic cytokines, Th1, Th2, Th17 and Treg cytokines simultaneously.

Meta-analyses (Potvin et al., 2008; Miller et al., 2011) demonstrated a notable heterogeneity of results in existing studies, possibly as a consequence of several confounding factors, such as use of medications and clinical features. The acute or (sub)chronic use of antipsychotic drugs, which have significant immune-regulatory effects (Maes et al., 2000; MacDowell et al., 2013; Tourjman et al., 2013), is one of those factors that may modify the levels of cytokines measured. Therefore, the analysis of the immune state in drug naïve patients is of paramount importance to examine the levels of monocytic, Th1, Th2, Th17 and Treg cytokines. Uptegrove et al. (2014) recently published a meta-analysis examining patients with drug naïve first episode psychosis (FEP). They found an elevation in pro-inflammatory cytokine (and receptor) levels in the serum of FEP patients with higher levels of IL-1 β , soluble IL-2 receptor (sIL-2R), IL-6 and TNF- α , a profile suggesting M1 and Th1 activation.

The immune-inflammatory profile of patients with psychosis seems to be modulated by clinical characteristics. For example, a more disordered immune-inflammatory profile may be found in patients with a more severe course of the disorder (Noto et al., 2011; Asevedo et al., 2013; Noto et al., 2013). Another important clinical factor is the presence of depressive symptoms in patients with psychosis. The prevalence of depression in schizophrenia may be as high as 61% (Gozdzik-Zelazny et al., 2011) and in FEP the prevalence may be as high as 80% (Uptegrove et al., 2010; Sonmez et al., 2014). Despite being different disorders, schizophrenia and depression shared some clinical and biological characteristics. Both present cognitive and neurostructural changes suggestive of neuroprogressive processes. There is consistent evidence that depression is an immune-inflammatory disorder accompanied by increases in macrophage (M1), Th1, Th2 and Th17-like cytokines and lowered levels of Treg cytokines (Leonard and Maes, 2012; Noto et al., 2014b). Both schizophrenia and depression share significant overlaps in immune-inflammatory pathways, including increased levels of pro-inflammatory cytokines and Th1 cytokines (Maes et al., 1990; Leonard and Maes, 2012; Anderson et al., 2013a; Noto et al., 2014b). They also shared other biological pathways, such as activation of oxidative and nitrosative stress, decreased antioxidant levels, and activation of the tryptophan catabolite pathway through induction of indoleamine-2,3-dioxygenase (IDO). The association between both disorders is related with poor quality of life, impairments in social and vocational functioning, and higher rates of relapse. It may cause a worse outcome and increased suicide, even at early stages (Conley et al., 2007; Challis et al., 2013; Noto et al., 2013; Bjorkenstam et al., 2014; Schennach et al., 2014). At the FEP symptoms as loss of self-confidence, feelings of guilt and suicidal thoughts are one of the most prevalent (an der Heiden et al., 2005). Based on these findings it was hypothesized that schizophrenia is primed for an increased expression of depression via activated immune-inflammatory pathways (Anderson et al., 2013b).

The aims of the present study were to examine whether a) FEP is characterized by a specific cytokine profile indicating macrophage, Th1, Th2, Th17 or Treg activation (IL-2, IL-10, IL-4, IL-6, IFN γ , TNF α and IL-17); and b) the presence of depressive symptoms in FEP individuals may be related to a specific cytokine profile.

2. Subjects and methods

2.1. Subjects

This study is part of a prospective cohort performed in Sao Paulo, Brazil, that combines the assessment of different characteristics of

drug naïve FEP patients, such as gene expression, methylation, immune-inflammatory, and oxidative and nitrosative stress profiles. Further, patients were treated and followed, with analyses of the effects of antipsychotic treatment on these biomarkers (Noto et al., 2014a; Ota et al., 2014a,b).

For the current study, fifty-five drug naïve FEP patients with acute symptoms were recruited from an emergency unit, between July of 2011 and June of 2013. The diagnosis of a psychotic disorder was established according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), using the Structured Clinical Interview of the DSM-IV (SCID-I). All assessments were performed by trained psychiatrists. To determine the beginning of the psychotic episode, retrospective assessment of the period before the first episode was conducted to identify: 1 – the last period before any behavioral alteration; 2 – the onset of psychotic sub-threshold symptoms; and 3 – the point in which psychotic experiences allowed a formal DSM-IV diagnosis. When the information was not clear, medical records and familial informants were contacted to best estimate. The mean time between the onset of psychotic symptoms and the assessment was 223 days (\pm 435). Only patients between 16 and 40 years of age, who had never used any antipsychotic drugs before were included. All patients fulfilled the criteria for one of the following psychotic diagnoses according to the DSM-IV TR: schizophrenia (66.7%), schizophreniform disorder (7.1%), brief psychotic disorder (2.7%) and psychotic disorder not otherwise specified (3.6%). Patients with psychotic episodes due to a general medical condition, substance-induced psychotic disorder or intellectual disability were excluded, and patients with diagnoses of bipolar or major depressive disorders with psychotic features were also excluded. Alcohol and drug misuse was assessed by the SCID and familiar interview, but were not an exclusion criteria. Patients who fulfilled the diagnosis of substance-induced psychotic disorder and patients who suffered from acute intoxications were excluded to participate.

The comparison group consisted of fifty-seven drug naïve, healthy volunteers who neither themselves nor their first-degree family members had a current or previous history of a major psychiatric disorder, including dementia and intellectual disability, according to the criteria of the SCID-I. Acute and chronic general medical conditions associated with an imbalance in inflammatory responses such as infections, HIV, allergies, pregnancy or the postpartum period, rheumatologic and immunological conditions were the exclusion criteria for both cases and controls. In addition, individuals using medications with immunomodulatory effects such as non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants were excluded in both groups.

The relative severity of illness dimensions was assessed using a) PANSS (Positive and Negative Syndrome Scale (Kay et al., 1987); b) CDSS (Calgary Depression Scale for Schizophrenia) (Addington et al., 1990). The CDSS is a 9 item-scale (1. Depression, 2. Hopelessness, 3. Self Depreciation, 4. Guilty Ideas of Reference, 5. Pathological Guilt, 6. Morning Depression, 7. Early Wakening, 8. Suicide, 9. Observed Depression), specifically developed for the assessment of the level of depression in schizophrenia. The division of the groups “depressed” or “non-depressed” was established using a threshold of CDSS > 5. Accordingly to the Brazilian version of CDSS, this cut off presents a specificity of 92% and a sensitivity of 77% to identify a major depression (Bressan et al., 1998). This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Research Ethics Committee of UNIFESP (Sao Paulo, Brazil) approved the research protocol, and all participants provided SCH06240 written informed consent prior the enrollment.

2.2. Methods

A blood sample of 10 mL was withdrawn from all the individuals. In FEP patients we sampled blood for the assay of cytokines before the administration of the first dose of antipsychotics. Blood was immediately centrifuged, and the serum was stored at -80°C until the assays

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