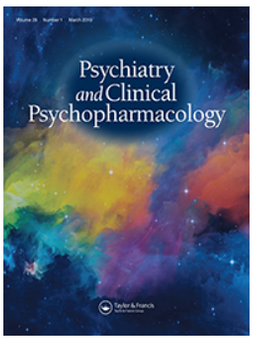

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The relationship between psychopathology and cognitive functions with cytokines in clinically stable patients with schizophrenia

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ABSTRACT

OBJECTIVES: Inflammation and the cytokine hypotheses have been proposed for schizophrenia. Several proinflammatory and anti-inflammatory cytokines have been studied in drug-naive, first-episode, and/or chronic schizophrenia patients. However, there were limited data on clinical stable outpatients reflecting daily routine. The aim of this study was to compare the serum levels of cytokines, including transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α), between clinically stable patients with schizophrenia and healthy controls, as well as to examine the relationship between these inflammation parameters and clinical variables (positive and negative symptom severity and cognitive functions).

METHODS: Thirty clinically stable outpatients with schizophrenia and 30 healthy controls with similar sex and age were included in this study. Serum IL-6, TGF-β, and TNF-α levels were assessed by enzyme-linked immunosorbent assay (ELISA) and immunoenzyme microplate measurement, respectively. Illness severity was evaluated using the Positive and Negative Syndrome Scale (PANSS), and the cognitive functions of the participants were assessed using a broad neuropsychological test battery.

RESULTS: The serum levels of IL-6 and TGF-β were significantly higher in patients with schizophrenia compared to healthy controls ($p = .048$, $p = .012$). There was no significant difference between groups in terms of TNF-α levels ($p = .726$). Global impairment of cognitive functions was observed in the patient group compared to healthy controls, and PANSS scores and cognitive functions showed no correlation with cytokine levels (IL-6, TNF-α, and TGF-β).

CONCLUSIONS: The present study demonstrated an increased inflammatory response in clinically stable patients with schizophrenia compared to healthy controls. However, symptom severity and cognitive functions showed no correlation with cytokine levels. Further research studies are needed to clarify the effects of cytokine levels on schizophrenia symptomatology and etiopathogenesis.

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Schizophrenia; inflammation; cytokines; cognition; psychopathology

Introduction and objective

Schizophrenia is a chronic and severe mental illness, which leads to a heterogeneous symptomatology, including hallucinations, delusions, negative symptoms, and deterioration in cognitive functions [1]. The aetiology of schizophrenia has a complex nature, and established risk factors with regard to inflammation include autoimmune and allergic diseases; genetic variations in the major histocompatibility complex (MHC) region on chromosome 6, which is related to immune system and inflammation; perinatal infections; or maternal immune activation [2,3].

Altered immune system function has been proposed for schizophrenia through activated inflammatory processes, variations in immune-related genes and cytokine levels, activated microglia in the brain, increased kynurenic acid levels related to tryptophan metabolism, and an impaired hypothalamic–pituitary–adrenal (HPA) axis [2,4,5]. These impairments have been blamed for the etiopathogenesis and symptomatology of schizophrenia [6]. As a result of these findings, authors have focused on non-steroidal anti-inflammatory drugs as a novel potential target for the treatment of schizophrenia [7,8].

Increased levels of cytokines, such as tumour necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), IL-1β, IL-1 receptor antagonist, soluble IL-2 receptor, and IL-12, have been identified in patients with schizophrenia; however, controversial findings have also been found across different studies [9,10]. Differences in the inclusion and exclusion criteria, study design, sample size, and clinical status of patients across studies; the comorbidity of metabolic and/or inflammatory diseases; the

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potential effects of body mass index (BMI); and smoking may all lead to these variations [9,11]. It was claimed that some cytokines (i.e. IL-1β, IL-6, and TGF-β) act as state markers for acute relapse, and others (i.e. IL-12, IFN-γ, TNF-α, and sIL2R) represent trait markers of schizophrenia [9].

Inflammatory and immunological processes have been associated with specific symptoms of schizophrenia. IL-8 and C-reactive protein (CRP) levels have been demonstrated to have positive correlations with the Positive and Negative Syndrome Scale (PANSS) negative subscale [12,13], IL-2 levels, and the PANSS cognitive factor [14], while a negative correlation was determined between IL-2 levels and the PANSS positive subscore [14], IL-6 levels, and cognitive functions [15]. Moreover, Dickerson et al. demonstrated that patients with elevated CRP levels (>5 mg/mL) have lower cognitive scores than patients with normal CRP levels [16].

With regard to schizophrenia, cytokine levels were investigated in first-episode, drug-naive, and treatment-resistant patients and in patients with psychotic exacerbation [12,14,17], but there are insufficient data related to clinically stable outpatients [9]. Thus, the aim of this study was to compare the serum levels of cytokines, including TGF-β, IL-6, and TNF-α, between clinically stable patients with schizophrenia and healthy controls. The present study also aimed to examine the relationship between these inflammation parameters and clinical variables (e.g. positive and negative symptom severity and cognitive functions).

Material and methods

Subjects

The sample of this study consisted of patients who applied to Marmara University Pendik Training and Research Hospital Psychiatry Outpatient Clinic between May 2015 and October 2015. Thirty clinically stable patients with schizophrenia (aged 18–65 years) and 30 healthy controls of similar sex and age were included in this cross-sectional study. The exclusion criteria were: (i) acute or chronic medical conditions, such as allergies, autoimmune disease, and current infections (more than a 10,000/mm^3 white blood cell count in the complete blood cell count); (ii) comorbid psychiatric axis I disorders; (iii) a history of substance use; (iv) current use of anti-inflammatory or immunosuppressant medications; (v) current use of clozapine as an antipsychotic treatment; and (vi) a history of severe head trauma or any major neurological illnesses, i.e. epilepsy and Parkinson's disease. Moreover, the presence of a diagnosis of schizophrenia in first-degree relatives was an exclusion criterion in the control group.

For the study population, psychiatric disorders were diagnosed according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Axis I Disorders (SCID-I) by the same psychiatrist. During the interview, patients diagnosed as schizophrenia were evaluated whether they were clinically stable or not. Similar to previous studies [18,19], the stability criteria were defined as follows: (1) an absence of an acute psychotic relapse, (2) no psychiatric hospitalization in the last 6 months, and (3) no changes in the use of antipsychotic group medications in the last 6 months.

While a neuropsychological battery was administered to all participants, PANSS was only applied to the patient group.

The study was approved by the Local Ethics Committee and performed in accordance with the Declaration Criteria of Helsinki. Written informed consent was obtained from each participant before the study.

Assessment instruments

Socio-demographic form

Socio-demographic variables (age, sex, educational status, marital status, occupation, BMI, alcohol use and smoking, etc.) of the participants and clinical characteristics of the patient group (age of illness onset, duration of untreated period (DUP), etc.) were recorded onto the data form prepared by the researchers.

Structured Clinical Interview for DSM-IV Axis I Disorders

The SCID-I is a psychiatric semi-structured interview technique for determining the presence of DSM-IV Axis I diagnoses [20]. The validity and reliability of the SCID-I have been established [21].

Positive and Negative Syndrome Scale

The PANSS is a 30-item clinician-rated symptom severity scale that was developed to provide a comprehensive assessment of the symptoms of schizophrenia [22]. It contains three sub-scales representing positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (16 items). All items were scored on a 7-point Likert scale ranging from 1 to 7 (absent to extreme severity). The Turkish validity and reliability study was conducted by Kostakoğlu et al. [23].

Neuropsychological battery

The Digit Span Test [24,25] for short-term auditory recall and attention; the Visual Reproduction Test [24,25] for visual memory; the Verbal Fluency Test [26,27] for complex attention functions, such as speech fluency, recall, and sustained attention; the Verbal Memory Processes Test (VMPT) [28] for verbal learning and memory; the Wisconsin Card Sorting Test

(WCST) [29,30] for executive functions; the Stroop Test [31,32] for selective attention, processing speed, cognitive flexibility, and executive functions; and the Trail-Making Test [33] for attention speed, mental flexibility, response inhibition, and motor speed were applied in the present study.

Analysis of inflammatory parameters

Serum samples were collected between 9 am and 10 am. The serum was separated, aliquoted, and stored at −80°C before and after use. Serum IL-6, TGF-β1, and TNF-α levels were measured in all subjects on the same day. Serum IL-6 and TGF-β1 levels were assessed by enzyme-linked immunosorbent assay (ELISA) using Human IL-6 and TGF-β1 Platinum kits (Vienna, Austria), respectively. Serum TNF-α levels were assessed by immunoenzyme microplate measurement using the DIAsource TNF-α enzyme-amplified sensitivity immunoassay (EASIA) kit (DIAsource ImmunoAssays S.A., Louvain-la-Neuve, Belgium).

Statistical method

Statistical analyses were performed using the software program SPSS Version 22.0 (IBM Corporation, Armonk, NY, USA). Normal distribution was assessed using the Kolmogorov–Smirnov test, while the Student's *t* test and the Mann–Whitney *U* test were used to compare continuous variables for normal and non-normal distributions, respectively. Pearson's chi-squared test and Fisher's exact test were used to compare categorical variables, and a correlation analysis was performed using Spearman's correlation (non-normal distribution) test. Statistical significance was evaluated at the level of $p < .05$.

Results

Thirty patients with schizophrenia and 29 healthy controls with similar age and sex were included in the study.

Baseline socio-demographic and clinical characteristics are shown in Table 1. Twenty-one participants in both groups were male, and the mean age of the participants was 36.43 ± 9.45 years for patients with schizophrenia and 36.52 ± 8.95 years for healthy controls. According to the marital status, the single participants were higher in schizophrenia group (80% single), while the participants in the healthy group were mostly married (31% single) ($p < .001$). There was no statistically significant difference between groups in terms of education level ($p = .787$), smoking ($p = .450$), and BMI ($p = .559$) (Table 1). The mean DUP was 13.77 ± 19.96 months, and the PANNS total score was 62.50 ± 15.71 in patients with schizophrenia.

Table 1. Baseline socio-demographic and clinical characteristics.

		Patient ($n = 30$)	Control ($n = 29$)	p
Age	Mean (SD)	36.43 (9.45)	36.52 (8.95)	.972[a]
Gender	Female (%)	9 (30)	8 (27.6)	.838[b]
	Male (%)	21 (70)	21 (72.4)	
Marital status	Single (%)	24 (80)	9 (31)	**<.05***[c]
	Married (%)	6 (20)	19 (65.5)	
	Divorced (%)	0	1 (3.4)	
Education (years)	Mean (SD)	10.37 (3.55)	10.1 (3.9)	.787[a]
BMI (kg/m^2)	Mean (SD)	27.2 (3.54)	26.59 (4.43)	.559[a]
Daily cigarette consumption	Median	6	2	.450[d]
Current smokers (%)		16 (53.3)	16 (55.2)	.887[b]
Alcohol ± (%)		0	3 (10.3)	.112[c]
Age of onset illness	25.97 ± 6.52			
Illness duration	Mean (SD)	11.40 ± 8.91		
DUP (month)	Mean (SD)	13.77 ± 19.96		
PANSS positive	Mean (SD)	14.87 (7.17)		
PANSS negative	Mean (SD)	17.20 (6.91)		
PANSS general	Mean (SD)	30.43 (6.58)		
PANSS total	Mean (SD)	62.50 (15.71)		

Note: SD: standard deviation; PANSS: Positive and Negative Syndrome Scale; DUP: duration of untreated period.
[a]Student's *t* test.
[b]Pearson chi-square test.
[c]Fisher's exact test.
[d]Mann–Whitney *U* test.
*$p < 0.05$.

All the levels of the inflammatory parameters were higher in patients with schizophrenia compared to the healthy controls. However, these differences reached significance only in terms of IL-6 ($p = .048$) and TGF-β ($p = .012$) levels. There was no significant difference between groups in terms of TNF-α levels ($p = .726$) (Table 2).

The patient group performed worse on the Backward Digit Span Test and in the category fluency task of the Verbal Fluency Test. Instant recall and delayed recall scores of the Visual Production Test; total right answers, completed category number, and conceptual response percentage of the WCST; learning, delayed recall, and delayed recognition scores of the VMPT in the patient group were significantly lower than in the control group. Time difference in the Stroop Test and all subtest scores of the Trail-making Test in the patient group were found to be significantly higher and impaired compared to the control group. Data regarding the neuropsychological battery between the groups are shown in Table 3.

According to the correlation analysis, PANSS scores and the subscale scores of the cognitive tests had no correlation with cytokine levels (IL-6, TNF-α, and TGF-β) in patients with schizophrenia (Table 4).

Table 2. Data regarding inflammatory parameters between the groups.

	Patient ($n = 30$) Median	Control ($n = 29$) (Median)	p[a]
IL-6 (pg/mL)	1.2	0.9	.048*
TNF-α (pg/mL)	6	5.9	.726
TGF-β (pg/mL)	1891.4	1319.8	.012*

[a]Mann–Whitney *U* test.
*$p < .05$.

Table 3. Data regarding neuropsychological battery between the groups.

	Patient ($n = 30$) Median (q1–q3)	Control ($n = 29$) Median (q1–q3)	p^a
Digit Span Test			
Forward	6 (5–6)	5 (5–6)	.392
Backward	4 (3–5)	4 (4–5)	.038*
Visual Reproduction Test			
Instant recall	10.5 (6–12)	13 (11–14)	.004**
Delayed recall	8.5 (5–11)	12 (9–14)	.002**
Verbal Fluency Test			
Category fluency test	18 (13–22)	22 (20–24)	.010*
Controlled oral word association test	32.5 (19–45)	35 (26–42)	.299
Wisconsin Card Sorting Test			
Correct answers	76 (58–89)	101 (91–106)	<.001*
Completed category number	3 (1–6)	7 (5–8)	<.001*
Conceptual response percentage	46.1 (31.3–64.1)	73.4 (64.1–79.7)	<.001*
Stroop Test			
Number of errors	1 (0–2)	1 (0–1)	.910
Time difference	60 (38–93)	42 (32–55)	.050*
Trail-Making Test			
A (time)	48.5 (39–70)	38 (30–44)	.002*
B (time)	118.5 (91–226)	76 (60–103)	.001*
B-A (time)	69 (40–152)	43 (23–60)	.002*
Verbal Memory Processes Test			
Immediate recall	6 (5–7)	7 (6–8)	.095
Learning score	119 (94–128)	127 (110–135)	.034*
Delayed recall	10.5 (10–14)	14 (12–15)	.003*
Delayed recognition	4.5 (1–5)	1 (0–2)	.001*

[a]Mann–Whitney *U* test.
*$p < .05$.

Discussion

In this study, it was demonstrated that (1) IL-6 and TGF-β levels were statistically significantly higher in clinically stable patients with schizophrenia compared to the healthy controls (Table 2); (2) the schizophrenia patients had significantly impaired cognitive functions (Table 3); and (3) IL-6, TNF-α, and TGF-β levels were not correlated with the scores of cognitive tests and the PANSS scores in the patient group (Table 4).

Table 4. Correlation analysis between inflammatory parameters and cognitive test, and PANNS scores.

	IL-6		TNF-α		TGF-β	
	r	*p*	*r*	*p*	*r*	*p*
Digit Span Test						
Forward	−.096	.619	.135	.476	.212	.261
Backward	.292	.124	.043	.821	.053	.782
Visual Reproduction Test						
Instant recall	.141	.465	−.082	.668	.119	.530
Delayed recall	.077	.692	−.087	.647	.118	.536
Verbal Fluency Test						
Category fluency test	−.175	.364	.001	.994	.086	.651
Controlled oral word association test	−.177	.359	−.138	.468	.136	.473
Wisconsin Card Sorting Test						
Correct answers	−.236	.218	−.011	.954	.305	.101
Completed category number	−.100	.607	−.019	.919	.301	.106
Conceptual response percentage	−.141	.464	.036	.852	.325	.079
Stroop Test						
Number of errors	.043	.827	.215	.253	−.119	.532
Time difference	−.070	.719	.097	.610	−.103	.590
Trail-Making Test						
A (time)	.106	.586	−.195	.302	−.095	.617
B (time)	.083	.667	.042	.825	−.259	.167
B-A (time)	.064	.743	.135	.477	−.309	.097
Verbal Memory Processes Test						
Immediate recall	.001	.995	.023	.902	−.002	.990
Learning score	−.027	.890	.057	.765	−.031	.872
Delayed recall	.143	.460	.015	.938	.197	.296
Delayed recognition	−.153	.429	−.008	.965	−.190	.313
Positive and Negative Syndrome Scale (PANNS)						
PANSS positive	−.131	.497	.065	.733	.268	.153
PANSS negative	−.162	.402	−.034	.860	.216	.251
PANSS general	−.117	.547	.064	.736	−.038	.843
PANSS total	−.210	.275	−.039	.839	.253	.178

Note: *r*: Spearman korelasyon katsayısı.

Increased levels of IL-6 and TGF-β in patients with schizophrenia in the present study are coherent with the literature [9,12,34–38]. IL-6, which is the most studied cytokine in schizophrenia patients, plays a fundamental role in inflammatory response. TGF-β plays an important role in the anti-inflammatory activity and in controlling the inflammatory response of inflammation [39]. Consistent with our findings, a recently published study demonstrated higher levels of TGF-β in clinically stable patients with schizophrenia [40]. The results of the present study support the role of inflammation in the etiopathogenesis of schizophrenia.

In this study, an increased TNF-α level was determined in the patient group, but this difference could not reach statistical significance. Similar to the present study, Hori et al. [41] assessed TNF-α levels in clinically stable patients with schizophrenia, and they found no difference compared to healthy controls. There are controversial findings regarding TNF-α levels in patients with schizophrenia [35,42]. Meta-analyses have revealed that both increased and similar TNF-α levels were found in first-episode psychosis compared to healthy controls [36,38].

In comparison with previous studies in this field, the present study has some different findings regarding cytokine levels. First, IL-6 and TGF-β were defined as state markers that increase during acute exacerbations and normalize with antipsychotic treatment [9]. Second, TNF-α was defined as a trait marker, which means it would increase in acute exacerbation and remain stable during antipsychotic treatment [9]. However, increased levels of IL-6 and TGF-β were demonstrated in patients with schizophrenia in the present study. There was no difference in terms of TNF-α levels between patients and healthy controls. Some studies did not exclude the contributing factors of inflammation, such as BMI, smoking, and taking a blood sample at a standardized time of day [9]. It would be appropriate to consider these factors when evaluating the different results in the studies. Controlling these confounding factors between schizophrenia patients and healthy controls is one of the strengths of the present study.

Cognitive functions were evaluated with a broad neuropsychological battery, and prevalent cognitive impairment was found in patients with schizophrenia. These results are consistent with previous meta-analyses, which defined remaining cognitive impairment in all domains during all clinical phases of the illness [43].

This study found no significant correlation of IL-6, TNF-α, and TGF-β serum levels with PANNS scores and cognitive test scores (Table 4). Controversial findings were determined in previous studies. In a previous study, serum IL-6 levels were increased and negatively correlated with cognitive functioning in patients with schizophrenia [15]. In the two studies looking for the correlation of cytokine levels with PANSS scores and cognitive functions in clinically stable schizophrenia patients; the first assessed TGF-β, while the other evaluated IL-6 and TNF-α levels. Both studies showed no correlation of cytokine levels with PANSS scores and cognitive functions [40,41].

Some previous studies evaluated the cognitive functions using the subscale of PANNS, and they did not use specific tests for the evaluation of cognitive functions, which was identified as a limitation in these studies [14,42]. Thus, our results might be more useful in clarifying the relationship between cytokine levels and cognition in clinically stable patients with schizophrenia.

As our patient group is clinically stable, this might have affected cytokine levels. Besides, while it is widely known that cognitive impairment in schizophrenia occurs in the prodromal stage and remains stable over the lifespan [43], some studies show variation in cognitive tests in different periods of the illness [44,45]. Considering these, our results might be affected by the aforementioned confounders.

Limitations of the present study could be mentioned as follows. Our patient group is not homogenous in terms of educational status, which may reflect premorbid cognitive functions. Due to the cross-sectional design of the present study, we could not evaluate the premorbid cognitive functions of the participants. Therefore, we could not estimate the effect of the illness on cognitive functions precisely. As mentioned above, this might influence our results. Second, the small sample size should be considered another limitation. A small sample size is a common limitation of such studies [12,13,35], and the population of the present study reflects real life. Third, although there are several cytokines that affect inflammation, we could measure limited cytokines. Although we did not include all cytokines involved in inflammation, such as IL-10 and IL-12, cytokines frequently observed in schizophrenia in the literature were included in the present study. Fourth, all our patients were medicated, and they were not homogenous in terms of their antipsychotic medications. It is known that antipsychotic treatment may affect alterations in cytokine levels. However, a recent meta-analysis demonstrated no association between the levels of IL-6, TNF-α, TGF-β, IL-2, IL-4, IL-10 and antipsychotic treatment, except for clozapine [46]. The exclusion of patients using clozapine is another strength of this study. Besides, some side effects of these antipsychotics (dyslipidaemia, hyperglycaemia, and metabolic syndrome) might also affect cytokine levels. The final limitation is that the present study did not control for the side effects of the antipsychotics.

Despite its limitations, this study is important in terms of evaluating the relation between clinical variables and cognitive tests and inflammatory parameters in clinically stable patients with schizophrenia.

Conclusion

In summary, our data demonstrated that serum levels of IL-6 and TGF-β were significantly higher in patients with schizophrenia than in healthy controls. However, we could not demonstrate any correlation of symptom severity and cognitive functions with IL-6, TNF-α, and TGF-β serum levels in our cross-sectional study. Thus, further studies including distinct groups of patients with schizophrenia, such as drug-naive, first-episode, and clinically stable patients, in larger samples and using a longitudinal design are needed to clarify the effects of cytokine levels on schizophrenia symptomatology and etiopathogenesis.

Disclosure statement

No potential conflict of interest was reported by the authors.

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