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The effect of antipsychotic drugs on nonspecific inflammation markers in the first episode of schizophrenia

Efekat antipsihotika na nespecifične markere inflamacije u prvoj epizodi shizofrenije

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Abstract

Background/Aim. Immune system disorder, including inflammation, takes a significant place when considering still unclear etiology of schizophrenia. The aim of this study was to determine the blood levels of nonspecific inflammation markers in the first episode of schizophrenia and their relation to the therapy response. **Methods.** In this study we determined the blood levels of nonspecific inflammation markers: white blood cells count (WBC), C-reactive protein (CRP), erythrocytes sedimentation rate (ESR) and the elements of differential white blood cell counts (or the leukocyte formula): granulocytes (Gra), lymphocytes (Lym) and monocytes (Mon), in the first episode of schizofrenia, in 78 patients hospitalized at the Clinic for Psychiatric Disorders "Dr Laza Lazarević" in Belgrade. The levels were measured at admission to the clinic, as well as after 4 weeks of antipsychotic treatment. The Positive and negative syndrome scale for schizophrenia (PANSS) was applied to measure the severity of psychopathology and response to the treatment. **Results.** During the first episode of schizophrenia, before initiation of antipsychotic treatment, the frequency of abnormal values was high (≥ 25% of the patients) for the following non-specific inflammation markers: WBC, CRP, ESR and Gra, in the leukocyte formula, but dropped after 4 weeks of antipsychotic treatment at the level of high statistical significance for WBC and Gra ($p < 0.001$). The ESR remained unchanged in as many as 50% of the patients even after 4-week antipsychotic treatment, at the level of statistical significance in the non-responders compared to the responders ($p = 0.045$). **Conclusion.** The obtained results indicate that in the first episode of schizophrenia the blood levels of non-specific inflammation markers (WBS, CRP, ESR and Gra from the leukocyte formula) were high in the subpopulation of patients with the tendency towards normalization of inflammation parameters after a 4-week antipsychotic treatment.

Key words:
schizophrenia; antipsychotic agents; inflammation mediators; sensitivity and specificity; predictive value of tests.

Apstrakt

Uvod/Cilj. U razmatranju još uvek nepoznate etiologije shizofrenije, disfunkcija imunskog sistema koja uključuje i inflamaciju zauzima značajno mesto. Cilj našeg rada bio je da se odrede koncentracije nespecifičnih markera zapaljenja u krvi, u prvoj epizodi shizofrenije i njihova povezanost sa terapijskim odgovorom na antipsihotike. **Metode.** U radu smo određivali koncentracije nespecifičnih markera zapaljenja u krvi: leukocita (WBC), C-reaktivnog proteina (CRP), sedimentacije eritrocita (SE) i elemenata leukocitarne formule: granulocita (Gra), limfocita (Lym) i monocita (Mon), i to u prvoj epizodi šizofrenije, kod 78 hospitalizovanih bolesnika u Klinici za psihijatrijske bolesti „Dr Laza Lazarević" u Beogradu. Njihove koncentracije određivali smo pri prijemu i četiri sedmice nakon antipsihotičke terapije. Težinu psihopatologije i farmakoterapijski odgovor pratili smo primenom Skale pozitivnih i negativnih sindroma shizofrenije (Positive and negative syndrome scale for schizophrenia – PANSS). **Rezultati.** U prvoj epizodi shizofrenije, pre uvođenja antipsihotika, postojala je visoka učestalost abnormalnih laboratorijskih vrednosti (≥ 25% bolesnika) sledećih ne-

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specifičnih markera inflamacije: WBC, CRP i SE, kao i Gra u leukocitarnoj formuli, ali i smanjenje svih njih nakon četiri sedmice antipsihotičke terapije, na nivou visoke statističke značajnosti za WBC i Gra ($p < 0.001$). Sedimentacija eritrocita ostala je povećana kod čak 50% bolesnika i nakon 4-sedmičnog antipsihotičkog lečenja, na nivou statističke značajnosti kod onih koji nisu reagovali na terapiju u odnosu na one koji jesu ($p = 0.045$). **Zaključak.** Dobijeni rezultati pokazuju da u prvoj epizodi shizofrenije kod subpopulacije bolesnika postoje povećane vrednosti nespecifičnih markera inflamacije u krvi (WBC, CRP , SE i Gra iz leukocitarne formule), sa tendencijom njihove normalizacije nakon četiri sedmice antipsihotičkog tretmana.

Ključne reči:
shizofrenija; antipsihotici; zapaljenje, medijatori; osetljivost i specifičnost; testovi, prognostička vrednost.

Introduction

Schizophrenia is a heterogeneous disorder with still unclear etiology that affects about 1% of the world population. Numerous theories have been considering the possible causes of this devastating disease [1].

Recent researches related to neuroinflammation in schizophrenia give an increasing importance to prolonged microglial activation [2–4], when pro-inflammatory cytokines and free radicals lead to apoptosis of cortical neurons and oligodendrocytes as well as changes of the synaptic organization in the brain [5, 6].

Increased serum concentrations of various cytokines and their soluble receptors, as well as interleukin-6 (IL-6), soluble interleukin-6 receptor (sIL-6R), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-4 (IL-4), and tumor necrosis factor-alpha (TNF-α) were observed in schizophrenic patients [7].

The effect of antipsychotics in terms of reduction and normalization of various proinflammatory immune parameters is an important factor which contributes to the clinical efficacy in the treatment of psychotic symptoms [8–10].

Inflammation in schizophrenia is also associated with the increased production of prostaglandin E2, and the increased expression of cyclooxygenase-2 (COX-2), of which the inhibitors can have a significant role in the treatment of schizophrenia, particularly in the early stage of the disease [11].

There is growing evidence of significant effects of pro- and anti-inflammatory cytokines in the tryptophan/kynurenine metabolism when the increased production of kynurenine acid leads to glutamatergic hypofunction and consequent dopaminergic dysfunction in schizophrenia [12]. In the subpopulation of psychotic patients there is a high degree of comorbidity with chronic inflammatory and autoimmune disorders, which suggests a common immune disorder background [13].

The proteins and immunoglobulins of the acute phase are nonspecific markers of the immune system changes. Their levels may be affected by a variety of conditions, infection, inflammation and stress. As isolated parameters they cannot be directly linked to the development of schizophrenic psychoses but can be used as an additional parameter in explaining the role of specific immune subsystems.

The aim of our study was to establish the blood levels of nonspecific inflammation markers [white blood cells (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)] and the elements of the leukocyte formula) in patients with the first episode of schizophrenia, who up to then did not take antipsychotics (druge naive), as well as the effect of antipsychotic treatment after four weeks of treatment in correlation with clinical treatment response by implementing the Positive and negative syndrome scale for shizophrenia (PANSS).

Methods

The study included 78 patients hospitalized at the Clinic of Psychiatric Disorders “Dr. Laza Lazarevic” in Belgrade, during a 6-month period. At admission to the Clinic all subjects met the criteria of the International Classification of Diseases, 10th revision, for the first episode of schizophrenia (F 20). The patients signed the consent to participate in the study abiding by the principles of Good Clinical Practice and prior approval of the Ethics Committee of the Clinic. The study protocol was in compliance with the Declaration of Helsinki.

The inclusion criteria were the age between 18 and 45 years, both genders, and that the patients had not previously received antipsychotic drugs (drug naive).

The exclusion criteria were comorbidity with inflammatory, neurodegenerative, malignant diseases, congestive heart disease and infectious diseases, as well as patients who were identified as alcohol or psychoactive substance abusers.

The patients were divided into 3 groups depending on the applied antipsychotic therapy, the group I of patients treated with first-generation antipsychotics (FGAs), a total of 38 patients; the group II of 22 patients treated with second-generation antipsychotics (SGAs), and the group III of 18 patients treated with combined antipsychotic therapy (antipsychotic combination of the first and second generation antipsychotics).

The protocol procedures implied three planned visits. The following activities were conducted at admission: clinical psychiatric exploration that included a structured clinical interview in order to evaluate the diagnosis of schizophrenia according to the criteria of the International statistical classification of diseases and related health problems, 10th revision (ICD-10); application of the PANSS for the assessment and clinical monitoring of the disease course and pharmacotherapeutic response; as well as the physical examination including measuring of vital parameters (heart rate, arterial blood pressure, respiratory rate per minute, body temperature); venous blood sampling after a 12-hour overnight fast, between 8 and 8.30 a.m., prior to antipsychotic therapy (leukocytes, lymphocytes, monocytes, granulocytes, ESP, CRP) .

The attending psychiatrist prescribed antipsychotic treatment for the patients, pursuant to the Good Clinical Practice Guidelines.

The applied drug dosages were as follows: haloperidol – from 2 to 15 mg/pd (approximately 12.7 mg/pd at admission, average 8.8 g/day at dismissal), risperidone – from 2 to 6 mg/day (approximately 3.6 mg/day); olanzapine – from 2 to 20 mg/day (approximately 8.3 mg/day), and clozapine – from 25 to 125 mg/day (approximately 67.3 mg/day).

The patients were hospitalized during the entire treatment. All study procedures from the first visit (day 0), except for the already completed questionnaires, were also conducted after 30 days of hospital treatment, as well as at the final third visit. The second visit, two weeks after admission included clinical exploration.

The laboratory hematologic tests were carried out using a hematology analyzer ABX MICROS 60-OT (UK).

The primary obtained data were analyzed by the descriptive statistical methods and the application of the regression model. As for the descriptive statistical methods, the central tendency measures (arithmetic mean and median), the variability measures (standard deviation and variation interval) and the data structures expressed in percentages were applied. The methods for testing the difference of numerical data (scores on the PANSS scales, hematological and biochemical variables) included *t*-test and one-way analysis of variance. When conditions for the application of parametric statistical methods were not met we applied the Mann-Whitney test and the Kruskal-Wallis test. For testing the differences of categorical data (gender, education, marital status, treatment, and categorically transformed numeric data) Pearson's χ^2-test and Fisher's exact probability test were applied. The repeated measurements of continuous numeric data were analyzed using the repeated measures analysis of variance, and when appropriate conditions were not met, we applied the Wilcoxon test. Statistical hypotheses were tested at the level of significance of 0.05.

Results

This study included 45 (57.7%) female, and 33 (42.3%) male patients out of a total of 78.

The socio-demographic characteristics indicate that in relation to gender, there was a statistically significant difference between males and females with regard to education (p = 0.002) and employment (p = 0.028) (Table 1).

Table 1

Socio-demographic characteristics of the study participants

Characteristics	Male (n = 33)	Female (n = 45)	*p*
Age (years), n (%)	16 (49)	13 (29)	0.192
18–30	9 (27)	19 (42)	
31–40	8 (24)	13 (29)	
≥ 41			
Married, n (%)	4 (12)	10 (22)	0.251
Education, n (%)			0.002**
Elementary school	3 (9)	7 (16)	
High school	26 (79)	18 (40)	
University	4 (12)	20 (44)	
Employment, n (%)	5 (15)	17 (38)	0.028*
Heredity, n (%)	11 (33)	14 (31)	0.835
Method of hospitalisation, n (%)			0.085
voluntary	18 (55)	33 (73)	
forced	15 (45)	12 (27)	
Cigarete smoking, n (%)	15 (45)	19 (42)	0.776
DUP, n (%)			
up to 30 days	7 (21)	13 (29)	0.443
2–6 months	8 (24)	14 (31)	
> 6 months	18 (55)	18 (40)	

***p* < 0.05 ; ****p* < 0.01; DUP – duration of untreated psychosis.**

Figure 1 shows the percentage of abnormal laboratory values of nonspecific inflammation markers (WBC, Gra, Lym, Mon, ESR, CRP), at admission and after a 4-week antipsychotic treatment. In our study, abnormal values were defined as those higher than the reference range.

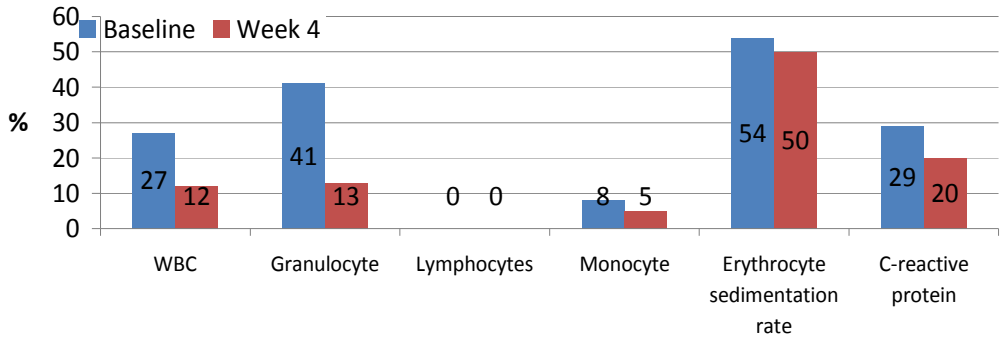

Fig. 1 – The percentage of patients with abnormal laboratory values of nonspecific inflammation markers at admission and after 4 weeks of antipsychotic treatment.

Note: abnormal is defined as levels of values higher than the reference range: white blood cells (WBC) – 3.5–10 × 10^9/L; granulocytes – 43.0–76.0%; lymphocytes – 17.0–78.0%; monocytes – 4.3–10.0%; erythrocyte sedimentation rate – 2–12 mm/h; C-reactive protein – 0–5 ng/L.

With regard to the observed values of PANSS scores (total and subscales: positive, negative and general psychopathology) and nonspecific markers of inflammation at the admission and after four weeks antipsychotic treatment, there was no statistical significance only when ESR and C-reactive protein were concerned (p = 0.970 and p = 0.359, respectively) (Table 2).

The responders had statistically less values at the PANSS total score and subscales compared to the non-responders after 4 weeks of antipsychotic treatment ($p < 0.001$), while there were no statistically significant differences in the therapy response among the antipsychotic therapy groups (p = 0.215) (Table 3).

The differences between the therapy responders and non-responders in relation to the nonspecific inflammation markers at admission and after 4 weeks of antipsychotic therapy showed a statistical significance with regard to ESR (p = 0.045) (Table 4).

Table 2

The values of positive and negative syndrome scale for schizophrenia (PANSS) scores and nonspecific markers of inflammation at admission and after 4 weeks of antipsychotic treatment (control visit)

Parameters	Baseline ($\bar{x}$ ± SD)	Control visit ($\bar{x}$ ± SD)	p
PANSS positive subscore	25.4 ± 5.7	12.2 ± 5.7	< 0.001**
PANSS negative subscore	21.8 ± 5.8	12.9 ± 6.3	< 0.001**
PANSS general psychopathology	52.9 ± 6.5	29.9 ± 11.5	< 0.001**
PANSS total score	100.1 ± 13.0	55.0 ± 21.8	< 0.001**
WBC ($\times 10^9$/L)	9.1 ± 3.1	7.8 ± 5.4	< 0.001**
Granulocytes (%)	72.3 ± 11.0	65.9 ± 9.1	< 0.001**
Lymphocytes (%)	22.5 ± 8.9	27.9 ± 7.7	< 0.001**
Monocytes (%)	5.2 ± 2.9	6.7 ± 4.4	0.001*
ESR (mm/h)	18.1 ± 16.2	17.9 ± 17.1	0.970
C-reactive protein (ng/L)	7.8 ± 20.9	3.7 ± 2.1	0.359

***p* < 0.01; ****p* < 0.001; WBC – white blood cells; ESR– erythrocyte sedimentation rate.**

Table 3

The differences between the therapy responders and non-responders in relation to the antipsychotic groups and positive and negative syndrome scale for schizophrenia (PANSS) scores at admission and after 4 weeks of antipsychotic treatment

Characteristics	Responders (n = 36)	Non-responders (n = 42)	p
Antipsychotic therapy, n (%)			0.215
first generation antipsychotics	14 (38)	24 (57)	
second generation antipsychotics	11 (31)	11 (26)	
antipsychotic combination	11 (31)	7 (17)	
Scores at baseline, $\bar{x}$ ± SD			
PANSS positive subscore	26.1± 5.3	24.8 ± 6.0	0.460
PANSS negative subscore	22.8± 4.9	20.9 ± 6.4	0.119
PANSS general psychopathology	53.4 ± 4.8	52.5 ± 7.7	0.845
PANSS total score	102.3 ± 10.8	98.2 ± 15.5	0.405
Scores at week 4, $\bar{x}$ ± SD			
PANSS positive subscore	8.6 ± 2.1	15.3 ± 6.1	< 0.001*
PANSS negative subscore	8.7 ± 3.0	16.4 ± 6.3	< 0.001*
PANSS general psychopathology	21.0 ± 4.9	37.6 ±10.0	< 0.001*
PANSS total score	38.4 ± 7.8	69.2 ± 19.7	< 0.001*

***p* < 0.001; Antipsychotic combination – combination of the first and second generation antipsychotics.**

Table 4

The differences between the therapy responders and non-responders in relation to nonspecific inflammation markers at admission and after 4 weeks of antipsychotic treatment

Characteristics	Responders (n = 36)	Non-responders (n = 42)	p
Values at baseline, $\bar{x}$ ± SD			
WBC ($\times 10^9$/L)	9.5 ± 3.6	8.7 ± 2.5	0.584
Granulocytes (%)	71.5 ± 11.4	72.8 ± 10.6	0.690
Lymphocytes (%)	23.1 ± 9.5	22.0 ± 8.3	0.902
Monocytes (%)	5.4 ± 2.9	5.1 ± 2.9	0.627
ESR (mm/h)	15.8 ± 15.4	20.0 ± 16.4	0.193
C-reactive protein (ng/L)	9.6 ± 27.9	5.8 ± 10.6	0.518
Values at week 4, $\bar{x}$ ± SD			
WBC ($\times 10^9$/L)	8.8 ± 7.6	6.9 ± 1.7	0.186
Granulocytes (%)	67.0 ± 10.2	64.8 ± 7.9	0.355
Lymphocytes (%)	27.0 ± 8.8	28.6 ± 6.6	0.387
Monocytes (%)	6.0 ± 2.2	7.4 ± 5.6	0.216
ESR (mm/h)	15.1 ± 15.6	20.8 ± 18.1	0.045*
C-reactive protein (ng/L)	3.5 ± 2.2	7.3 ± 20.3	0.161

***p* < 0.05 ; WBC – white blood cells; ESR – erythrocyte sedimentation rate.**

The combination of the first and second generation antipsychotics had weaker influence on nonspecific inflammation markers comparing to the first generation antipsychotics and second generation antipsychotics after a 4-week treatment, showing a statistical significance with regard to the value of WBC and lymphocytes, but no statistical significant changes in the blood concentrations of granulocytes and monocytes (Table 5).

Table 5

Effect of different groups of antipsychotics on nonspecific inflammation markers after four weeks of treatment

Antipsychotics	Baseline ($\bar{x} \pm SD$)	Control ($\bar{x} \pm SD$)	*p*
First generation antipsychotics			
WBC ($\times 10^9$/L)	9.1 ± 2.9	7.3 ± 2.1	0.001***
Granulocytes (%)	71.4 ± 11.6	66.8 ± 8.9	0.007**
Lymphocytes (%)	23.8 ± 9.9	27.1 ± 7.4	0.029*
Monocytes (%)	4.9 ± 2.3	6.0 ± 2.4	0.008**
ESR (mm/h)	19.3 ± 17.6	20.0 ± 18.2	0.579
C-reactive protein (ng/L)	6.7 ± 12.6	4.0 ± 2.5	0.872
Second generation antipsychotics			
WBC (x 10^9/L)	9.2 ± 3.3	8.7 ± 9.5	0.005**
Granulocytes (%)	72.9 ± 10.0	63.2 ± 8.4	0.001***
Lymphocytes (%)	21.± 8.0	29.6 ± 7.4	0.001**
Monocytes (%)	5.2 ± 2.8	8.8 ± 7.0	0.002**
ESR (mm/h)	20.2 ± 18.5	15.5 ± 16.9	0.133
C-Reactive protein (ng/L)	13.8 ± 35.1	3.5 ± 2.1	0.089
Antipsychotic combination			
WBC ($\times 10^9$/L)	9.0 ± 3.2	7.5 ± 2.1	0.050*
Granulocytes (%)	73.6 ± 11.7	67.2 ± 10.0	0.065
Lymphocytes (%)	20.5 ± 8.0	27.2 ± 8.7	0.025*
Monocytes (%)	5.,8 ± 4.1	5.5 ± 2.1	0.943
ESR (mm/h)	12.9 ± 6.8	16.1 ± 14.8	0.437
C-reactive protein (ng/L)	3.1 ± 2.4	3.4 ± 1.5	0.636

***p* < 0.05; ***p* < 0.01; ****p* < 0.001; WBC – white blood cells; ESR – erythrocyte sedimentation rate; Antipsychotic combination – combination of the first and second generation antipsychotics.**

due to antipsychotic therapy [16]. Prompted by many years of our clinical experience in work with psychotic patients and the numerous studies supporting the hypothesis that inflammation is involved in the etiopathogenesis of psychotic disorders [9, 15, 17], we came to the idea to do our study.

Having defined the blood levels of nonspecific inflammation markers (WBC with leukocyte formula, CRP, ESR) in patients with the first episode of schizophrenia before initiation of antipsychotic therapy, we discovered increased values of nonspecific inflammation markers in this subpopulation of patients (WBC in 27%, Gra in 41%, CRP in 29%, ESR in 54%, of patients). None of the patients had any subjective or objective indicators of acute infection syndrome, which was confirmed by internal examination. During a 4-week of hospital treatment no patient received antibiotic or anti-inflammatory therapy.

Discussion

In treatment of the first psychotic episode, the clinician's attention should be drawn to both the psychological and somatic symptoms as well as the laboratory parameters. Careful evaluation is especially important in the purpose of excluding many potential somatic and neurological causes of psychosis.

Research data indicate that the disorders of various body systems in schizophrenia (inflammation and immune processes, metabolic disorders, fatty acids metabolism, plasma antioxidants) do not have to be of secondary character, but may be an inherent part of schizophrenic disease itself [14]. Studies on antipsychotic-naive patients with first-episode psychosis find that inflammation is present already at this stage. Some of these abnormalities resolve after the initiation of treatment, suggesting that they are state markers of acute psychosis, but other abnormalities persist [15]. For this reason continuous monitoring of laboratory parameters is imposed as necessary already at the very beginning of the treatment, in order to clearly distinguish those abnormalities that are direct consequences of the disease itself from the disorders

Literature data related to research of nonspecific inflammation markers in schizophrenia are mainly focused on single inflammation markers.

WBC count is a well-established and widely used inflammatory marker [18]. Some studies support the fact that leukocytosis is found in patients with acute psychosis, and that under the antipsychotic therapy effect the number of leukocytes decrease [19, 20]. According to some authors higher white blood cell counts are associated with the increased risk for metabolic syndrome and more severe psychopathology (especially negative symptoms and symptoms of anxiety and depression, independent of age, gender, race, age of illness onset, smoking status and antipsychotic agent used [18, 21].

The results of one study indicate that a relative lymphopenia in the context of a relative granulocytosis appe-

ars to mark familial vulnerability for schizophrenia [20]. Recent researches indicate that the absolute levels of total lymphocytes were significantly increased in drug-naive first-episode psychosis [22]. Increased blood monocytes have been reported in schizophrenia [13, 23], and another study on intraindividual changes in blood monocyte levels found an association between monocytosis and worsening of psychotic symptoms [24]. The results of our study have shown a statistically significant decrease in WBC and Gra values after four weeks of antipsychotic treatment. In our study, however, monocytosis was present in only 8% of the patients at admission in the acute phase of the disease, while all patients had the lymphocyte counts within the reference laboratory range, which is not in compliance with the literature data.

C-reactive protein as acute phase protein is well-known as a nonspecific inflammation marker. Some recent studies have proved CRP increase in patients with schizophrenia [25, 26]. While according to some authors the elevated serum levels of C-reactive protein in schizophrenia are associated with the severity of cognitive impairment but not of psychiatric symptoms measured by the PANSS scale [27], the results of other authors indicate that elevated serum levels of CRP are associated with higher total scores on the PANSS, as well as higher scores on the Negative symptom subscale and the General psychopathology subscale of the PANSS [28]. A large number of studies have also confirmed the significant connection of increased CRP and some metabolic syndrome components (body mass index, HDL cholesterol) in schizophrenic patients [26]. Our study proved that 29% of the patients had increased CRP at admission, while CRP remained increased in 20% of the patients after four weeks of antipsychotic treatment.

Erythrocyte sedimentation rate is used as an indirect measure of the concentration of acute phase proteins [29]. One study revealed ESR increase in 17% of the patients with acute psychosis which decreased to normal values after eight weeks of antipsychotic treatment in 2/3 of those patients, with the reduction of psychopathological manifestations [30]. According to the claims of those authors, possibly those who had a high ESR, without a known physical illness, represent a subgroup of schizophrenia, thus ESR might possibly serve as a biological indication of the remission and relapse of the disease [30]. Waist circumference as a clinical measure of abdominal obesity, is reported to be significantly associated with an increased ESR. According to these authors there is also a strong correlation between systolic and diastolic and increased erythrocyte sedimentation which might potentially have everyday clinic significance by highlighting the correlation between blood pressure and intensity of inflammatory processes, which can be found in the background of metabolic syndrome development in patients suffering from schizophrenia [29].

Our study proved a high erythrocyte sedimentation rate in even 50% patients after a 4-week of antipsychotic treatment, that decreased only after applying the second generation antipsychotics. Whether ESR is a possible biological marker of early response to treatment, or is it a potential predictive marker of relapse in chronic patients, remains an issue for further prospective research in this direction.

The underlying mechanisms relating inflammation as reflected by elevated levels of WBC and CRP to schizophrenia are not well understood [21]. Also, there is no clear understanding as to how inflammatory-related pathways can precipitate the onset of psychiatric symptoms [31].

According to literature data, schizophrenic patients with high levels of inflammatory markers should be carefully monitored for metabolic syndrome. It dominantly prevails in schizophrenic patients and is correlated with low level chronic inflammation [26]. Monitoring for metabolic changes may be important within the first eight weeks of treatment, as changes can be determined very early in antipsychotic treatment [32]. Moreover, strategies to reduce inflammation may prevent metabolic syndrome in patients with schizophrenia who take atypical antipsychotic medication [18]. Early detection and consequent prevention of the metabolic syndrome is aimed to decrease diabetes and cardiovascular diseases risk that are the leading cause of mortality in schizophrenic patients [16].

In addition, it has been suggested that antidepressants, mood stabilizers and antipsychotic drugs act on inflammation-related pathways and therefore measuring levels of inflammation-related proteins in blood may be useful in monitoring treatment responsiveness [31]. Hence, we came to the idea that measuring levels of blood non-specific inflammation markers before and after antipsychotic treatment might be useful for measuring responsiveness to drug treatment.

Clinically significant response to therapy implies at least 50% reduction of the PANSS score [33]. According to this criterion, the results of our study show that there were 36 responders, or 46% patients, and 42 non-responders or 54% patients. They are in compliance with data from the literature which indicate that 40–50% patients have no optimum therapy response to antipsychotics [34]. Observing the nonspecific inflammation markers in correlation to the therapy response by implementing the PANSS scale, our results show that only the erythrocyte sedimentation values were statistically significantly higher in the non-responders compared to the responders.

Several studies have investigated the effects of antipsychotics on inflammation. Given the association between inflammation and schizophrenia, antipsychotics would be expected to have an anti-inflammatory effect. However, the anti-inflammatory effects of antipsychotics vary based on whether the antipsychotic is typical or atypical [35]. To date, there have been conflicting reports regarding the effects of antipsychotics on cytokine levels, and no antipsychotic has been shown to have consistent anti-inflammatory action [36].

The literature has largely ignored possible direct (not explained by metabolic syndrome) effects of antipsychotics on CRP and other inflammatory markers [37]. According to the results of our study, after 4 weeks of antipsychotic treatment there was a decrease of blood levels of non-specific inflammation markers (WBC, Gra, ESR, CRP), but the different antipsychotic therapy groups had different effects on

certain non-specific inflammation markers. Variable blood levels of nonspecific inflammation markers after antipsychotic treatment could possibly explain their still undefined mechanism of action in schizophrenia.

Lately, several trials have been conducted investigating the potential of anti-inflammatory agents to improve symptoms of schizophrenia [17, 15]. With regard to their usage and efficacy in adjuvant antipsychotic therapy in schizophrenia, the literature in this field is fraught with significant heterogeneity, including contradictory findings. Some of them claim that the results of aspirin addition to antipsychotic treatment seem promising, provided information on the efficacy on symptom severity [17], while the results of the other study indicate that adjunctive nonsteroidal anti-inflammatory drugs (NSAIDs) for schizophrenia may not benefit patients treated with first-line antipsychotics judged by the PANSS total score change. However, due to a limited database, further controlled studies are needed, especially in first-episode patients [38].

The limitations of our study relate to the relatively short follow-up period and assessment of a limited number of nonspecific inflammation markers, as well as the lack of personal experience related to the anti-inflammatory therapy application in the purpose of antipsychotic therapy augmentation.

Conclusion

The results of our study show that there is a subpopulation of patients in first-episode schizophrenia with increased values of nonspecific inflammation markers (WBC, CRP, ESR), tending to their normalization after 4-weeks of antipsychotic treatment.

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