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Serum PGE2, 15d-PGJ, PPARγ and CRP levels in patients with schizophrenia

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ABSTRACT

Many hypotheses have been proposed for the development of schizophrenia, including the one proposing that exogenous and endogenous factors are linked to inflammatory processes. There is strong evidence about the immunological and inflammatory dysfunction in schizophrenia. In this study, we aimed to measure serum 15-deoxy-delta(12,14)-prostaglandin J (15d-PGJ), peroxisome proliferator-activated receptor gamma(PPARγ), prostaglandin E2 (PGE2) and C-reactive protein (CRP) levels. Forty-four patients and 39 healthy volunteers were included in the study. Serum PGE2, 15d-PGJ, PPARγ and CRP levels were measured in both the groups. Demographic data forms were filled out for the patient group, and the Positive and Negative Syndrome Scale, Clinical Global Impression-Severity scale and Calgary Depression scale were used to assess patients' clinical status. Serum PGE2, 15d-PGJ and PPARγ levels were found to be significantly lower in patients with schizophrenia than in healthy controls. There was no significant relationship between the serum PGE2, 15d-PGJ and PPARγ levels and CRP levels.In this study, the evidence of systemic inflammatory conditions in patients with schizophrenia was found. The duration of the disease has been found to be the only variable that independently affects all three biomarker levels in the patients with schizophrenia.

1. Introduction

Schizoprenia is a severe, chronic and debilitating psychiatric disorder characterised by delusions, hallucinations, apathy, cognitive deficits and social withdrawal. Despite genetic, environmental, immunological and biochemical research, the etiology of schizophrenia remains to be elucidated (Tandon et al., 2008; Misiak et al., 2018).

Many hypotheses have been proposed, including the one proposing the involvement of inflammatory processes, which develop due to exogenous and endogenous factors (Lucas et al., 2006; García-Bueno et al., 2014; Miller et al., 2011). Schizophrenia has been described to be associated with chronic inflammation in the central nervous system (Anderson et al., 2013). Epidemiological studies that suggest association between infection and systemic inflammation supported the possible link between schizophrenia and immune system (Brown and Derkits, 2009; Khandaker et al., 2012, 2013).

Besides, the presence of systemic inflammation has been associated with poor functioning in patients with first-episode psychosis and schizophrenia (González-Blanco et al., 2018, 2019). The role of the immune system on cognition has also been studied on immune mediated demantia, and positive results of immune therapies have been reported (Chandra et al., 2019).

Researchers evaluated various molecules to investigate the role of inflammation in etiology and course of schizophrenia and one of them was C reactive protein(CRP). CRP is a commonly used low-grade inflammatory marker that has been studied in many disorders, including schizophrenia (Dickerson et al., 2007). Elevated serum CRP levels have been found in patients with schizophrenia (Miller et al., 2013) and are associated with a severe psychopathology (Fan et al., 2007a, b) and cognitive impairment (Dickerson et al., 2007).

Increased proinflammatory cytokine levels; decreased anti-inflammatory cytokine and interleukin-1 receptor antagonist levels; increased inflammatory mediator, like prostaglandin E2 (PGE2), levels (Kaiya et al., 1989); increased cyclooxygenase-2 activity and up-regulation of inflammation-related genes (Das and Khan, 1998; Saetre et al., 2007) have been reported in patients with schizophrenia (Arolt et al., 2000; Lewis and Gonzalez-Burgos, 2006). A possible association suggested between first-onset postpartum psychosis and

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proinflammatory cytokine IL-8 (Sathyanarayanan et al., 2019).

Besides other cytokines and molecules, the peroxisome proliferator-activated receptors (PPARs) have attracted much attention for their roles in inflammation and neuropsychiatric disaeses. PPARS are a group of nuclear receptor proteins involved in the regulation of transcription factors that regulate gene expression (Gervois et al., 2007). They play an important role in the regulation of cell differentiation and growth; carbohydrate, lipid and protein metabolism and tumorigenesis (Bensinger and Tontonoz, 2008). PPARs have three subtypes: PPARα, β and γ. These subtypes exhibit structural and functional differences, but all of them are primarily involved inglucose–lipid metabolism and inflammation (Bensinger and Tontonoz, 2008; Rolland et al., 2013; Hamblin et al., 2009). Due to their pharmacological properties, PPARs have been frequently studied in cardiovascular diseases, which are closely related with the lipid anomalies and inflammatory processes (Hamblin et al., 2009). PPARα agonists (fenofibrates), PPARγ agonists (thiazolidinediones) and PPAR dual agonist (for example, saroglitazar) have been investigated in cardiovascular and metabolic pathologies. Besides, PPARs are considered to play therapeutic roles in psychiatric disorders by reducing inflammation, modulating neurotransmitters and regulating metabolism (Benson et al., 2004; Erzin et al., 2018).

PPARs are expressed in the brain in large amounts (Cimini et al., 2005; Cristiano et al., 2005). Available data support the hypothesis that PPARs affect the direct regulation of neuronal proteins, which play a role in the diffusion of synaptic transmissions and nerve signals (Gervois et al., 2007). Therefore, modulation of PPARs may be affected by a particular neurotransmitter system in the brain. Thus, we suggest that the use of different PPAR agonists in specific pathologies may constitute a direct symptomatic treatment (Gervois et al., 2007).

The aim of this study was to evaluate the PPARγ levels, in patients with schizophrenia. The reason for choosing PPARγ in our study, among the other PPARs, is that quite a lot of studies have been conducted recently on the cognitive effects of PPARγ agonists and it is the most mentioned receptor among the three PPARs concerned with cognition and the brain.

In literature, there is limited data on PPARγ and schizophrenia. Martínez–Gras et al. have reported a significant decrease in15-deoxy-delta(12,14)-prostaglandin J(15d-PGJ2) and its nuclear receptor PPARγ levels in patients undergoing treatment for chronic schizophrenia (Martínez-Gras et al., 2011). With inspiration from their research, we aimed to investigate the same three biomarkers (15-PGJ2, PPARγ and PGE2) in another sample of patients with schizophrenia that included patients with acute exacerbation to consolidate the data. 15d-PGJ2, proinflammatory PGE2 and CRP were chosen to determine a possible systemic inflammatory condition.

In summary, the aim of this research is to evaluate the aforementioned markers to contribute to the understanding of the etiology and pathophysiology of schizophrenia from the perspective of inflammation.

2. Materials and methods

2.1. Sample

In total, 60 consecutive patients who were admitted to the Ankara Numune Training and Research Hospital, Psychiatric Clinic, between October 2014 and February 2015 due to exacerbation of schizophrenia were invited to study and 44 patients who met study criteria included in the study. Forty-six volunteers who had no known psychiatric or neurological disease were included in this study as healthy controls. The criteria for inclusion were 18–65 years of age and the diagnosis of schizophrenia by clinical evaluation by at least two interviewers. The exclusion criteria were as follows: mental retardation, dementia, alcohol and drug dependency and the presence of other comorbid psychiatric or neurological disorders. Four different parameters evaluated in both patient and control groups, the sample size could not be increased due to the unfortunately subsequent financial resource constraint.

2.2. Methods

A sociodemographic data form was filled out by the clinician. The clinical status of the patients was assessed using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression-Severity scale (CGI-S), and the Calgary Depression Scale for Schizophrenia (CDSS). For blood examination, 5 mL of peripheral venous blood was collected from the patients. All of the patients were drug-free (antipsychotics and other drugs) at the time of sample collection. The routine biochemistry, lipid, CRP and whole blood count results obtained from each patient admitted to the psychiatry clinic were recorded. The height and weight of the patients were measured.

2.3. Materials used in the study

2.3.1. Sociodemographic data form

A data form was used in the study to obtain details on age, sex, marital status, educational level, duration of the treatment, any ongoing treatment, known medical conditions, presence of medical or psychiatric anamnesis in the family and presence of tobacco, alcohol or substance use.

2.3.2. PANSS

This is a semi-structured interview scale developed by Kay et al. (1987). It comprises positive symptoms, negative symptoms and the general psychopathology sub-scales.

2.3.3. CDSS

This scale has been developed by Addington et al. (1993) for the evaluation of depression in patients with schizophrenia and the measurement of the level and severity of depressive symptoms. We used the Turkish form of CDSS that is shown to be valid and reliable to exclude patients with depression because depression may affect the biochemical conditions (Aydemir et al., 2000).

2.3.4. Clinical global impression-severity scale

This scale comprises three items: ‘Severity of the disease’, ‘Improvement’ and ‘Severity of side effects’. Only the first item was used in our study.

2.4. Biochemistry evaluation

All serum samples were obtained from the antecubital vein; the blood sample were centrifuged at the end of the clotting time (30–60 min) in a horizontal rotor (swing-out head) for 20 min at 1100–1300 g at room temperature and placed in Eppendorf tubes at 80 °C till the analysis.

After sample collection, an enzyme-linked immunosorbent assay was used to measure serum PPARγ, 15d-PGJ2 and PGE2 levels on the Biotek Synergy device using Boster (USA, EKO985), Human PPARγ (Sunred, lot no.: 201506, ref no.: DZE201124528), Human 15d-PGJ2 (Sunred, lot no.: 201506, ref no.: DZE201125622) and Human PGE2 (Sunred, lot no.: 201506, ref no.: DZE201125292) kits.

2.5. Statistical analysis

Data analysis was performed via the SPSS for Windows 11.5 software package. The distribution of continuous and discrete numerical variables was evaluated using Kolmogorov–Smirnov test to determine whether the distribution was normal. Descriptive statistics were shown as mean ± standard deviation or as median (minimum–maximum) for continuous or discrete numerical variables and as the number of cases (%) for nominal variables.

The significance of the differences in the mean values among the groups was investigated via the Student's t-test; whereas, the significance in the median values was investigated with the Mann–Whitney *U* test The nominal variables were evaluated with Person's Chi-Square or the likelihood-ratio test. The existence of a significant relationship between the continuous variables was investigated with the Spearman's correlation test.

Multiple linear regression analysis was used for the determination of the factor(s) that are the most determining in the prediction of the 15d-PGJ2, PGE2 and PPARγ levels, in the case group. All variables that were defined as $p < 0.15$, as a result of the single variable statistical analysis, were included in the multiple variable models as candidate factors. The regression coefficient of each variable was calculated with a 95% confidence interval and t-statistics. Since the 15d-PGJ2, PGE2 and PPARγ variables did not display any distribution close to the normal distribution, a logarithmic conversion was performed on the regression analysis.

Unless indicated otherwise, results were accepted as significant at $p < 0.05$. However, the Bonferroni correction was performed in order to control Type I errors in all probable multiple comparisons.

3. Results

There were no statistically significant differences between the control and the case groups in the mean ages ($p = 0.705$) and gender ($p = 0.651$).

The demographical and clinical characteristics of the case group are shown in Table1.

Serum 15d-PGJ2, PGE2 and PPARγ levels were significantly lower in patients with schizophrenia than in the healthy controls (Table 2).

No statistically significant correlation was observed between the lower and upper limits of alpha and beta rhythm frequency, the lower and upper levels of amplitudes and the PPARγ measurements within the control group ($p > 0.05$).

After the evaluation of the collective effects of all the risk factors, considered to be affecting the prediction of the changes in the 15d-PGJ2, PGE2 and PPARγ levels, via a multiple variable linear regression analysis following the single variable statistical analysis, it was determined that the duration of the disease was an independent risk factor affecting the prediction of the changes in the 15d-PGJ2 levels.

Table 1
The demographical and clinical characteristics of the case group.

Variables	n = 44
Occupational status	
Working	5 (11.4%)
Not working	39 (88.6%)
Marital status	
Married	19 (43.2%)
Single/Divorced	25 (56.8%)
Education period (years)	9 (0–16)
Additional diseases	10 (22.7%)
Duration of the disease (years)	5.5 (1–34)
Number of hospitalisations	2 (1–9)
Medication use	20 (45.5%)
Psychiatric diseases in the family	11 (25.0%)
Medical condition in the family	22 (50.0%)
CGIS	5 (4–7)
AIMS	0 (0–7)
CDSS	1 (0–7)
Smoking (packs/year)	20 (0–50)
Body mass index (kg/m^2)	26.6 ± 5.0
G TOTAL	42 (30–57)
P TOTAL	26.5 (10–44)
N TOTAL	20.5 (10–34)
PANSS TOTAL	88.5 (55–125)
CRP	3 (0–10)

CGIS: Clinical Global Impression-Severity Scale, AIMS: Abnormal Involuntary Movement Scale, CDSS: Calgary Depression Scale for Schizophrenia, G TOTAL: General Psychopatology Scale Total, P TOTAL: Positive Scale Total, N TOTAL: Negative Scale TOTAL, PANSS TOTAL: Positive and Negative Syndrome Scale, CRP: C-Reactive Protein.

Table 2
Biochemical measurements in the control and case groups.

Variables	Control group (n = 40)	Case group (n = 44)	p-value[a]
15d-PGJ2(ng/L)	36.4 (16.7–178.0)	26.9 (18.0–160.0)	**0.002**
PGE2 (ng/L)	183.3 (43.6–625.0)	105.8 (55.2–407.6)	< **0.001**
PPARγ (ng/mL)	126.7 (31.2–560.0)	88.2 (46.0–339.7)	< **0.001**

15d-PGJ2: 15-deoxy-delta (12,14)-prostaglandin J, PGE2: prostaglandin E2, PPARγ: peroxisome proliferator-activated receptor gamma.
[a] Mann–Whitney *U* test.

4. Discussion

Previous studies suggest that inflammation plays a role in the etiology of schizophrenia (Fan et al., 2007a, b; Kneeland and Fatemi, 2013).

A systemic imbalance has been reported in the plasma proinflammatory and anti-inflammatory prostaglandin levels in the patients with schizophrenia (Martínez-Gras et al., 2011). Endogenous mechanisms, which are activated as a response to inflammation or immune stimuli, are being investigated (Galea et al., 2003) and one of these mechanisms is the activation of the PPARs (Kapadia et al., 2008). PPARs are the main regulators of cerebral physiology and are potential therapeutic targets for neuropathological conditions (García-Bueno et al., 2008; Kapadia and Sakic, 2011).

The serum PGE2, 15d-PGJ2 and PPARγ levels in patients with schizophrenia, who consulted us with acute exacerbation, have been observed to be statistically significantly lower than in the healthy controls. While the observed low 15d-PGJ2 and PPARγ levels are consistent with the results of the studies in the literature (Feinstein, 2003),in our study, the PGE2 levels have been observed to be low as well, contrary to the study conducted by Martínez-Gras et al. (2011). Another study in the literature has also pointed out higher levels of proinflammatory PGE2 (Kaiya et al., 1989). Furthermore, an imbalance was observed in the products of the cyclooxygenase (COX) pathway in the patients with schizophrenia, and PGE2 levels were observed to be elevated in the patients with schizophrenia in a study published in 2008 by Muller and Schwarz (2008). It is considered that these mechanisms may be affected by many conditions such as the progression of the disease, the present condition of the disease and the present phase, as well as genetic factors. However, a clear explanation of these mechanisms is not possible. Our sample consisted of patients with schizophrenia in the acute exacerbation phase, and this may have affected the results of our study.

In addition, the significantly low levels of PPARγ levels, which is one of the main intracellular anti-inflammatory regulator, are supportive of the chronic inflammation hypothesis in schizophrenia (Saetre et al., 2007).

When the relationship of the measured PGE2, 15d-PGJ2 and PPARγ levels with variables such as the age, gender, marital status, occupational status, duration of the disease, medication use, CRP levels, presence or absence of additional diseases, PANSS total and sub-scale scores is considered, it can be inferred that the serum PGE2, 15d-PGJ2 and PPARγ levels are only affected by the duration of disease. As the duration of schizophrenia lengthens, the levels of the biomarkers decrease even further. If further analysis is conducted, it can be observed that the scores of the negative symptoms assessment scale (N total) and the working status affect the levels of the biomarkers as well; however, there still remains a statistically significant relationship between the duration of the diseases and the biomarker levels, even if the working

status and N total scores are fixed. The decrease in the prostaglandin levels, which prevent inflammation, may be a factor that affects the chronic and destructive nature of the disease. However, since our study is a cross-sectional case-control study, it is not possible to clearly identify whether the prostaglandin levels decreased during the chronic progress or whether the disease became chronic due to a systemic inflammation affecting the brain. In addition, levels of CRP, a low-grade inflammation marker, were not correlated with levels of PGE2, 15d-PGJ2 and PPARγ. Yüksel et al. (2018) found high levels of another inflammation marker, the neutrophil-lymphocyte ratio (NLR), in patients with schizophrenia and showed that there was no association between CRP and NLR. In the light of these results, we state that there are changes related to inflammation in schizophrenia, but the findings related to inflammation in schizophrenia are complex, different mechanisms.

In conclusion, the detection of biological markers for schizophrenia will be beneficial for the diagnosis and the monitoring of the disease as well as the individuals under risk, decreasing the probable morbidities.

Even though not sufficiently proven, under the light of the data in the literature and the results of our study, it can be inferred that pro and anti-inflammatory COX products such as 15d-PGJ2 and PGE2, as well as the nuclear PPARs are potential research fields for schizophrenia.

Contributions

Rabia Nazik Yüksel, Makbule Cigdem Aydemir and Erol Göka designed the study and wrote the protocol. Turan Turhan, Cevdet Züngün and Kubranur Ünal contributed to biochemical data analysis. Gamze Erzin, Ayşe Pınar Titiz, Elif Tatlıdil Yaylacı and Rabia Nazik Yüksel wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding resource

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Declaration of Competing Interest

No potential conflict of interest was reported by the authors.

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