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Peripheral interleukin-2 level is associated with negative symptoms and cognitive performance in schizophrenia

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HIGHLIGHTS

- Peripheral IL-2 levels correlated positively with performance in tests of working memory and intelligence in patients with schizophrenia.
- IL-2 levels correlated negatively with scores in the negative subscale of PANSS.
- These associations pose IL-2 as a possible marker of cognitive and affective preservation in schizophrenia.

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ABSTRACT

Although several studies have pointed to a possible role of interleukin 2 (IL-2) in schizophrenia (SZ), association between IL-2 and the different groups of symptoms has not been explored. The objective of this study was to investigate a possible correlation of peripheral IL-2 levels with symptoms and cognitive performance in patients with SZ. In addition, we compared the plasma levels of IL-2 between patients with SZ and healthy controls. Twenty-nine chronically medicated outpatients with SZ according to DSM-IV were compared with twenty-six healthy controls. The patients were evaluated with the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale for Schizophrenia (CDSS), the Clinical Global Impression (CGI) and the Global Assessment of Functioning (GAF). All the participants had blood collected into EDTA tubes by venipuncture between 9:00 and 10:00 AM. Plasma concentrations of IL-2 were determined by cytometric bead array. A computerized neuropsychological battery assessed verbal learning, verbal fluency, working memory, set shifting, executive function, inhibition and intelligence. Patients with SZ had lower levels of IL-2 than healthy controls ($p < 0.001$). In the SZ group, IL-2 levels were positively correlated with scores in the digit span test (rho = 0.416, $P = 0.025$) and intelligence (rho = 0.464, $P = 0.011$). We also found a negative correlation between IL-2 and total score in the negative subscale of PANSS (rho = −0.447, $p = 0.015$). Our findings suggest that IL-2 may be involved in the mechanisms related to cognitive deterioration and negative symptomatology in schizophrenia.

1. Introduction

Schizophrenia (SZ) is a chronic, severe and highly prevalent mental disorder that is frequently associated with significant disability [1]. Symptoms of SZ are often divided into two clusters: positive symptoms (hallucinations, delusions, disorganized speech and behavior) and negative symptoms (blunted affect, social withdrawal, loss of volition and alogia) [1]. In addition to the positive and negative syndromes, cognitive impairment is an essential feature of SZ that seems to be directly associated with functional disability in work, poor social functioning and difficulties in daily life activities [2,3]. When compared with healthy individuals, people diagnosed with SZ display deficits in several domains

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of cognition, such as episodic memory, processing speed, attention, inhibition, language and executive functions [4]. Notwithstanding recent advances, causes underlying SZ as well as its different symptomatic manifestations remain largely unknown. Considering the lack of reliable biomarkers, diagnosis, assessment and prognosis of SZ are based on symptomatology alone, which hinders the implementation of personalized treatments [5].

In the last decade, immunological alterations in individuals affected by major mental disorders, such as SZ, have received great attention, as they can aid to further elucidate related pathophysiological pathways [6–9]. One of the most promising approaches to evaluate immune changes in SZ is the measurement of cytokines in serum or plasma [10]. Cytokines are molecular mediators of the immune system. They are involved in a complex and redundant network that communicates immune and non immune cells [11].

Interleukin 2 (IL-2) is a cytokine of 15.5kd discovered more than 30 years ago. First described as a T cell growth factor, IL-2 is mainly produced by T cells after interaction of MHC/antigen/T-cell receptor (TCR) and co-stimulatory molecules. IL-2 acts as an autocrine and paracrine third signal, inducing clonal expansion and effector T and B-cells development. It also plays an important role on innate immunity, leading to activation and proliferation of natural killer (NK) cells [12]. Several studies have pointed to a potential role of IL-2 in SZ, with most studies reporting altered peripheral levels of IL-2 when compared with healthy controls [13,14], as well as a reduction in production of IL-2 by leukocytes after mitogen stimulation [15–18]. Nevertheless, association between IL-2 and different groups of symptoms of SZ, namely positive, negative and cognitive, has not been explored.

The objective of this study was to investigate a possible correlation of peripheral IL-2 levels with symptomatology and cognitive performance of patients with SZ. In addition, we compared serum levels of this cytokine between patients with SZ and healthy controls. We hypothesized that individuals with SZ would exhibit decreased levels of IL-2 when compared to healthy controls. Moreover, we expected to demonstrate that decreased levels of IL-2 are associated with worse psychopathological features and lower cognitive performance.

2. Material and methods

The study protocol was approved by the Ethics Committee of the Universidade Federal de São Paulo (UNIFESP), in São Paulo, Brazil, and all individuals provided their written informed consent before inclusion in the study. This study is part of a large protocol entitled "Prevention of Schizophrenia and Bipolar Disorder from Neuroscience to Community: a Multistaging, Multimodal and Translational Platform to Investigation and Intervention" developed by the Department of Psychiatry of Universidade Federal de São Paulo (UNIFESP). The sample investigated here had already been evaluated regarding other biomarkers and outcomes [8,19].

2.1. Study population

Twenty-nine chronically medicated outpatients were compared with twenty-six healthy controls. The diagnosis of SZ was established according to the Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (DSM-IV), using the Structured Clinical Interview for DSM-IV (SCID). The patients were also evaluated with the Positive and Negative Syndrome Scale (PANSS) for severity of psychotic symptoms, the Calgary Depression Scale for Schizophrenia (CDSS) for severity of depressive symptoms, the Clinical Global Impression (CGI) and the Global Assessment of Functioning (GAF) scales for functioning assessment. All patients were under treatment with atypical antipsychotics with stable doses for at least 6 weeks prior to the inclusion. Patients were using Olanzapine ($n = 13$), Clozapine ($n = 10$), Risperidone/Paliperidone ($n = 4$) and Quetiapine ($n = 2$). The healthy volunteers group was matched for age, ethnicity and educational level and had no current or lifetime psychiatric history according SCID, as well as no first-degree relative with history of psychiatric disorders.

Acute and chronic general medical conditions traditionally associated with a significant inflammatory response such as flu-like syndrome, HIV infection, allergies, pregnancy or postpartum period, rheumatologic or immunological conditions were considered exclusion criteria for both groups. Individuals using medications with immunomodulatory effects, such as non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants, were also excluded.

2.2. Collection of blood samples and procedures to biomarker measurement

All the participants had blood collected into EDTA tubes by venipuncture between 9:00 and 10:00 AM. The samples were immediately processed and plasma stored at −80 °C. Plasma concentrations of IL-2 were evaluated using a BD cytometric bead array (BD Biosciences, USA).

2.3. Neuropsychological assessment

A computerized neuropsychological battery assessed the following domains of cognition (for a detailed description of the tests, see previous publication [20]):

2.3.1. Verbal learning: the Hopkins Verbal Learning Test [21];

2.3.2. Verbal fluency: phonemic and semantic verbal fluency;

2.3.3. Working memory: Visual Working Memory [22,23], Keep Track Task [24], Letter Memory Task [25] and the forward digit span of the Wechsler Adult Intelligence Scale [26];

2.3.4. Set shifting (Plus–minus task [27], Number–letter task [28]);

2.3.5. Executive function: Tower of London [29] and Shortened version of the Wisconsin Card Sorting Test [30]);

2.3.6. Inhibition: Computerized Stroop Task [31], Semantic Generation Task [32,33]).

2.3.7. Intelligence: the non-verbal intelligence task (R-1) was used to assess intelligence. This scale allows measures of intelligence in low literacy populations, such as Brazilian schizophrenics. This test highly correlates with the Raven's Colored Progressive Matrices Test ($r = 0.76$, $p = 0.001$) [34].

2.4. Statistical analysis

Statistical analyses were performed using SPSS 20.0 for Mac. All the distributions of quantitative data were tested for normality using the Kolmogorov–Smirnov test. Comparisons of clinical and demographic variables between SZ group and healthy volunteers group were performed using X^2, Student t-test and Mann–Whitney U-test when appropriate. Differences in IL-2 levels between the two groups were evaluated using the Mann–Whitney U-test. Correlation between cognitive tests and biomarker levels was tested using the Spearman correlation coefficient. Statistical significance was set in alpha ≤ 0.05.

3. Results

Clinical and demographic characteristics of the sample are described in Table 1. Comparison of levels of IL-2 demonstrated that patients with SZ had lower levels of this mediator (median = 0.98 pg/mL; mean (M) = 0.699 pg/mL; standard error of the mean (SE) = 0.105) than healthy control (HC) individuals (median = 1.31 pg/mL; M = 1.146 pg/mL; SE = 0.120) (Mann–Whitney test $U = 177.5$, $P < 0.001$).

In order to clarify a possible influence of the difference in marital status on IL-2 levels, we compared IL-2 levels between married (M = 1.084 pg/mL; SE = 0.157) and non-married ($M = 1.110$ pg/mL; SE = 0.220) controls and found no significant differences (Mann–Whitney test $U = 62$, $P = 0.602$). In addition, we compared IL-2 levels between male ($M = 1.212$ pg/mL; SE = 0.180) and female ($M = 1.089$ pg/mL; SE = 0.166) controls and also found no significant differences (Mann–Whitney test $U = 75$, $P = 0.667$). The low number of married and