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Inflammation and Oxidative Stress in Deficit Schizophrenia

Eksiklik Sendromu Olan Şizofrenide İnflamasyon ve Oksidatif Stres

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ABSTRACT

Introduction: Differences in parameters related to inflammatory and oxidative stress in deficit (DS) and nondeficit schizophrenia (non-DS) may support the DS/non-DS categorization of schizophrenia. For DS patients, non-DS patients, and for healthy controls, this study aims to evaluate the serum levels of: proinflammatory cytokines of interleukin (IL) 1β, tumor necrosis factor (TNF) α, Interferon (IFN) γ, IL-12, and IL-17; anti-inflammatory cytokines of IL-10, IFN-α, and transforming growth factor (TGF) β; and antioxidant biomarkers of paraoxonase1 (PON1) and Total Antioxidant Capacity (TAOC).

Method: Serum IL-1β, TNF-α, IFN-γ, IL-12, IL-17, IL-10, IFN-α, TGF-β, PON1 and TAOC levels were measured and performed in DS (n=26), non-DS (n=28), and healthy control (n=28) groups.

Results: Patients in the DS group had higher IL-17 levels than the non-DS group did. TGF-β values for both patient groups were significantly higher than those of the controls. PON1 and TAOC values for both patient groups were significantly lower than those of the controls.

Conclusion: Our findings may be evidence for the consideration that DS reflects a coherent entity within schizophrenia. Increased levels of IL-17 from pro-inflammatory cytokines may be related with DS.

Keywords: Deficit schizophrenia, schizophrenia, inflammation, cytokine, oxidative stress

ÖZ

Amaç: İnflamasyon ve oksidatif stress (OS) düzeyindeki farklılıklar eksiklik sendromu (ES) olan ve olmayan şizofreni ayrımını destekleyebilir. Bu çalışmada ES olan, olmayan şizofreni tanılı hastalar ve sağlıklı kontrollerin interlökin (IL) 1β, Tümör Nekroz Faktör (TNF) α, İnterferon (IFN) γ, IL-12 ve IL-17'den oluşan serum proinflamatuvar sitokin düzeyleri, IL-10, IFN-α ve Transforming Growth Faktör (TGF) β'dan oluşan serum anti-inflamatuvar sitokin düzeyleri ve paraoksonaz 1 (PON1) ile Total Antioksidan Kapasite'den (TAOK) oluşan antioksidan belirteç düzeylerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Çalışmamızda ES olan (n=26) ve olmayan (n=28) şizofreni tanılı hastalar ile sağlıklı kontrollerin (n=28) IL-1β, TNF-α, IFN-γ, IL-12, IL-17, IL-10, IFN-α, TGF-β'dan oluşan serum sitokin düzeyleri ve PON1 ile TAOK'den oluşan serum antioksidan belirteç düzeyleri ölçülüp değerlendirilmiştir.

Bulgular: ES olan grupta, olmayan gruba göre IL-17 seviyesi daha yüksek saptandı. Her iki hasta grubunda TGF-β düzeyi, sağlıklı kontrol grubundan anlamlı derecede yüksekti. TAOK ve PON1 değerleri her iki hasta grubunda sağlıklı kontrollerden anlamlı derecede düşük olarak saptandı.

Sonuç: Bulgularımız ES'nin şizofreni tanısı içinde farklı özellikler gösteren bir bozukluk olduğu görüşünü destekleyebilir. Proinflamatuvar sitokinlerden IL-17 düzeyindeki yükseklik ES ile ilişkili olabilir.

Anahtar Kelimeler: Eksiklik sendromu, şizofreni, inflamasyon, sitokin, oksidatif stres

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INTRODUCTION

An etiopathophysiological role for immunologic abnormalities in schizophrenia was reported about 45 years ago (1). In recent years, three hypotheses for the relationship between the immune system and schizophrenia have emerged: The macrophage-T-lymphocyte theory that interleukin (IL)-1, IL-2, tumor necrosis factor (TNF), interferon (IFN)-α, and IFN-γ, all produced by macrophages and T-lymphocytes (both chronically activated), are the fundamental mediators of schizophrenia (2); The Th2 hypothesis, which claims that a shift away from cytotoxic Th1-cell immune function and toward antibody-dependent Th2-cell immune responses is potent in schizophrenia (3); and the microglial hypothesis, which suggests that the release of proinflammatory cytokines by activated central nervous system microglia causes abnormal neurogenesis and neuronal degradation that in turn contribute to the pathophysiology of schizophrenia (4). Cytokines are mediators that link the central nervous system and immune system in a way that may be related to clinical psychiatry (5).

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Activation of immune-inflammatory pathways is associated with oxidative stress (OS) and damage to lipids, DNA, and proteins (6). Increased production of reactive oxygen species or a reduction of antioxidant defenses gives rise to OS, causing damage to membrane phospholipids, proteins, and genes. OS may lead to impairment in signal transmission and plasticity, thus being possibly associated with neurodevelopmental disorders such as schizophrenia (7–9).

It is reported that certain negative symptoms in schizophrenia depend on illness effects and medications, but that they are essentially present at the onset; it is therefore necessary to discriminate between primary DS and secondary negative symptoms to fully understand the psychopathology. DS is defined as a more homogeneous and consistent subtype of schizophrenia with the primary, enduring negative symptoms. Restricted affect, diminished emotional range, poverty of speech with curbing of interest and decrease in curiosity, diminished sense of purpose, and diminished social drive are the significant negative symptoms for DS which are not fully accounted for depression or anxiety, drug effect or environmental deprivation (10). DS may reflect a coherent entity within schizophrenia. DS/non-DS distinction may reduce the heterogeneity of schizophrenia (11–13).

Patients with DS have lower pre-onset functionality, more impaired cognitive functions, lower remission rates with poorer respond to treatments as medications and social skills training, and poorer insight and prognosis (10–13). In the current study, we test the hypothesis that patients with DS would also differ from non-DS patients with regard to pro-/anti-inflammatory cytokines and antioxidant status concentrations. This difference may contribute to the argument of DS/non-DS categorization. In this context, the present study aims to assess the levels of pro-/anti-inflammatory cytokines and the serum levels of antioxidants such as IL-1β, TNF-α, IFN-γ, IL-12, IL-17, IL-10, IFN-α, TGF-β, PON1, and TAOC in three groups; DS, non-DS patients, and the healthy controls.

METHODS

Setting and Sample

The study included 57 patients (28 DS and 29 non-DS, matched by age and gender) diagnosed with schizophrenia; they were followed up at the outpatient clinic of Eskişehir Osmangazi University School of Medicine Department of Psychiatry between September 2014 and May 2015. A healthy control group (n=28), matched by age and gender, was also included in the study. Serum samples of 57 patients and 28 controls were performed. Nevertheless, two participants from DS group and one from non-DS group were excluded from the study due to the measurement error of the device. Neither the patients nor the control subjects had smoked during the 12 hours before blood samples were taken, none suffered from substance abuse/dependence, and all were free of immunosuppressive medication. The patients were under antipsychotic medication. The study was described to each participant (and/or a family member) and written informed consent was obtained from all.

Schizophrenia and DS were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (14, 15) and the Schedule for Deficit Syndrome (SDS) (16, 17). Both patient groups were evaluated using the Positive and Negative Syndrome Scale (PANSS) (18, 19).

Collection of Blood Samples and Separation Of Serum

After a 12-hour fast, blood samples were collected between 9:30 and 10:30 a. m., using a standard venipuncture technique. A 10 mL blood sample was withdrawn from each individual. Serum samples were separated immediately after centrifugation at 3000 rpm for four minutes and stored at -20°C until analysis, which was performed in a single run to avoid analytical variation between runs. The ELISA kits provided for this study were used according to manufacturer's instructions to determine inflammatory and antioxidant markers. The following kits were used: Human T-AOC ELISA kit, Bioassay Tech Lab, China (TAOC); Human PON1 ELISA kit, Bioassay Tech Lab, China (PON1); Human TGF-β1 ELISA kit, Boster Bio, CA, USA) (TGF-β1); Human IL-12 ELISA kit, Diaclone SAS, France (IL-12); Human IL-10 ELISA kit, Diaclone SAS, France (IL-10); Human IL-1β ELISA kit, Diaclone SAS, France (IL-1β); Human IL-17 ELISA kit, Diaclone SAS, France (IL-17); Human IFN-α ELISA kit, Diaclone SAS, France (IFN-α); Human IFN-γ ELISA kit, Diaclone SAS, France (IFN-γ); and Human TNF-α ELISA kit, Diaclone SAS, France (TNF-α).

Statistical Analysis

Statistical tests were performed using version 17.0 for Windows of SPSS (Statistical Package for the Social Sciences). Study groups were compared by Mann-Whitney U Test and Kruskal-Wallis Test. Analysis of categorical variables was carried out using the Chi-square test. All statistical tests were considered significant at the 0.05 probability level.

Ethics

All participants gave written informed consent prior to participation. The study protocol was approved by the Clinical Trials Ethics Committee of Eskişehir Osmangazi University.

RESULTS

There were no significant differences in age (H=0.456, p=0.796) and gender (χ^2=2.670, p=0.263) among all three groups. However, the duration of education of the control group was higher (H=16.99, p<0.001). In the DS group 22 patients were taking atypical, 4 patients were taking atypical and typical antipsychotic, while in the non-DS group, 1 patient was taking typical, 24 patients were taking atypical, and 3 patients were taking atypical and typical antipsychotics. There was no significant difference between the groups in terms of antipsychotic use (χ^2=1.157, p=0.561). No statistically significant difference was noted in age of onset, number of hospitalizations, duration of disorder, or number of psychotic episodes in DS and non-DS patients (z=0.633, p=0.527; z=0.623, p=0.533; z=-0.667, p=0.505; z=1.098, p=0.272 respectively) (Table 1).

Table 1. Demographic and clinic characteristics of the patients with and without deficit syndrome and controls

	DS (+) (n=26)	DS (-) (n=28)	Control (n=28)	Statistical Analysis
Gender Male/Female (n)	16/10	11/17	14/14	χ^2=2.670, p=0.263
Age, mean ± sd (years)	41.19±10.91	40.36±10.15	39.11±10.40	H=0.456, p=0.796
Education, mean ± sd (years)	9.27±3.96	10.14±3.56	13.43±3.08	H=16.99, p<0.001*
Age of onset	25.15±7.89	26.50±8.06		z=0.633, p=0.527
Hospitalization	3.23±3.17	3.71±4.21		z=0.623, p=0.533
Duration of disorder (years)	15.65±10.30	13.89±9.63		z=-0.667, p=0.505
Psychotic episodes	3.58±2.98	4.61±4.21		z=1.098, p=0.272

DS, deficit syndrome.
*p<0.001

Table 2. Comparison of the mean positive and negative syndrome scale scores of the patients with and without deficit syndrome

	DS (+) (n=26)		DS (-) (n=28)			
	Mean	**sd**	**Mean**	**sd**	**z**	**p**
PANSS						
Total	73.35	15.69	49.25	20.26	-4.407	<0.001**
Positive	8.58	1.86	11.71	5.73	2.013	0.044*
Negative	27.58	5.11	11.93	4.67	-6.069	<0.001**
General psychopathology	37.00	12.10	25.61	11.64	-3.540	<0.001**
Anxiety	1.38	0.75	2.07	1.12	2.746	0.046*
Depression	2.38	1.30	1.61	0.88	-2.356	0.018*
Motor retardation	3.96	1.34	1.57	0 79	-5.215	<0.001**
Uncooperativeness	2.85	1.76	1.36	0.62	-3.087	0.002*
Disorientation	1.69	1.35	1.11	0 42	-2.014	0.044*
Poor attention	2.85	1.35	1.46	0.84	-3.839	<0.001**
Lack of judgment and insight	3.12	1.63	1.61	0.96	-3.515	<0.001**
Disturbance of volition	2.88	1.56	1.64	0.99	-3.000	0.003*
Active social avoidance	4.00	1.41	1.64	0.91	-5.176	<0.001**

DS, deficit syndrome; PANSS, positive and negative syndrome scale; sd, standard deviation.
*p<0.05, **p<0.001

PANSS total, PANSS negative subscale, and PANSS general psychopathology mean subscale scores were significantly higher in the DS group (z=-4.407, p<0.001; z=-6.069, p<0.001; z=-3.540, p<0.001 respectively). The mean scores of the PANSS positive subscale was significantly higher in the non-DS group (z=2.013, p=0.044). In general psychopathology subscales; depression, motor retardation, uncooperativeness, disorientation, poor attention, lack of judgment and insight, disturbance of volition, and active social avoidance mean scores were significantly higher in the DS group (Table 2).

The IL-17 levels of DS patients were significantly higher than those of non-DS patients (H=6.468, p=0.034). TGF-β values for DS and non-DS patient groups were significantly higher than those of the controls (H=52.898, p<0.001). Furthermore, the TGF-β levels of the DS group were significantly lower than those of non-DS patients (H=52.898, p=0.003). Multiple comparisons and post hoc test (Bonferroni) were performed and the results did not vary (For IL 17 F=4.050, p=0.021; for TGF β F=73.877, p<0.001). IL-1β levels were below measurable values in all three groups (Table 3).

Table 3. Comparison of the mean pro-/anti-inflammatory cytokine levels in the patients with and without deficit syndrome and controls

Cytokine (pg/mL)	**DS (+) (mean ± sd)**	**DS (-) (mean ± sd)**	**Control (mean ± sd)**	**Kruskal-Wallis Test**	**Pairwise Comparison**
TNF-α	31.28±21.96	25.00±0.00	25.67±3.54	H=4.014 p=0.134	
IFN-γ	12.78±4.63	17.79±19.81	13.18±5.32	H=1.413 p=0.493	
IL-12	172.36±167.53	162.14±254.18	125.77±145.64	H=0.482 p=0.786	
IL-17	6.67±5.70	3.86±2.82	4.29±2.50	H=6.468 p=0.039	DS (+) – Control p=0.841 DS (-) – Control p=0.419 DS (+) – DS (-) p=0.034*
IL-10	10.00±0.00	10.00±0.00	10.21±1.09	H=1.929 p=0.381	
IFN-α	329.73±128.11	331.46±113.99	472.48±503.51	H=1.753 p=0.416	
TGF-β	819.57±358.34	1102.52±79.53	198.32±333.92	H=52.898 p<0.001	DS (+)– Control p<0.001** DS (-)– Control p<0.001** DS (+)– DS (-) p=0.003*

DS, deficit syndrome; sd, standard deviation.
*p<0.05, **p<0.001

Table 4. Comparison of the mean total antioxidant capacity and paraoxonase-1 levels in the patients with and without deficit syndrome and controls

	DS (+) (mean ± sd)	**DS (-) (mean ± sd)**	**Control (mean ± sd)**	**Kruskal-Wallis Test**	**Pairwise Comparison**
PON-1 (ng/mL)	98.22±39.00	99.67±85.88	208.52±160.30	H=15.003 P=0.01	DS (+)– Control p=0.041* DS (-)– Control p<0.001** DS (+)– DS (-) p=0.606
TAOC (U/mL)	4.80±6.08	6.17±4.30	19.51±21.22	H=18.959 P=0.001	DS (+)– Control p<0.001** DS (-)– Control p=0.049* DS (+)– DS (-) p=0.142

DS, deficit syndrome; PON-1, paraoxonase-1; TAOC, total antioxidant capacity; sd, standard deviation.
*p<0.05, **p<0.001

PON1 and TAOC values for DS and non-DS groups were significantly lower than those of the controls (H=15.003, p<0.001 and H=18.959, p<0.001) (Table 4).

A significant correlation was not found between cytokines and the antioxidant status parameters.

DISCUSSION

DS is continuous, independent of such secondary factors as depression, medication, paranoia and characterized by predominant primary negative symptoms. We found more severe negative and general psychopathology symptoms in DS group. The severity of general psychopathology was associated with depression, motor retardation, uncooperativeness, disorientation, poor attention, lack of judgment and insight, disturbance of volition, and active social avoidance. Active social avoidance, depression, motor retardation, poor attention and lack of judgment and insight may be associated with DS. However, SDS is used to identify DS based on evaluation of clinical status during the previous year. Additionally, PANSS is ordinarily used to assess the clinical status of patients to evaluate treatment follow-up and it is more cross-sectional than the SDS. Although we think it is difficult to distinguish the DS, we may assume that we evaluated this distinction in our study.

Recent evidence increasingly supports the hypothesis that immune-inflammatory pathways are involved in the pathophysiology of schizophrenia. However, the results of studies conflict with each other. Increased levels of IL-1RA, sIL-2R, and IL-6, together with decreased levels of IL-2, were reported in schizophrenia (20). IL-1β, IL-6, and TGF-β are qualified as state markers for acute exacerbations, while IL-12, IFN-γ, TNF-α, and sIL-2R are qualified as trait markers for schizophrenia (21).

IL-6 and CRP levels were found to be higher in patients with DS than non-DS and the authors of this study claimed that this result provides further evidence for the validity of the deficit/nondeficit categorization (22). Goldsmith et al. found association between TNF α, IL-6 and DS, and reported that DS is associated with increased inflammation (23). We found higher levels of the pro-inflammatory cytokine IL-17 in patients with DS than non-DS and higher levels of the anti-inflammatory cytokine TGF-β in both patient groups than in the control group. Elevation of TGF-β may indicate an increase in anti-inflammatory activity to balance the inflammatory activity that is known to increase in schizophrenia. However, there is growing evidence that Th17 pathway and IL23/IL17 axis may fill the gap about inflammation– autoimmunity theory of schizophrenia (24). Nevertheless, studies investigating levels of IL-17 are conflicting. Increased levels of IL-17 (25), and decreased levels of IL-17 in drug naïve, first episode schizophrenia patients were reported (26). There was not a categorization as DS/non-DS in these studies and this may have influenced the findings. Hence, increased levels of IL-17 may be related with DS as IL-6. However, it is still unclear whether the differences in cytokine levels detected in schizophrenia are the result of the disorder or due to the etiology.

We found PON1 and TAOC levels lower in both patient groups than in the control group. Although they were also lower in DS group than non-DS group, the difference was not statistically significant. There is increasing evidence that OS exists in schizophrenia (8, 9, 27). In two studies, serum PON1 levels were found to be lower in schizophrenia patients who had been treated with antipsychotics than they were in control groups (28, 29). In a recent study, serum PON1 levels were also found to be low in schizophrenia patients who had not been medicated (30). Our findings support the hypothesis that schizophrenia involves an impairment in the antioxidant defense system. It has been reported that the level of PON1 is negatively correlated with the levels of the inflammatory cytokines IL-6, IL-4 and IL-10 in schizophrenia (30). We did not find a significant correlation between cytokines and the antioxidant status parameters in our study. The patients were under antipsychotic medication and this might affect the correlation between pro-/anti-inflammatory cytokines and antioxidant concentrations.

To our knowledge, this is the first study to evaluate the markers of inflammation and OS together in DS, but it has some potential limitations to consider. First, this is a cross-sectional study. Second, we had no data on the metabolic syndrome or body mass index in most of the patients, so analysis of possible associations was not possible. Third, the study included a naturalistic sample of patients using antipsychotic treatment, although all patients received antipsychotic treatment, the majority being medicated with antipsychotics with similar mechanisms of action. Finally, although the participants did not use tobacco during the 12-hour period before the samples were taken, tobacco use disorder might contribute to lower serum PON1 and TAOC activity and higher levels of cytokines.

CONCLUSION

Our study suggests that immune-inflammatory pathways are involved in the pathophysiology of schizophrenia. Increased levels of IL 17 from pro-inflammatory cytokines may be releated with DS. Our findings may support the DS/non-DS categorization in schizophrenia. The findings in our study would be greatly strengthened if they could be replicated in larger samples. Future studies evaluating Th17 pathway and IL23/IL17 axis will make an important contribution to immune-inflammatory pathophysiology of schizophrenia.

Ethics Committee Approval: The study protocol was approved by the Clinical Trials Ethics Committee of Eskişehir Osmangazi University.

Informed Consent: All participants gave written informed consent prior to participation.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - FK, AE, GG, SY; Design - FK, AE, GG, SY; Supervision - FK, RDK, SSD, SY; Resource - FK, RDK, SSD, SY; Materials - FK, RDK, SSD, SY; Data Collection and/ or Processing - FK, RDK, SSD, SY; Analysis and/or Interpretation - FK, AE, GG, SY; Literature Search - FK, AE, SY, SSD, RDK; Writing - FK, AE, GG, SY, SSD, RDK; Critical Reviews - FK, AE, GG, SY, SSD, RDK.

Conflict of Interest: The authors have no competing interests to report.

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