DOI: 10.5455/bcp.20110418011851

Serum IL–1β, IL–2, IL–6, and IL–8 Levels in Schizophrenia Subtypes

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ÖZET:

Şizofreni alt tiplerinde serum IL-1β, IL-2, IL-6 ve IL-8 düzeyleri

Amaç: Sitokinler şizofrenide immünolojik çalışmalarda önemli bir konu olarak değerlendirilmektedir. Bu klinik çalışmada şizofreni alt tipleri ve kontrol grubu arasında IL-1β, IL-2, IL-6 ve IL-8 seviyelerini karşılaştırmak amaçlanmıştır.

Metod: DSM- IV'e göre şizofreni tanısı konulan 61 hasta ve 25 sağlıklı kontrol çalışmaya alındı. Hastalara sosyodemografik ve klinik bilgilendirme formu uygulandı. Hastalardan ve kontrol grubundan venöz kan örnekleri sabah 8.00-9.00 arasında alındı, serum IL-1β, IL-2, IL-6 ve IL-8 seviyeleri ELISA yöntemi ile değerlendirildi.

Bulgular: Serum IL-1β seviyeleri, paranoid şizofrenili hastalarda dezorganize alt tip ve kontrol grubuna göre istatistiksel olarak daha yüksekti ($p<0.05$). IL-2 seviyeleri bakımından rezidüel, paranoid, dezorganize ve farklılaşmamış alt tip ile kontrol grubu arasında istatistiksel olarak anlamlı fark gözlendi ($p<0.01$). IL-6 seviyelerine bakıldığında rezidüel şizofreni ve kontrol grubu arasında hafif anlamlı bir fark gözlendi ($p<0.05$). Ancak bu fark, dezorganize ve paranoid alt tiplerle kontrol grubu arasında çok daha anlamlı idi ($p<0.001$). Serum IL-8 seviyeleri, paranoid şizofrenili hastalarda, dezorganize, farklılaşmamış, rezidüel ve kontrol grubuna göre istatistiksel olarak anlamlı şekilde yüksekti ($p<0.001$).

Sonuç: Sonuçlarımız şizofrenide bazı immünolojik değişiklikler olduğunu ve bu durumun şizofreni alt tiplerindeki klinik farklılık ile ilişkili olabileceğini düşündürmektedir.

Anahtar sözcükler: Şizofreni, sitokin, interlökin

Klinik Psikofarmakoloji Bülteni 2011;21(3):193-200

ABSTRACT:

Serum IL–1β, IL–2, IL–6, and IL–8 levels in schizophrenia subtypes

Objective: The cytokines are considered to be an important topic in immunological studies of schizophrenia. In this clinical study IL-1β, IL-2, IL-6, and IL-8 levels were compared among schizophrenia subtypes and a control group.

Method: Sixty-one patients diagnosed with schizophrenia according to the DSM-IV and 25 healthy controls were studied. The clinical and demographic information form was completed for all patients. Morning venous blood samples were collected between 8:00 and 9:00 AM from the patients and the control group. The serum IL-1β, IL-2, IL-6 and IL-8 levels were assessed by the ELISA method.

Results: Serum IL-1β levels were statistically higher than the control group in patients with paranoid schizophrenia and the disorganized subtype ($p<0.05$). According to IL-2 levels there was a significant difference between the residual, paranoid, disorganized, and undifferentiated subtypes and the control group ($p<0.01$). Based on IL-6 levels a mild significant difference was observed between the residual schizophrenia subtype and the control group ($p<0.05$), but this difference was much more significant in the disorganized and paranoid subtypes compared to the control group ($p<0.001$). Serum IL-8 levels in patients with paranoid schizophrenia were statistically significantly higher than the disorganized, undifferentiated or residual subtypes, and the control group ($p<0.001$).

Conclusions: Our results show some immunological changes in schizophrenia and these changes may be related to clinical differences in the sub-types of schizophrenia.

Key words: Schizophrenia, cytokine, interleukin

Bulletin of Clinical Psychopharmacology 2011;21(3):193-200

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Gönderme tarihi / Date of submission: 22 Şubat 2011 / February 22, 2011

Kabul tarihi / Date of acceptance: 25 Ağustos 2011 / August 25, 2011

Bağıntı beyanı:
M.K., Y.B., A.U., O.G., B.U.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
M.K., Y.B., A.U., O.G., B.U.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Malfunction of the immunological system in schizophrenia patients is one of the suggested important factors in the pathogenesis of schizophrenia (1,2). The evidence supporting the immune hypothesis of schizophrenia includes some immunological changes such as increasing levels of immunoglobulin similar to that seen in autoimmune diseases, higher levels of antinuclear antibody compared to control groups, morphologically abnormal lymphocytes and changes of the lymphocyte population (T4/T8, CD5), increase of CD4+ cells, presence of gliosis similar to autoimmune diseases of the brain, lower levels of mutagen response, and different levels of cytokines (3-5).

The cytokines have possible effects on central nerve system (CNS). They decrease survival of serotonergic and dopaminergic (6), hippocampal (7), and cortical neurons

(8). On the other hand, inflammatory cytokines also have been implicated in hypoxic-ischemic injury to the developing brain. (9,10). The cytokines play a major role in the pathophysiology of both infectious and hypoxic-ischemic complications and offer a unifying mechanism of action for these risk factors for schizophrenia.

It is known that the cytokines have critical roles among various immune system cells. IL-1 has a role as an astroglial growth factor in the process of brain development and in the host defense of the CNS and it is also reported that it should be an intrinsic neuromodulator in the various metabolic functions of acute phase reactants (11). IL-2 is released from activated T-cells and has an important influence in activation and proliferation of T and B cells. IL-6 is released from the monocyte-macrophage series and has a role as a mediator at the peripheral acute phase reaction (12). IL-8 is a characteristic member of the chemokine subfamily. It is released from monocytes, macrophages, endothelial cells, and activated T cells and it has a role in cell adhesion and the angiogenesis part of the immune response (13,14).

It is suggested that immunity might be an important etiological factor in schizophrenia (4). Although there are many studies on cytokines in schizophrenia, we have not found any detailed study, which investigates the relationship between the cytokines and schizophrenia subtypes. Therefore, we hypothesized that cytokine levels could change to different degrees in schizophrenia subtypes. Based on these data, we aimed to investigate serum IL-1β, IL-2, IL-6, and IL-8 levels in schizophrenia subtypes.

METHODS

Subjects and Designs

A total of sixty-one out- or in-patients, who applied to the Psychiatry Department of Fırat University Fırat Medical Center and were diagnosed with schizophrenia based on The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (15) criteria, were included in the study. The patients were either drug naive or had not been using any psychotropic drugs for at least one month prior to the study. In addition, based on the criteria for the study, the patient and control groups were matched in terms of age and gender. Twenty-five healthy women (n=10) and men (n=15) served as the control group.

Each patient underwent a detailed diagnostic evaluation by psychiatrists in training (M.K., O.G.) by using The Structured Clinical Interview for DSM-IV (SCID) (16) and they completed a sociodemographic data form. The patients were divided into 4 groups according to the subtypes of schizophrenia: paranoid (n=18), disorganized (n=16), undifferentiated (n=15), and residual schizophrenia (n=12).

Exclusion criteria for the patients included being under age of 18; having a chronic organic disease or an infectious disease at present; using a drug that affects the immune-endocrine system; presence of alcohol or substance abuse and/or dependence; having difficulties during psychiatric evaluation because of socio-cultural level or education or language communication problems. Exclusion criteria for the controls included presence of individual or familial psychiatric disease history, stressful life event, or a medical treatment history within last three months.

After a brief initial interview, if the subjects appeared suitable for the study, they were thoroughly informed about the details of the research. The written informed consent to participate in the study was obtained from the subjects. The Local Ethics Committee in accordance with the Declaration of Helsinki approved the research protocol.

Biochemical Analysis

Venous blood samples were taken from the patients and controls between 8.00–9.00 a.m. to determine interleukin levels. Parameters, IL-2, IL-6, and IL-8 were measured by using a BioSource International Inc. ELISA kit (California USA) and IL-1β was measured by using a MedSystems Diagnostics GmbH ELISA kit (Vienna, Austria). Inter- and intra-assay CVs were 5.1% and 8.56% for IL-1β, 4.7% and 6.9% for IL-2, 5.2% and 9.9% for IL-6, and 3.7% and 4.2% for IL-8.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS). As a nonparametric test, the chi-square test was used to compare nominal values and as parametric tests the One-way ANOVA, Post Hoc Tukey HSD, and Student-t tests were used to compare

numeric values. Two-tailed hypothesis tests were used for statistical analysis. Statistical significance was set at the $p<0.05$ level. The data gained from the study are presented as mean ± standard deviation.

RESULTS

Patients and controls were similar according their genders and ages. Sixty-one patients with schizophrenia (33 men and 28 women) and 25 healthy subjects (15 men and 10 women) as the control group were included in the study ($p>0.05$). Mean age of the patients was 33.2±7.2 years and that of control group was 31.4±6.8 years ($p>0.05$). The initial mean age of onset of the illness was 24.6±5.9 years. The detailed sociodemographic data of the patients is summarized in Table 1.

Table 1: Sociodemographic features of patients and control subjects*

	Control (n=25)	Schizophrenia (n=61)			
		Paranoid (n=18)	Disorganized (n=16)	Undifferentiated (n=15)	Residual (n=12)
Age 31.4±6.8	34.1±5.9	32.4±4.7	33.6±5.0	30.4±6.1	
Gender (M/F)	15/10	11/7	9/7	7/8	6/6
Duration of Disease					
0-5 Year		10	9	8	4
5-10 Year		4	7	6	3
10-20 Year		2	-	1	2
20 years and more		2	-	-	2
Education					
Non-educated	-	1	7	2	1
Primary	2	1	9	5	5
Secondary-High	12	10	-	5	4
University	11	6	-	3	2
Marital Status					
Married	15	10	-	5	5
Single	10	8	16	10	7
Hospitalization Period					
Short		9	-	2	5
Long		9	1	13	7
Number of Psychotic Episodes					
0-1 episode		9	1	2	5
2 and more		9	15	13	7
Smoking					
Smoker	10	14	16	12	8
Non-smoker	15	4	-	3	4

*p>0.05 for each sociodemographic features (Chi-square test)

Serum IL–1β levels in the paranoid, disorganized, undifferentiated, and residual schizophrenia subtypes were 2.665±0.981 pg/mL, 1.792±0.430 pg/mL, 2.551±0.962 pg/mL, and 2.267±0.421 pg/mL respectively. IL–1β level of the control group was determined to be 1.989±0.860 pg/mL. Serum IL–1β levels of the paranoid subtype group were significantly higher compared to the disorganized, control, and undifferentiated groups (for all $p<0.05$).

Serum IL–2 levels in the paranoid, disorganized, undifferentiated, and residual schizophrenia subtypes were 8.669±2.810 pg/mL, 9.663±4.210 pg/mL, 9.138±4.120 pg/mL, and 6.524±1.750 pg/mL, respectively. The IL–2 level of the control group was determined to be 1.483±0.450 pg/mL. When schizophrenia subtypes and control group were compared with each other, a significant difference was determined between the residual subtype of schizophrenia and the control group ($p<0.01$), and between patients in the paranoid, disorganized, and undifferentiated subtypes and the control group ($p<0.0001$ for each evaluation).

In the control group, IL-6 levels were determined as 5.639±1.190 pg/mL. In the patients with paranoid, disorganized, undifferentiated, and residual subtype schizophrenia, the measured IL-6 levels were 10.378±2.770 pg/mL, 11.506±4.020 pg/mL, 9.081±2.090 pg/mL, and

Table 2: IL levels of patient and control groups

	Groups					
		Schizophrenia subtypes (n=61)				
	Control (n=25)	Paranoid (n=18)	Disorganized (n=16)	Undifferentiated (n=15)	Residual (n=12)	p
IL-1β	1,989±0,860	2,665±0,981	1,792±0,430	2,551±0,962	2,267±0,421	p<0.05; PS-Control, PS-DS, DS-US
IL-2	1,483±0,450	8,669±2,810	9,663±4,210	9,138±4,120	6,524±1,750	p<0.01; RS-Control p<0.001; PS-Control, DS-Control, US-Control
IL-6	5,639±1,190	10,378±2,770	11,506±4,020	9,081±2,090	6,801±2,031	p<0.05; RS-Control p<0.01; US-Control p<0.001; DS-RS
IL -8	2,773±0,910	12,719±5,680	4,579±1,720	2,985±0,890	4,155±1,360	p<0.001; PS-Control, DS-Control p<0.05; DS-Control p<0.001; PS-Control, PS-DS, PS-US, PS-RS

PS: paranoid schizophrenia, DS: disorganized schizophrenia, US: undifferentiated schizophrenia, RS: residual schizophrenia.

6.801±2.031 pg/mL, respectively. There was a mild significant difference between the patients with the residual subtype of schizophrenia and the control group ($p<0.05$) regarding IL-6. This difference was much more significant between the undifferentiated group and the control group ($p<0.01$), and between the disorganized, and residual subtypes, and the paranoid and disorganized subtypes and the control group (for the last three comparisons $p<0.001$).

Serum IL–8 levels in the paranoid, disorganized, undifferentiated, and residual schizophrenia subtypes were 12.719±5.680 pg/mL, 4.579±1.720 pg/mL, 2.985±0.890 pg/mL, and 4.155±1.360 pg/mL, respectively. IL-8 level of control group was determined as 2.773±0.910 pg/mL. Serum IL–8 levels of the patients who had the diagnosis of paranoid schizophrenia compared to the disorganized, undifferentiated, residual subtypes, and the control group were statistically and significantly higher ($p<0.001$). Likewise, serum IL-8 levels in the disorganized subtype were statistically higher than that of control group ($p<0.05$). The brief interleukin levels of patients and the control group are given in Table 2.

DISCUSSION

Recently, data obtained from research studying the relationship between schizophrenia and immune system gave rise to a new hypothesis describing cytokines as "immunoneurotransmitters" in schizophrenia. Recent studies have demonstrated evidence of the probability of a malfunction in the cytokine network in schizophrenia (3,17,18).

IL-1β is a pro-inflammatory cytokine involved in modulating inflammation and stress responses in the brain. Central administration of IL-1β impairs both memory functions and long-term potentiation (LTP) induction. (19). In this study, serum IL-1β levels were significantly higher in the paranoid schizophrenia group than those of the disorganized and control groups. Concordant with our study, Katila et al. (20) showed higher serum IL-1β

concentrations in 60 acute, hospitalized schizophrenic patients compared to that of 60 controls. In the same study, no difference was found in chronic schizophrenic patients. Likewise, Baker et al. (3) found no difference in IL-1β levels between chronic schizophrenic patients and healthy controls. Araujo and Cotman (7) suggested that the glial-derived lymphokines IL-1β and IL-2 may have different functions in the CNS. Whereas IL-1β may have an important role in the developing brain as a maintenance and growth-promoting factor, IL-2 may function as an inhibitory factor, and may be of significance only in instances where it accumulates in sufficiently high concentrations in the vicinity of neurons. IL–2 is a potent modulator of dopamine (DA) activity in the mesocorticolimbic and mesostriatal systems. It is also associated with behavioral changes (increased motor activity) and psychopathological outcomes (schizophrenia, Parkinson's disease, cognitive deficits) that at least partly reflect aberrations in central dopaminergic transmission (21).

Zalcman et al. (21) noted that IL-2 increased hypothalamic and hippocampal norepinephrine (NE) utilization, and DA turnover in the prefrontal cortex without affecting serotonin metabolism in mice. In addition, it has been shown that IL-2 stimulates DA release from striatal cells (22). Petitto et al. (23) reported that IL-2 dose-dependently modulated veratrine-evoked release of endogenous dopamine in a biphasic pattern, increasing release at lower concentrations and inhibiting release at a high concentration of the cytokine. This biphasic pattern can demonstrate the roles of different IL-2 levels in the pathophysiology of schizophrenia. Ganguli et al. (24) demonstrated a significant negative correlation between IL-2 levels and negative symptoms of schizophrenia. All these data suggest that CSF or blood IL-2 levels are different in varied biological subtypes of schizophrenia. Kim et al. (25) found that the plasma levels of IL-2 and homovanilic acid (HVA) were significantly higher in patients compared to controls. In schizophrenic patients, there were significant correlations between IL-2 and HVA, IL-2 and the Scale of Assessment of Positive Symptoms (SAPS), and HVA and SAPS during the acute state of the illness. Changes in IL-2 and HVA significantly correlated to those in HVA and SAPS, respectively. These results strongly suggest that the cytokines may modulate dopaminergic metabolism and symptomatology in schizophrenia.

We found a significant difference in IL-2 levels between patients with the diagnosis of residual subtype of schizophrenia and the control group. This difference was statistically significant between the patients displaying paranoid, disorganized, and undifferentiated subtypes and the control group. Wilke et al. (26) found that the production of IL-2 showed a trend toward reduction in paranoid patients, but not in residual schizophrenics. The serum sIL-2R levels were elevated slightly in schizophrenics when compared with controls. Concordant with these data, Gattaz et al. (27) reported no difference between serum IL-2 and IFN-gamma levels of schizophrenic patients and normal controls. Thus they failed to support the hypothesis of an immunological abnormality in schizophrenia on the basis of the determination of IL-2 and IFNs serum levels. Additionally, Zhang et al. (28) showed elevated levels of IL-2, IL-6 and IL-8 levels in chronic schizophrenic patients. And also they reported that the dysfunction of interaction or inter-adjustment among different cytokines may exist in schizophrenic patients.

In our study, there was a significant difference in IL-6 levels in all subtypes of schizophrenia compared with the control group. Also a significant difference was detected between paranoid and disorganized subtypes and the control group. Van Kammen et al. (29) indicated that IL-6 levels may be altered in schizophrenia. The relative decrease in patients with exacerbations of the disease following haloperidol withdrawal may be indicative of a compensatory response of plasma IL-6 levels during relapse. Despite the above-mentioned positive results, there are various studies in the literature that had shown no difference of IL-6 levels between schizophrenic patients and control groups (20,3).

IL-6 is released by both neurons and microglia cells (30). It has been reported to exert trophic effects on glial cells, including oligodendroglia, producing increased expression of glial fibrillary-acidic protein (31). Paradoxically, IL-6 increases intracellular calcium levels during NMDA-receptor activation, enhancing neurotoxicity and cell death in granular neurons (32). Thus, IL-6 can have both neurotrophic and neurotoxic effects in different neuronal types and at different developmental stages. Additionally, it affects the HPA axis strongly, and stimulates release of GHRH, TSH, LH, GH and prolactin from the hypophysis (33). Elevated plasma and CSF IL-6 levels can also be seen in autoimmune

diseases (34). In particular, IL-6 is a pleiotropic cytokine, present at elevated levels in patients with rheumatoid arthritis (35). Shintani et al. (36) has suggested a link between schizophrenia and immune response, which could be either autoimmune or a process induced by reactivation of viruses, since higher levels of IL-6 are characteristically found in several autoimmune disorders.

In our study, serum IL-8 levels were significantly higher in paranoid schizophrenia than in the disorganized, undifferentiated and residual subtypes and the control group. In addition, IL-8 levels were higher in the disorganized subtype than the control group. In most studies it has been found that IL-8 levels were higher in schizophrenics than that of control group (17,28). This may be related to the activation of the monocyte-macrophage branch of cell-mediated immunity. On the other hand, Turkoglu et al. couldn't find any difference between schizophrenic and control groups in terms of IL-6 and IL-8 levels; however, they did find an increase in serum IL-6 levels after four weeks of antipsychotic treatment (37).

IL-8 levels may be increased by IL-1 and TNF-α that have been shown to be elevated in schizophrenia and released from monocytes and macrophages (13). IL-8 levels may also be elevated in blood in some autoimmune diseases. It has been asserted that IL-8, IL-6 and TNF-α levels may be elevated in children with untreated autoimmune hepatitis and also IL-6 and IL-8 levels may be elevated in Graves disease (38). Thus, it has been suggested that schizophrenia might be an autoimmune neuropsychiatric spectrum disorder, which appears during an autoimmune central nervous system disease (39). In addition, several distinct findings have been observed with regard to patient demographics and disease variables in rheumatoid arthritis patients (40). Higher levels of IL-8 correlated with established/late disease. There are several interesting differences in cytokine patterns with respect to age at onset, current age, and disease severity.

The results of studies reported in the literature have been frequently opposite. Low patient numbers, different methods of cytokine measurements, usage of different diagnostic systems, and various sociodemographic features of the patient populations may be some of the reasons for the differing results. In addition, cytokine levels are sensitive to factors like age, gender, smoking, and psychotropic medications. Clozapine, lithium, and antidepressants are some of the psychotropic drugs affecting serum cytokine levels. In addition, infectious diseases, cardiovascular diseases, obesity, and endocrine diseases affect cytokine levels (41-44). The method of collecting blood, the standing time of the serum, and the properties of blood collection tubes may also affect the cytokine levels (25). All these factors may explain the contrary results among studies.

Our results support the possibility of an immune dysfunction in schizophrenia. Moreover, schizophrenia subtypes show a different pattern for cytokines suggesting the existence of various etiopathogenic factors. Immune changes exhibit the relationship between cytokines and clinical variables in schizophrenia. To help to illuminate the etiopathogenesis of schizophrenia and develop new treatment strategies future studies in this area will be needed.

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