ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
June 2019; 18(3):262-268.

Alteration of Serum Levels of Cytokines in Schizophrenic Patients before and after Treatment with Risperidone

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Received: 10 July 2018; Received in revised form: 16 October 2018; Accepted: 23 October 2018

ABSTRACT

A growing body of evidence suggests the existence of abnormalities in the immune system of schizophrenic patients. The current study examined serum levels of interleukin (IL) -1β, IL-6, IL-2,interferon(IFN) -γ, and tumor necrosis factor(TNF)-α in schizophrenic patients before and after treatment with risperidone and correlated levels of these cytokines with symptomatology.

The study group consisted of 24 schizophrenic patients as defined by Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria and 24 healthy controls. Serum cytokine levels were examined using enzyme-linked immunosorbent assay (ELISA). Schizophrenic symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS) questionnaire.

The serum levels of TNF-α, IL-1β and IL-6 were significantly higher in participants before treatment compared with the healthy controls and after treatment (p<0.001). IFN-γ and IL-2 levels were significantly lower in participants after treatment compared with before treatment and the healthy controls (p<0.001). Except for IL-6 (p<0.05), there was no significant difference in the levels of TNF-α and IL-1β between the patients receiving treatment and the healthy subjects. Moreover, there was no significant difference in levels of IFN-γ and IL-2 between patients before treatment and the healthy subjects.

There were no significant correlations between the concentration of cytokines studied and the PANSS. Positive intercorrelations between the production of IFN-γ and IL-2 were detected for sums of all groups(r=0.33, p=0.005). Clinical improvement of treated patients was associated with a reduction in the studied cytokines. It seems that changes in the cytokines level may play a significant role in the psychopathology of these patients.

Keywords: Antipsychotics; Cytokines; Schizophrenia

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INTRODUCTION

Schizophrenia is a disabling psychiatric disorder. The etiopathology of schizophrenia remains unknown.

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cytokines in the serum, plasma, and cerebrospinal fluid (CSF) of schizophrenic patients have been extensively studied.[1] The main evidences support the presence of abnormality in levels of pro-inflammatory and T helper 1 cytokines in the serum of drug-naïve first-episode schizophrenia patients.[2]Peripheral cytokines can partially penetrate the blood brain barrier and bind to receptors on neurons and glial cells in the brain,[3] Cytokines contribute to dopaminergic, noradrenergic, and serotonergic neurotransmissions,[4]suggesting that cytokines directly influence neuronal function. Previous studies have reported antipsychotic medications have a variety of effects on cytokine levels.[5] However, the effects of antipsychotics may not be direct and the effect is a secondary phenomenon. Antipsychotic drugs reduce levels of Tumor Necrosis Factor (TNF)-α and interleukin (IL)-6 in the animal model of neuroinflammation.[6] A number of studies have shown that, decreased levels of IL-1β and interferon (IFN)-γ after antipsychotic treatment in schizophrenic patients.[5] Maes et al showed that typical antipsychotics decreased plasma IL-6 and atypical antipsychotics increased TNF-α and IL-6.[7,8] Risperidone seems to induce higher IL-6 and TNF-α plasma concentration.[9] Whereas, Kato et al. found that risperidone reduce IL-1β, IL-6, and TNF-α.[10] Overall, reported data is variable and even contradictory. Therefore, the aim of the current study was to analyze the changes in the serum levels of proinflammatory (IL-6, TNF-α, and IL-1β) and Th1 (IL-2, IFN-γ) cytokines in schizophrenic patients before treatment (drug-naive patients) and 3 months after treatment and compare them with those of healthy controls. Also, an attempt was made to determine potential correlations of cytokine levels and cytokine ratios with symptomatology (positive, negative, and general) in schizophrenia.

MATERIALS AND METHODS

Study Design

This case-control study was conducted at the Roozbeh Hospital, affiliated with Tehran University of Medical Sciences (Tehran, Iran) between April 2016 and February 2018. It was approved by the Ethics Committee of Tarbiat Modares University (IR.TMU.REC.1394.159).

Subjects

Thirty patients who a group of psychiatrists confirmed the schizophrenia diagnoses using the Diagnostic and Statistical Manual of Mental Disorders4th edition (DSM-IV) were selected for this study. In the second sampling stage, six patients were excluded for switch to a different antipsychotic (3 subjects), noncompliance therapy (1 subjects) lack of enough serum sample (1 subject), and Cancellation of participation in the study (1 subjects).The final sample consisted of 24 (17 males and 7 females) patients who were diagnosed for the first time or individuals whose disease relapsed due to a lack of compliance with therapy (assigned as the before treatment group). Patients were treated with risperidone (generic name: Risperidone, trade name: Risperdal, manufacturer: SOBHAN DAROO CO) for three months based on each patient's condition (assigned as the after treatment group).The mean dose of risperidone used during the study was 5 mg/day. And compared with a group of 24 age- and gender-matched healthy volunteers (assigned as the control group) with the following inclusion criteria: (i) no family history of mental disorder; (ii) no antidepressant, antipsychotic, or mood stabilizing drug use within the last one month; and (iii) normal C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) value. All participants signed an informed consent form prior to any involvement in the study. Furthermore, the positive and negative symptoms of the patients (before and after treatment) were assessed using a Positive and Negative Syndrome Scale (PANSS). The exclusion criteria for patient and control groups were: (i) use of any non-psychotropic drugs interfering with immune function; (ii) acute infections or allergic/ inflammatory responses within at least one month prior to blood sampling; (iii) chronic medical illness known to be accompanied by changes in immune functions such as autoimmune disorders, inflammatory bowel disease, or acquired immunodeficiency syndrome; and (iv) alcohol or drug abuse.

Serum Cytokine Measurements

Before treatment, venous blood samples were collected from patients in tubes containing no anticoagulant under sterile conditions. The samples were left at room temperature for 1 h to allow clotting, and then centrifuged at 1000 g for 15 min to obtain serum. The serum was quickly frozen at −70°C and stored until further assessment. Sampling was repeated three months after the start of treatment in the patient group. A sample of 5-7 ml of venous blood was also

taken from each individual in the control group, and the serum was separated in the same conditions as described above. Serum levels of TNF-α, IL-1 β, IL-6, IFN-γ, and IL-2 were measured using commercial Sandwich Enzyme-Linked Immunosorbent Assay (ELISA, R&D Systems Inc., Minneapolis, USA), in accordance with the manufacturer's instructions. The absorbance (OD) measurement was carried out using a Multiskan MS Microplate Reader (Labsystems, Vantaa, Finland) at a 490 nm wavelength. The values obtained were correlated linearly with standard concentrations, and a calibration curve was formed for each measurement. All samples were assayed in duplicate and expressed as pg/mL. Cytokine assays of all patient samples were performed simultaneously with the matched samples of the control group.

Statistical Analysis

The results are described as the mean, standard deviation (SD), and standard error (SE). The normal distribution of data was tested using the Shapiro–Wilk and the Kolmogorov–Smirnov tests; assuming the normality of data was accepted. One-way analysis was used for significant differences between means of serum cytokine levels among the three study groups, and thereafter, pairwise T- tests were performed for post hoc comparisons. The psychopathology on the PANSS was compared between the patient groups by one-way ANOVA and correlated with TNF-α, IL-1 β, IL-6, IFN-γ, and IL-2 levels within the patient groups by calculating Pearson correlation coefficients. Differences at a level of $p<0.05$ were considered to be significant.

RESULTS

Demographic data

Table 1 shows the demographic characteristics of the patient and control group participants. The results showed that in the patient group, mean age of onset was 34.12±5.81 years. The sensitivity levels of IL-2, IFN-γ, IL-6, TNF-α, and IL-1β were 7 Pg/mL, 8 Pg/mL, 0.7 Pg/mL, 5.5 Pg/mL and 1.0 pg/mL, respectively, indicating that age of onset had no significant correlation with TNF-α, IL-1β, IL-6, IFN-γ, or IL-2 serum levels in the patient group.

Serum Cytokines Levels

Proinflammatory Cytokines

Before and after treatment cytokine concentrations were evaluated using the T-tests statistical analysis, indicating that serum levels of three proinflammatory cytokines (IL-1β=35.39±18.37 pg/ml, IL-6=95.22±70.52 pg/ml, and TNF-α=118.70±84.93 pg/mL) were significantly higher in patients before treatment than after treatment (IL-1β=12.48±6.96 pg/mL, IL-6=39.22±9.95 pg/ml, and TNF-α=24.52±16.70 pg/mL, $p=0.008$, $p=0.001$, $p\leq0.001$ respectively) and control group (IL-1β=11.96±3.54 pg/mL, IL-6=15.30±5.69 pg/mL, and TNF-α=15.96±9.61 pg/mL, $p=0.008$, $p\leq0.001$, $p\leq0.001$respectively). The findings also showed that there were no significant differences in terms of serum levels of IL-1β and TNF-α between the after treatment and control groups. Serum levels of IL-6 were significantly increased in after treatment group comparing with the control group ($p<0.02$) (Figure 1). There was no significant relation between the scores of psychopathology (total, positive, and negative scores) and the serum concentrations of TNF-α, IL-1 β, and IL-6 before or after treatment, also no significant intercorrelations was seen between the production of TNF-α, IL-1 β, and IL-6.

Th1- Cytokines

Serum levels of both Th1-cytokines IFN-γ (18.65±6.96 pg/ml) and IL-2 (30.70±10.65 pg/ml) were significantly lower in the after treatment group than in the before treatment group(IFN-γ = 24.04±7.31 pg/mLand IL-2=40.91±14.94 pg/mL(p= 0.009 and $p=0.005$ respectively) or the healthy controls (IFN-γ=26.87±8.13 pg/mL and IL-2=44.09±15.04 pg/mL) ($p=0.006$ and $p=0.003$ respectively).

No significant differences were observed between the before treatment group and the healthy controls in serum levels of IL-2 and IFN-γ (Figure 2).There was no significant relation between the scores of psychopathology (total, positive, and negative scores) and the serum concentrations of IFN-γ, and IL-2 before or after treatment. Positive intercorrelations between the production of IFN-γ and IL-2 were detected for sums of the patients (before and after treatment) and control groups. (r=0.33, $p=0.005$) (Figure 3). It means that these cytokines increase or decrease in the same direction at most of the patients and control.

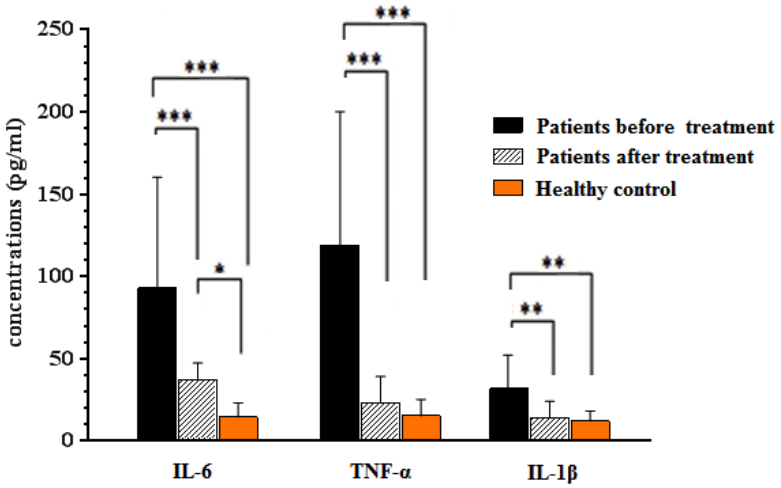

Figure 1. Serum concentrations of IL-1β, IL-6, and TNF-α in schizophrenia patients after treatment with risperidone (n=24) compared with before treatment (n=24) and healthy controls (n=24). Serum levels of IL-1β(35.39±18.37 pg/mL), IL-6(95.22±70.52 pg/mL), and TNF-α(118.70±84.93 pg/mL) in patients before treatment with Risperidone were significantly higher than after treatment with risperidone (IL-1β = 12.48±6.96 pg/mL, IL-6 = 39.22±9.95pg/mL, and TNF-α =24.52±16.70 pg/mL) (p=0.008, *p*=0.001, *p*≤0.001 respectively) and control group(IL-1β=11.96±3.54 pg/mL, IL-6=15.30±5.69pg/mL, and TNF-α =15.96±9.61 pg/mL) (p=0.008, *p*≤0.001, *p*≤0.001 respectively). The findings also showed that there were no significant differences in terms of serum levels of IL-1β and TNF-α between the after treatment with risperidone and control groups. In the after treatment with Risperidone group, serum level of IL-6 was significantly higher than control group (*p*=0.02). Data are expressed as the mean±SEM of triplicate wells and are representative of three independent experiments. **p*≤0.05, ***p*≤0.01, ****p*≤0.001.P value was calculated by pairwise T- tests.IL-1β: Interleukin-1β, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-α

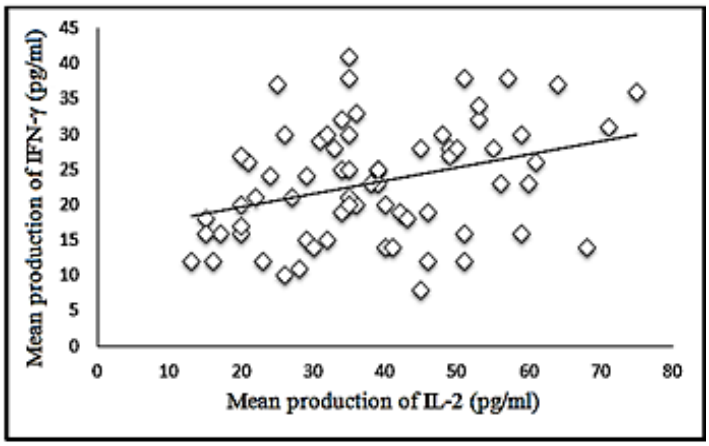

Figure 3. Scatter plot of mean production of IFN-γ and IL-2 in the patients (before and after treatment with risperidone) and control groups (Pearson test). The graph shows a positive relationship between the production rates of the IFN-γ (y axis) and IL-2 (x-axis) for patients and control group (r=0.33, *p*=0.005).
IL-2: Interleukin-2, IFN-γ: interferon-γ

Table 1. Demographic characteristics and PANSS symptoms scale of the schizophrenia patients before and after treatment with risperidone and healthy controls

Parameter	patient		healthy controls (n=24)	*p*-Value
	Before treatment (n=24)	after treatment (n=24)		
Sex (M/F)	24(17/7)	24(17/7)	24(17/7)	
Age* (years, mean±SD)	34.12±5.81	34.12±5.81	33.82±5.23	0.531
Positive symptoms (mean±SD)	22.73±4.61	15.48±5.32		0.000
Negative symptoms (mean±SD)	19.51±4.12	14.61±5.09		0.002
General psychopathology (mean±SD)	42.78±6.58	30.65±5.47		0.000
PANSS total score	85.02±15.31	60.74±15.88		0.000

* The descriptive statistical results were expressed as a mean±standard deviation. Significant *p* value calculated using Independent Samples T-test and statistical significance level was set at $p<0.05$.M/F: male/female. PANSS :Positive and Negative Syndrome Scale.

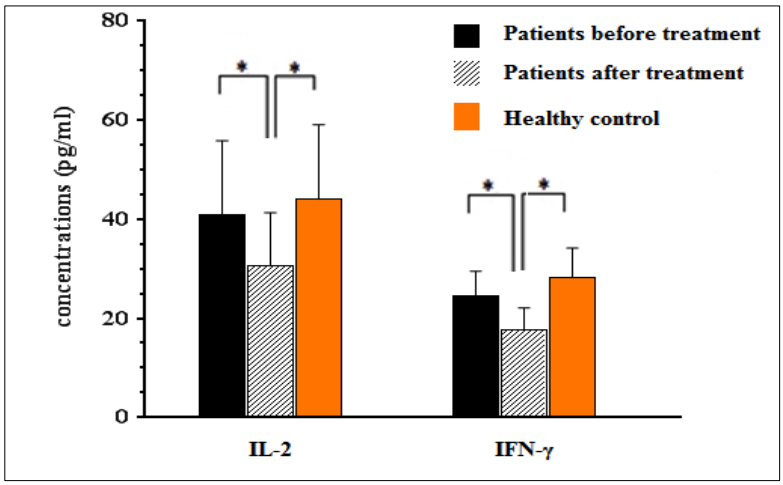

Figure 2. Serum concentrations of IL-2 and IFN-γ in schizophrenia patients after treatment with Risperidone (n=24) compared with before treatment (n=24) and healthy control (n=24). Serum levels of IFN-γ (18.65±6.96 pg/mL) and IL-2 (30.70±10.65 pg/mL) after treatment were found to be significantly lower than those before treatment (IFN-γ=24.04±7.31 pg/mL, IL-2 = 40.91±14.94 pg/mL) (p=0.009 and p=0.005 respectively) and healthy controls (IFN-γ=26.87±8.13 pg/mL, IL-2 = 44.09±15.04 pg/mL) (p=0.006 and p=0.003 respectively). No significant differences were observed between the before treatment group and the healthy controls in serum levels of IL-2 and IFN-γ.Data are expressed as the mean±SEM of triplicate wells and are representative of three independent experiments. *$p\leq0.01$, **$p\leq0.001$.p value was calculated by pairwise T- tests.

DISCUSSION

The results of the current study showed that the baseline levels of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) were significantly higher in drug-naïve patients when compared to healthy controls, but IL-1β and TNF-α were decreased after three months of risperidone treatment, whereas T helper 1 cytokines

(IL-2 and IFN-γ) levels reduced. Although risperidone had an effect on IL-6 serum levels, but IL-6 serum levels was still significantly higher in patients after treatment than in the healthy control group. These results are in agreement with most studies that have found elevated levels of IL-1β, TNF-α and IL-6 in schizophrenia will reduce significantly after risperidone treatment.[11,12] Song and et al. found increased levels of IL-1β, IL-6, and TNF-α in patients before treatment with risperidone compared to controls.[13] These data suggest that schizophrenic patients have activated macrophages and treatment with risperidone helps restore normal macrophage function and cytokine production. It has been shown that schizophrenia is associated with several infections in early childhood,[14] which may sensitize the immune system so that, in later stages of life, any stimulation of the immune system may cause a boosted release of some cytokines, leading to neurotransmitter disturbances.[15] Cytokines in peripheral blood access the CNS through numerous hormonal pathways acting in parallel.[16]suggested a systemic cause for elevated levels of IL-6 and TNF-α, contributing to psychopathological symptoms in early-onset schizophrenia.[17]Our results showed that patients after treatment had lower peripheral levels of IL-2 and IFN-γ compared with the before treatment and healthy control groups. The results of this study are in agreement with previous studies.[18]Carlo L. Cazzullo and et al show that use of risperidone was associated with decreased IFN-γ production by PBMC in culture medium.[19]In a meta-analysis study, 23 studies were included showing that antipsychotics may have effect on cytokine levels.[5] The current results also showed that peripheral levels of IL-2 and IFN-γ were decreased in patients before treatment compared to the healthy controls, but on the whole, not significant. IL-2 and IFN-γ have immunostimulatory and immunosuppressive functions and suppress autoimmune diseases.[20] Reductions in IL-2 in some autoimmune diseases have been reported.[21] Schizophrenia patients experience elevated morbidity from autoimmune diseases.[22] Decreased IFN-γ has been associated with acute exacerbation of schizophrenia.[23] There is no consensus on cytokine changes in schizophrenia patients, and it has not yet been conclusively proven that cytokine alterations are an etiological factor in schizophrenia. The lack of consensus may be due to different study methods, differences in conditions (time and fasting), differences in the tested sample (serum or plasma), sampling in different stages of the disease (acute or chronic), or differences in the subtype of schizophrenia patient.[11] Moreover, it may be due to differences in other variables, such as long duration of illness and drug treatment,[24] weight gain, metabolic disorders, obesity,[25] age, gender, smoking, alcohol and drug use, that are potentially involved in the cytokine alterations.[26] Therefore, these factors should be considered in studies. Also, cytokine expression may be influenced by environmental factors and interaction between cytokine genes.[27] The role of genetic polymorphisms in the production of cytokines can be helpful. We found that no significant relation between the scores of psychopathology (total, positive, and negative scores) and the serum concentrations before and after treatment. The results of previous studies on the relationship between serum cytokine levels and psychopathology in schizophrenic patients have been inconsistent.[28,29] There may be variations observed in the level of circulating cytokines as only a secondary phenomenon that can be the manifestation of another systemic problem in patients with schizophrenia. Therefore, further studies are needed. The current study had some limitations. Firstly, the sample size was small with a gender imbalance. Secondly, since altered levels of cytokines in patients may be related to the differential body mass index (BMI), BMI should be considered as variable in this study to avoid false results. In summary, the current results demonstrated changes in the levels of cytokines in schizophrenia patients and the possible role of cytokines in the development of schizophrenia. The results also showed the possible effects of antipsychotics on cytokines. More research is needed to be able to use these cytokines as biomarkers of schizophrenia.

ACKNOWLEDGEMENTS

We thank all the medical staff of Roozbeh Hospital for their cooperation.

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