

IL-4, TGF- β , NF- κ B and MPO Levels in Patients With Treatment Resistant Schizophrenia



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SUMMARY

Objective: Schizophrenia is a chronic psychotic disorder in which genetics and environmental factors such as infection and the corresponding immune response play a role in the etiopathogenesis. The aim of this study was to compare some immune factors such as nuclear factor- κ B (NF- κ B) activation, myeloperoxidase (MPO), the anti-inflammatory cytokine interleukin-4 (IL-4), and regulatory cytokine transforming growth factor- β (TGF- β) in schizophrenia patients and an age- and gender-matched control group.

Method: Plasma levels of IL-4, TGF- β , MPO, and NF- κ B activation in 20 subjects with treatment-resistant schizophrenia and 20 age- and gender-matched healthy controls were analyzed. Disease severity was evaluated using the Brief Psychiatric Rating Scale (BPRS).

Results: Plasma TGF- β levels were found to be significantly lower and NF- κ B to be significantly higher in antipsychotic treatment-resistant schizophrenia patients than in controls in this study. No significant differences were found between the patient and control groups for serum IL-4 and MPO levels.

Conclusion: The low TGF- β level in treatment-resistant schizophrenia patients in the symptom exacerbation period indicates that there is inadequate Th1/Th2 balance. Large-scale studies are required to investigate whether this is responsible for resistance in schizophrenia. The fact that the increase in NF- κ B that we found in treatment-resistant schizophrenia patients in this study has also been reported in the first attack in untreated schizophrenia patients in previous studies indicates that NF- κ B plays a role in the disorder's physiopathology from the beginning.

Keywords: Schizophrenia, IL-4, TGF-beta, NF-kappa B, myeloperoxidase

INTRODUCTION

Schizophrenia is chronic psychotic disease affecting 1% of the world's population (Tandon et al. 2008). Although many factors are known to play a role in its etiology, the interaction between a genetic predisposition and environmental stress is important (Harrison and Weinberger 2005, McDonald and Murray 2000). The strong presence of inflammatory processes among the environmental stress factors has been emphasized (Fan et al. 2007, Potvin et al. 2008, Drexhage et

al. 2010). Numerous studies have shown that maternal infections such as toxoplasmosis, borna disease, influenza, and rubella increase the incidence of schizophrenia (Brown and Patterson 2011). Studies in adult schizophrenia patients have revealed changes in the levels of inflammatory factors such as cytokines and cytokine receptors. Increased immune response and inflammatory parameters have been reported to be related to the severity of the psychopathology (Fan et al. 2007, Hope et al. 2013, Potvin et al. 2008).

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Inflammatory cytokines are signal proteins of soluble polypeptide structure that play a role in the initiation and maintenance of the immune response to infection (Rothwell 1999). In the central nervous system, they are mainly expressed in microglial cells and activated macrophages (Vitkovic et al. 2000, Potvin et al. 2008). Cytokines can be classified as type-1 (Th1), pro-inflammatory (interleukin (IL)-1 β , IL-2, IL-6, IL-12, IL-18, tumor necrosis factor-alpha (TNF- α), and interferon (IFN)- γ); or type-2 (Th2), anti-inflammatory (IL-4, IL-10, IL-17) and regulatory cytokines (TGF- β , IL-27 and IL-6) (Abbas et al. 2007). Increased levels of pro-inflammatory cytokines dependent on the activation of the nitrosative and oxidative stress pathways and the hyperactivation of the Th1 response have been found in schizophrenia (Ng et al. 2008, Wang et al. 2009, Anderson et al. 2013). Pathologic changes such as oxidative damage in the brain and decreasing antioxidant levels indicating oxidative stress can partially contribute to the pharmacologic treatment of the disease (Looney and Childs 1934, Dean et al. 2009, Wang et al. 2009). Schwarz et al. (2001) found a shift from the Th1 cellular response to Th2 humoral response in schizophrenia in their study and proposed the Th2 hypothesis. Two meta-analyses investigating the relationship between schizophrenia and abnormal cytokine levels have been conducted based on this hypothesis (Potvin et al. 2008).

Other markers of inflammation are Nuclear Factor-kappa B (NF- κ B) and myeloperoxidase (MPO), acting in the early stages of the immune response. NF- κ B is included in the cellular response against stimulants such as stress, cytokines, and free radicals. It also plays a fundamental role in regulating the immune response against infection. Additionally it has revealed have a role in synaptic plasticity and memory processes (Albensi and Mattson 2000). MPO is usually secreted from polymorphonuclear leukocytes stimulated in inflammation regions and is active in the emergence of tissue disruption by using reactive oxygen and nitrogen (Abu-Soud and Hazen 2000).

While there have been many discussions on the potential for changes in the pro-inflammatory cytokines in schizophrenia, the role of the anti-inflammatory signals has drawn less attention in this regard; this is striking in terms of the intertwined nature of the anti-inflammatory and pro-inflammatory systems (Gallin et al. 1999). In this study, we therefore aimed to investigate anti-inflammatory cytokines such as IL-4 and TGF- β , which have been less intensively studied and have produced contradictory results, and the levels of other inflammatory markers such as NF- κ B and MPO that are included in the early stages of the immune response in treatment-resistant schizophrenia patients. The changes in inflammatory response are known to be more significant in treatment-resistant schizophrenia patients (Lin et al. 1998, Maes et al. 2000).

The effect of antipsychotic drugs on cytokine networks is also known as an important confounding factor (Altamura et al. 1999). This study's being conducted on treated and resistant schizophrenia patients will be important in terms of revealing whether a different inflammatory process is functioning in these patients.

METHODS

This study was conducted at the Psychiatry Department of Inonu University Faculty of Medicine. We included 20 patients diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders 4th Version (DSM IV) and 20 age- and gender-matched healthy controls in the study. All patients were resistant to antipsychotic treatment and treated as inpatients. The definition of resistant to treatment was "inability to receive a sufficient response to the use of two antipsychotic drugs from two different groups for an adequate duration (six weeks for each drug) and dose" (Kane et al. 1988, Meltzer et al. 1989). Eight patients had been taking clozapine (300 mg/day) + haloperidol (10 mg/day), and twelve had been taking clozapine (300 mg/day) + risperidone (6 mg/day) for about 12 weeks. However, the mean BPRS score was 67 despite 12 weeks of treatment. When a BPRS score of 60 and above is accepted as moderate resistance and 67 and above as severe resistance according to the model recommended by Brenner and Merlo (1995), the BPRS score was 67 and above (severe resistance) in 8 patients, between 60 to 67 (moderate resistance) in 9 patients, and between 55 to 60 (mild resistance) in 3 patients, as shown in Table 2. A detailed medical history was taken from the patients and control subjects followed by physical examination and laboratory tests. Those who were physically healthy and had no medical diseases that could affect the immune system were included in the study. Conditions such as severe organic disorders, epilepsy, head trauma that caused loss of consciousness, alcohol and other substance addictions (except cigarettes), and vitamin supplement use in the previous six months that could affect the results were determined as exclusion criteria. Disease severity was evaluated by using the Brief Psychiatric Review Scale (BPRS) (Overall and Gorham 1962). The control group was selected from participants without an axis I diagnosis or psychiatric disease in first degree relatives after evaluation by a psychiatry specialist with a structured clinical interview form according to DSM IV. None of those who were included in the study had a history of head trauma, major medical or endocrine disorders, history of neurological disease or lifetime alcohol and/or drug addiction. This study was conducted in accordance with the Helsinki Declaration and approved by the local ethics committee. All patients were

informed regarding the study protocol and informed consent was obtained.

Biochemical Analysis

Venous patient samples were collected from the patient and control group subjects between 07:00 and 10:00 in the morning following 12 hours of fasting and no tobacco use.

Peripheral blood mononuclear cell (PBMC) isolation: Minimal heparinized (2 U/mL) blood was spread on Histopaque-1077 (Sigma Chemical Co.) and was centrifuged at 24°C for 30 minutes (500xg). PBMC collected from the plasma/Histopaque interface was washed three times with phosphate buffered saline (PBS), resuspended in PBS, and frozen at -80oC until the analysis day.

NF-κB activation: NF-κB activation was measured in the nuclei of mononuclear fractions isolated from the whole blood of the patients and control subjects. The Cayman Nuclear Extraction kit (Ann Arbor, MI, USA) was used according to the manufacturer's instructions to obtain the nucleus and for NF-κB activity analysis.

MPO, TGF-β, and IL-4 measurement: ELISA kits for MPO and TGF-β were purchased from Cayman Chemicals Company (Ann Arbor, HI, USA) and the ELISA kit for IL-4 from Boster Biological Technology (Encyclopedia Circle, Fremont, CA, USA). Plasma MPO, IL-4, and TGF-β activities were analyzed using the ELISA technique following the procedures recommended by the manufacturer. All ELISA analyses were performed with the Brio-SEAC semi-automatic ELISA machine (Radim Company, Calenzano-Firenze, Italy).

Statistical Analysis

Statistical analyses were conducted with the Statistical Program for Social Sciences (SPSS), 17th version for Windows. Descriptive statistics are given as mean and standard deviation (SD) for continuous variables and as number and percentage for categorical variables. The Shapiro–Wilk test was used for data with a normal distribution. The demographic characteristics of the patient and control groups were compared with the unpaired t-test. The Pearson Chi-Square test was used to compare the groups in terms of gender. The Mann-Whitney U test was used for the BPRS, IL-4, MPO and NF-κB values, which did not show a normal distribution, and the unpaired t-test was used for the TGF-β values, which showed a normal distribution, in the analyses comparing the cytokine levels between the groups. The Spearman Correlation Test was used to evaluate the strength of the relationship between the cytokine levels and BPRS scores. A P value <0.05 was accepted as statistically significant.

RESULTS

The demographic data of the groups are shown in Table 1. There were no statistically significant differences between the patient and control groups in terms of age, gender, smoking rates, and weight ($p>0.05$). Clinical parameters of the patient group regarding disease severity are presented in Table 2.

A significant difference was found between the groups for TGF-β and NF-κB levels. TGF-β levels were lower and NF-κB levels higher in the patient group than in the control group ($p=0.0001$, $p=0.0001$, respectively). No statistically

Table 1. Demographic characteristics and BPRS scores of the patient and control groups

Demographic characteristics	Patient group (n = 20)	Control group (n = 20)	p value
Gender (Male/Female)	12/8	10/10	p=0.376
Age (year) (mean±SD)	29.45±5.65	29.80±9.38	p=0.887
smoking (+/-)	11/9	10/10	p=0.500
Weight (kg) (mean±SD)	75.50±10.78	72.65±10.34	p=0.399
BPRS	67		

n: number of subjects; SD: standard deviation; BPRS: Brief Psychiatric Rating Scale

Table 2. Disorder severity and related clinical parameters of the patient group

Patient no	Age of onset	Marital status	Disease duration (year)	Number of Episodes	Number of hospitalizations	BPRS
1	20	single	9	5	4	85.0
2	22	single	5	4	4	75.0
3	33	single	11	6	4	66.0
4	21	single	8	4	3	61.0
5	19	single	6	4	4	59.0
6	25	single	7	4	3	63.0
7	23	single	10	4	4	62.0
8	14	single	5	3	2	59.0
9	19	single	6	3	2	61.0
10	19	single	5	3	3	70.0
11	27	married	8	4	4	66.0
12	24	single	5	4	3	57.0
13	22	single	5	3	3	63.0
14	23	married	9	4	4	65.0
15	24	married	7	3	3	80.0
16	33	married	6	4	3	85.0
17	17	single	10	6	4	61.0
18	17	single	9	4	3	67.0
19	19	single	5	3	3	69.0
20	24	single	6	3	3	75.0

BPRS: Brief Psychiatric Rating Scale

Table 3. Comparison of the cytokine levels of the patient and control groups

	Patient group (n = 20) (mean±SD)	Control group (n = 20) (mean±SD)	p value
IL4 (pg/ml)	16.06±6.53	14.95±3.12	p=0.495
MPO (pg/ml)	198.26±76.23	175.24±14.57	p=0.192
NF-κB (ng/ml)	6.20±0.79	4.54±0.68	p=0.0001
TGF-β (pg/ml)	1.59±0.27	2.75±0.46	p=0.0001

n: number of subjects; SD: standard deviation

significant differences were found for MPO and IL-4 levels (p=0.192, p=0.495, respectively) (Table 3).

No statistically significant relationship was found between BPRS scores and cytokine levels in the patient group with correlation analysis (p>0.05).

DISCUSSION

The main aim of this study was to determine the levels of some inflammatory mediators in treatment-resistant schizophrenia patients. The main finding of our study was that the serum TGF-β levels in schizophrenia patients were significantly lower and NF-κB levels significantly higher than in the controls. Although serum IL-4 and MPO levels were also higher in the patients than in the controls, this increase was not statistically significant.

There is increasing evidence that certain inflammatory factors play a role in brain signalling and lead to neurochemical and behavioral changes (Kronfol and Remick 2000, Muller and Ackenheil 1998, Nawa and Takei 2006). The interaction between these complex systems has also been shown to be disrupted in psychiatric disorders such as schizophrenia (Altamura et al. 1999, Muller and Schwarz 2008, Ozawa et al. 2006, Strous and Shoenfeld 2006). Excessive cytokine secretion has been accepted an important mediator in pathogenesis of schizophrenia (Smith and Maes 1995). Cytokine-producing CD4-T helper lymphocytes have two different subtypes, Th1 and Th2. Th1 cells are responsible for the production of interleukin-2 (IL-2) and interferon-γ and are active in the type-1 immune response. Functional changes have been found in T helper-1 lymphocyte-mediated proinflammatory activity in schizophrenia patients, and an increase in serum/plasma levels of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8 and TNF-α has been demonstrated (Curfs et al. 1997, Gallin et al. 1999). Th2 cells represent the type 2 immune response, i.e., the humoral-antibody producing adaptive immune response, and are responsible for IL-4, IL-10, IL-5 and IL-13 production (Mills et al. 2000). Th2-type cytokines are known as anti-inflammatory agents that reduce the immune and inflammatory response (Xiu et al. 2014). It

is believed that schizophrenia may be related to an imbalance favoring Th2 in the Th1/Th2 system (Muller et al. 2000, Schwarz et al. 2001).

We investigated the changes in anti-inflammatory cytokines in this study. TGF-β and IL-4 are the two most important members of anti-inflammatory cytokines. TGF-β is a pleiotropic cytokine secreted by nonimmune cells, and it plays a fundamental role in many biological functions including embryonic development, cell differentiation, wound healing, and immune regulation (Moustakas et al. 2002, Curfs et al. 1997). It shows its anti-inflammatory and immunosuppressive effects in inflammation by inhibiting pro-inflammatory cytokine synthesis and decreasing natural killer cell activity together with T- and B-cell growth. However, TGF-β has been shown to have various pro-inflammatory functions through its stimulant effects on TH17 cells in recent years (Yoshimura et al. 2010). Schizophrenia has been reported to be associated with increased lymphocytic expression of peripheral free TGF-β protein and TGF-β receptors (Numata et al. 2008). No difference was found between the schizophrenia patients and controls when the TGF-β1 and TGF-β2 levels in cerebrospinal fluid (CSF) were compared in another study, and it was reported that the results did not support active neurodegeneration or an anti-inflammatory response (Vawter et al. 1997).

We found the TGF-β levels to be lower than in the controls in this study. This can be explained by our patients being resistant to treatment, as changes in the inflammatory response are known to be more marked in treatment-resistant schizophrenia patients (Lin et al. 1998, Maes et al. 2000). TGF-β is known to have a regulatory effect on the balance of Th1 and Th2 cytokines (Myint et al. 2005). The low TGF-β level in the period during which psychotic symptoms had exacerbated (mean BPRS score 67) in treatment-resistant schizophrenia patients can be explained by the inadequacy in providing Th1/Th2 balance.

Increased levels of IL-10 and IL-4, which are anti-inflammatory cytokines like TGF-β, have been reported in schizophrenia (Van Kammen et al. 1999, Mittleman et al. 1997). We also found increased IL-4 levels in the patient group, but this increase was not at a statistically significant level. Various and conflicting results have been reported from studies on the effects of antipsychotics on inflammatory factors (Zhang et al. 2005, Realeve et al. 2011). Müller and Schwarz (2010) showed that the type-2 response was increased in schizophrenia patients, while this was reversed with antipsychotics. No significant difference was found between the groups for IL-4 levels in this study, possibly because our patients were being treated with antipsychotics.

There was no difference in levels of MPO, one of the molecules focused on in this study, between the groups, while

there was an increase in NF- κ B activation. NF- κ B is another marker of inflammation and plays an important role in signal path axon growth, activity-dependent plasticity, and cognitive functions (Gutierrez and Davies 2011). Cytokines have been shown to be prototypic transcription factors sensitive to various genes including cell surface receptors and antioxidant enzymes (Baeuerle 1991). Evidence supporting the role of NF- κ B in schizophrenia is available. Higher levels of NF- κ B signaling activation have been found in peripheral blood mononuclear cells in first-episode schizophrenia patients who were not on medication in a study by Song et al. (Song et al. 2009). Similarly, we also found NF- κ B activation to be increased in treatment-resistant schizophrenia patients. Although the reason for this increase is not fully clear, it could be a result of the antipsychotics used. However, when evaluated with the results of the previous study, we can exclude the hypothesis that NF- κ B in schizophrenia may be increased only with the progress of the disease or as an effect of treatment. The high levels in the first attack and in untreated patients suggest that NF- κ B plays a role in the physiopathology of the disease from its onset (Song et al. 2009). However, the lack of a correlation between the NF- κ B level and disease severity does not completely support this relationship.

The result of this study should be interpreted under the light of its own limitations. First, a strong relationship is known to be present between different cytokines. We evaluated the blood levels of two cytokines in this study. However, pro-inflammatory cytokine levels were not investigated. Another limitation is the lack of a first-attack patient group not on medication, as well as a group that consisted of non-treatment-resistant schizophrenia patients who were not experiencing their first attack. In addition, the low number of subjects is a limitation.

The results of this study showed that the levels of TGF- β , which is a regulatory cytokine, were significantly lower and the levels of NF- κ B, which plays a role in plasticity and cognitive functions, were significantly higher in antipsychotic treatment-resistant schizophrenia patients than in the controls. No changes were found in the levels of IL-4 and MPO, which are other anti-inflammatory cytokines. Large-scale future studies where both pro-inflammatory and anti-inflammatory cytokines are included are required to reveal the role of inflammatory factors in schizophrenia development.

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