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Association of biomarkers and depressive symptoms in schizophrenia

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ABSTRACT

Emergence of depressive symptoms in schizophrenia results in a deteriorating course and poor prognosis. Schizophrenia and depressive disorder are both associated with low levels of brain-derived neurotrophic factor (BDNF) and with a longstanding low grade inflammatory state. The objective of this study is to analyze the relationship between these serum biomarkers and depressive and psychotic symptoms in schizophrenic patients. Thirty-nine individuals diagnosed with schizophrenia or schizoaffective disorder by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), assessed by Structured Clinical Interview for DSM-IV (SCID), were included. Interviews were conducted with The Positive and Negative Syndrome Scale (PANSS) and The Calgary Depression Scale for Schizophrenia (CDSS). Blood samples were collected for determination of BDNF, IL-1beta, IL-6, IL-8, IL-10, IL-12 and TNF-alpha measurements. Positive correlations between BDNF and CDSS and between IL-1beta and severity in PANSS scores were found. BDNF levels were not correlated with any cytokine or with PANSS scores. The results of this study suggest that depressive and psychotic symptoms may be associated with different profiles of biomarkers in the association between schizophrenia and depression.

1. Introduction

Depression in schizophrenia has been largely recognized as a particularly dangerous combination since the nineteenth century by authors such as Kraepelin and Bleuler [20,3]. Depressive states can occur in all stages of the disease, being classically described in prodromal and psychotic phases [4]. Even in stable periods, the rates of depression in psychotic patients are higher than in a healthy population [35]. Depressive symptoms are present in 25% of patients with schizophrenia and are related to long periods of hospitalization, poor response to medications, bad social and cognitive performance, and high rates of relapse [29]. In addition, depression is recognized as an important predictor of suicide in schizophrenia, being noted in approximately 60% of these cases [28].

Considering its relevance, concomitance of depressive symptoms in psychosis is surprisingly understudied, including its clinical and neurobiological aspects. One of the possible strategies to understand this association is to examine peripheral biomarkers that have been recognized as regulators of critical processes in neuronal survival and neuroplasticity. Among those are neurotrophins, such as the brain-derived neurotrophic factor (BDNF) and inflammatory cytokines, such as IL-1beta, IL-6, IL-8, IL-10, IL-12 and TNF-alpha.

BDNF is a polypeptide with neurotrophic properties which include neuronal growth, differentiation, survival, and repair. It is also implicated to plasticity of the dopaminergic, serotonergic, cholinergic, and glutamatergic systems [2,23]. Although the action of BDNF is exerted in the brain, it can be detected in the peripheral blood [18]. Convergent findings indicate that BDNF has its production decreased during depressive episodes [15] and tends to be normalized with efficient treatments including antidepressants, mood stabilizers, and eletroconvulsive therapy [1,25]. In schizophrenia, *post mortem* studies have shown reductions of BDNF mRNA and protein in prefrontal cortex [33,19] and both increase or decrease in the hippocampus [8]. Regarding peripheral levels of BDNF in schizophrenia, a recent review by Green et al. [16] concluded that the levels are significantly reduced in drug-naïve and medicated individuals. Nevertheless, there was a considerable

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Table 1
Clinical and demographic characteristics of the sample and levels of biomarkers.

	Minimum	Maximum	Mean	Std. deviation	Median	Interquartile range
Age (years)	16	68	34.8	12.2	32	–
Age of first episode (years)	14	62	22.7	8.5	22	–
Illness duration (years)	1	36	11.8	9.7	11	–
PANSS scores	32	115	64.5	17.4	67	–
CDSS scores	0	17	3.7	4.5	2	–
BDNF levels (pg/μg protein)	0.56	1.07	0.31	0.29	0.13	0.42
IL-8	0	152.87	24.44	25.81	16.36	14.77
IL-1beta	0	10.38	2.48	2.87	1.26	3.94
IL-6	0	14.02	3.22	4.33	1.2	4.78
IL-10	0	10.67	2.84	2.23	2.72	3
TNF-alpha	0	41.88	4.64	8.56	2.46	3.99
IL-12	0	45.21	9.04	8.72	7.53	9.16

BDNF and cytokine concentrations were expressed in pg/μg protein.

heterogeneity among studies, especially regarding differences in subgroups, which were not controlled.

In addition to BDNF, inflammatory mediators such as cytokines have also been recognized as regulators of cell survival and cell resilience [7]. Some cytokines, as IL-1beta, IL-6, and TGF-beta are understood as state-related markers, as they were increased during acute phase of psychosis and normalized with treatment [24]. In contrast, IL-12, interferon-gamma (INF-gamma), tumor necrosis factor-alpha (TNF-alpha) and soluble receptors for Interleukin-2 (IL-2) are trait markers [24]. Data available still have significant heterogeneity across studies and few of them explored particular clinical aspects (e.g. comorbidities, symptoms profile, severity of clinical course, subtypes, and refractoriness).

To our knowledge, this is the first study to investigate the association of BDNF and inflammatory cytokines in patients from the schizophrenia spectrum with depressive symptoms. Since both schizophrenia and depression seems to reduce BDNF, we had supposed that this association could be more damaging, with even lower levels of BDNF. Therefore, the objective of this study is to evaluate a possible association between BDNF and inflammatory cytokines with the severity of depressive and psychotic symptoms in individuals with schizophrenia.

2. Methods

Thirty-nine patients with schizophrenia (33 males; 6 females) were selected from the outpatient unit of Schizophrenia Program (PROESQ) at Universidade Federal de São Paulo (UNIFESP), Brazil. All the patients were under psychopharmacological treatment, including 13 individuals with clozapine. All individuals who agreed to participate in the study underwent an initial clinical evaluation that involves the application of the Structured Clinical Interview for DSM-IV axis 1 (SCID). Individuals who fulfilled criteria for schizophrenia according to DSM-IV were invited to be evaluated by an additional assessment with the following instruments: the Positive and Negative Syndrome Scale (PANSS) to assess positive and negative symptoms and general psychopathology of schizophrenia, and the Calgary Depression Scale for Schizophrenia (CDSS) to assess current depressive symptoms. Both instruments were previously translated and validated for the Brazilian social and cultural context [32,5].

This study protocol was approved by the Ethics Committee of the UNIFESP, Brazil. All subjects were advised about the procedure and provided written informed consent prior to participation in the study.

Acute and chronic general medical conditions associated with imbalances in inflammatory response such as infections, HIV, allergies, rheumatologic, or immunological conditions as well as immunomodulatory treatments were considered an exclusion criterion.

A blood sample of 5 mL was withdrawn of all the subjects. Blood was centrifugated and the plasma was stored at −80 °C until the measurement of biomarkers. BDNF plasma levels were assessed by the sandwich ELISA method according to the manufacturer's instructions (Chemicon, USA). Plasma concentrations of IL-1beta, IL-6, IL-8, IL-10, IL-12 and TNF-alpha were evaluated using a panel of cytokines by Luminex (Luminex, USA). This is a highly sensitive immunoassay for the determination of plasma cytokine. The detecting limits were 7.8 pg/mL for BDNF, 3.6 pg/mL for IL-8, 7.2 pg/mL for IL-1beta, 2.5 pg/mL for IL-6, 3.3 pg/mL for IL-10, 3.7 pg/mL for TNF-alpha and 1.9 pg/mL for IL-12. All samples were analyzed in duplicate.

Statistical analyses were performed using SPSS v. 17.0. All the distribution of quantitative data was tested for normality using Kolmogorov–Smirnov. As BDNF and cytokine levels present a non normal distribution, non-parametric tests were used. Statistical significance was set in alpha ≤ 0.05.

3. Results

Clinical and demographic data from all subjects are displayed in Table 1. Mean scores in PANSS and in CDSS were 64.14 and 3.57, respectively. Eight individuals had a CDSS score higher than 7, which is an acceptable cut-off score to predict depression [5]. A significant correlation between the PANSS total score and CDSS was found (correlation coefficient = 0.427; $p \leq 0.001$). BDNF levels presented a positive correlation with CDSS (correlation coefficient = 0.464; $p = 0.004$). Table 2 shows cytokine and BDNF mean levels in patients with CDSS score 7 or less and higher than 7. BDNF levels were not correlated with any cytokine or PANSS scores ($p = 0.883$). IL-1beta levels presented a positive correlation with total PANSS score (correlation coefficient = 0.374; $p = 0.023$), but were not correlated with CDSS score ($p = 0.683$). All cytokines and BDNF levels are displayed in Table 3, according PANSS scores (higher or lower than 65). All other cytokines levels were not correlated with CDSS scores.

Table 2
Cytokines and BDNF levels according CDSS scores.

	CDSS ≤ 7 Mean (SD)	CDSS > 7 Mean (SD)	*p*-Value
BDNF	0.28 (0.26)	0.42 (0.40)	0.223
IL-8	25.05 (28.46)	22.07 (11.78)	0.876
IL-1beta	2.36 (2.77)	2.95 (3.41)	0.263
IL-6	3.40 (4.25)	2.50 (4.85)	0.516
IL-10	3.05 (2.37)	2.06 (1.41)	0.321
TNF-alpha	4.89 (9.18)	3.66 (5.96)	0.901
IL-12	8.97 (9.15)	9.31 (7.38)	0.520

BDNF and cytokine concentrations were expressed in pg/μg protein.

Table 3
Cytokines and BDNF levels according PANSS scores.

	PANSS < 65 Mean (SD)	PANSS ≥ 65 Mean (SD)	*p*-Value
BDNF	0.26 (0.22)	0.34 (0.35)	0.632
IL-8	25.93 (33.33)	23.16 (17.84)	0.642
IL-1beta	2.04 (3.31)	2.86 (2.45)	0.097
IL-6	2.33 (3.81)	3.98 (4.68)	0.170
IL-10	2.95 (2.83)	2.75 (1.63)	0.725
TNF-alpha	6.26 (11.80)	3.25 (4.06)	0.411
IL-12	10.55 (11.20)	7.74 (5.84)	0.612

BDNF and cytokine concentrations were expressed in pg/μg protein.

4. Discussion

As far as we know, this is the first study evaluating BDNF and inflammatory cytokines in schizophrenic patients with depressive symptoms. The main result obtained was a positive correlation of BDNF and CDSS scores, indicating that subjects with higher depressive symptoms scores also have higher levels of BDNF. In addition, IL-1beta was positively correlated with total PANSS scores, indicating that the most severely psychotic have higher levels of this cytokine.

Surprisingly, the individuals with more severe depressive symptoms had higher levels of BDNF. These results are in line with previous studies that found that Brief Psychiatry Rating Scale (BPRS) scores have been positively correlated to BDNF serum levels [13]. In addition, CDSS scores would represent a more symptomatic group. The positive correlation between BDNF and CDSS could be a result of a compensatory reaction to the damage produced by other mediators largely present in illnesses activity, such as inflammatory cytokines [9,22] and oxidative stress [11,13,14,21]. Another possibility is that the chronic phase of the disorder may be a period of reduction of the severity of the metabolic aggression to the brain [13,12,31,27]. In fact, even considering the results of meta-analysis of Green and collaborators, increased BDNF serum levels had been found previously in patients with schizophrenia with long illness duration [12] as well as with severity and high medication daily dose [14,12,27]. Further studies should be addressed to elucidate if BDNF is a part of a compensatory mechanism or a state marker itself of chronically medicated patients with schizophrenia.

Our findings with cytokines are partially in line with current literature. Smith and Maes [30] proposed the macrophage-T-lymphocyte theory, which states that IL-1, IL-2, tumor necrosis factor, interferon-alpha, and IFN-gamma produced by chronically activated macrophages and T-lymphocytes, are the fundamental mediators of schizophrenia. Although two previous studies found a positive correlation between the IL-6 levels and total psychopathology scores [10,26], our data suggest this relationship with IL-1beta.

These preliminary data should be interpreted considering some limitations. A small sample size does not permit subgroup analysis regarding use of different medications (e.g. antidepressants and clozapine) that might impact BDNF production. In addition, depressive symptoms may be more common in schizophrenic patients treated with typical antipsychotics as a consequence of high striatal D_2 receptor occupancy [17,6]. Moreover, the absence of a healthy comparison group prevented inferences regarding possible differences between individuals with schizophrenia and healthy subjects. Finally, the small sample size of the patients with depression (eight individuals) also limited additional subgroup analyses.

5. Conclusion

This study opens a venue for investigation on the role of neurotrophins in neurotoxicity pathway in the course of schizophrenia. Present findings in literature lead us to the hypothesis that BDNF and cytokines are sensible to different states of the disease [24]. Considering depression as a distinct dimension of schizophrenia [34], perhaps these biomarkers have a specific role in those cases. However, new studies should be done to clarify the role of depression in peripheral biomarkers in schizophrenia.

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