Serum Interleukin-6 in Schizophrenia: Associations with Clinical and Sociodemographic Characteristics

Интерлейкин-6 сыворотки при шизофрении: ассоциация с клиническими и социодемографическими характеристиками

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Original Research

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ABSTRACT

BACKGROUND: Recently a significant part of schizophrenia studies have been focused on the role of cytokines, especially interleukin-6 (IL-6). Some authors have suggested a pathogenetic role for IL-6 in schizophrenia and concluded that therapy that centers on suppressing IL-6 activity may prove beneficial for certain categories of patients with the disorder. However, many questions about whether the changes in IL-6 levels in schizophrenia are primary, related to symptoms or caused by therapy, are concomitant metabolic disorders, are related to smoking or other secondary factors remain unanswered.

AIM: To assess the level of serum IL-6 in patients with schizophrenia in comparison with healthy controls, as well as to study its association with clinical and socio-demographic characteristics.

METHODS: Some 125 patients with schizophrenia and 95 healthy volunteers were examined. The evaluation of IL-6 was performed by enzyme immunoassay. All patients were assessed using standardized psychometric instruments. Information from patient medical records on the course of the disease and treatment was analyzed.

RESULTS: The level of IL-6 was significantly higher in the patients than in the healthy volunteers (z=2.58; p=0.0099), but among men the difference between the patients and volunteers was not significant. Statistically significant correlations were found between the level of serum IL-6 and the severity of the cognitive impairment of patients: (auditory [ρ=–0.31; p=0.00063] and working memory [ρ=−0.25; p=0.0065], hand-eye coordination [ρ=−0.29; p=0.0011], verbal fluency [ρ=−0.28; p=0.0019] and problem-solving capacity [ρ=−0.22; p=0.013]), total severity of schizophrenia symptoms (PANSS, ρ=0.22; p=0.016), PANSS positive subscale (ρ=0.18; p=0.048), and the age of manifestation (ρ=0.20; p=0.025) and disease duration (ρ=0.18; p=0.043). The level of IL-6 was the lowest in patients treated with third-generation antipsychotics, and the highest in those treated with a first-generation antipsychotics (H=6.36; p=0.042). Moreover, in hospital patients, the level of IL-6 was significantly higher than in outpatients and inpatients hospitals (H=18.59; p=0.0001).

CONCLUSION: The study confirmed that there there are associations between the serum IL-6 level and schizophrenia, the age of the patient, duration of the disease and how late in one's life cycle it began manisfesting itself, as well as a number of clinical characteristics. Considering that IL-6 is associated with a wide range of symptoms that are loosely controlled by antipsychotics, this biochemical marker needs to be studied to look into how closely its level tracks with an unfavorable course of schizophrenia. That would require further prospective studies.

АННОТАЦИЯ

ВВЕДЕНИЕ: В настоящее время при изучении шизофрении большое внимание уделяется роли различных цитокинов, при этом наиболее часто упоминаются изменения уровня интерлейкина-6 (IL-6). Некоторые авторы выдвигали предположения о патогенетической роли IL-6 при шизофрении и целесообразности терапии, направленной на подавление активности IL-6, у определенных категорий пациентов с этим расстройством. Однако до сих пор остается много вопросов о том, являются ли изменения уровня IL-6 при шизофрении первичными, связанными с симптомами, или вызваны терапией, сопутствующими метаболическими нарушениями, курением и другими вторичными факторами.

ЦЕЛЬ: Оценить уровень сывороточного IL-6 у больных шизофренией по сравнению со здоровым контролем, а также изучить его связь с клиническими и социально-демографическими характеристиками.

МЕТОДЫ: Обследовано 125 пациентов с шизофренией и 95 здоровых добровольцев. Оценку IL-6 проводили иммуноферментным анализом. Все пациенты были обследованы с использованием стандартизированных психометрических инструментов. Проанализированы данные медицинских карт о течении заболевания и лечении.

РЕЗУЛЬТАТЫ: Уровень IL-6 был статистически значимо выше у пациентов, чем у здоровых добровольцев (z=2,58; *p*=0,0099), однако среди мужчин разница между пациентами и добровольцами была незначительна. Выявлены статистически значимые корреляции между уровнем сывороточного IL-6 и выраженностью когнитивных нарушений у пациентов: (слуховой [ρ=−0,31; *p*=0,00063] и рабочей памяти [ρ=−0,25; *p*=0,0065], зрительно-моторной координации [ρ=−0,29; *p*=0,0011], беглости речи [ρ=−0,28; *p*=0,0019] и проблемно-решающего поведения [ρ=−0,22; *p*=0,013]), общей тяжестью симптомов шизофрении (PANSS, ρ=0,22; *p*=0,016), подшкалой продуктивных синдромов PANSS (ρ=0,18; *p*=0,048), возрастом манифестации (ρ=0,20; *p*=0,025) и длительности заболевания (ρ=0,18; *p*=0,043). Уровень IL-6 был самым низким у пациентов, получавших антипсихотики 3 поколения, и самым высоким у получавших антипсихотики 1 поколения (H=6,36; *p*=0,042). При этом у пациентов круглосуточного стационара уровень IL-6 был статистически значимо выше, чем у амбулаторных и пациентов дневного стационара (H=18,59; *p*=0,0001).

ЗАКЛЮЧЕНИЕ: Исследование подтвердило ассоциацию уровня IL-6 сыворотки крови с шизофренией, возрастом больных, длительностью заболевания и его более поздним началом, а также рядом клинических характеристик. Учитывая, что IL-6 связан с широким спектром симптомов, плохо контролирующихся антипсихотиками, данный биохимический маркер нуждается в изучении на предмет ассоциации с неблагоприятным течением шизофрении, что требует дальнейших проспективных исследований.

Keywords: *interleukin-6; schizophrenia; cognitive symptoms*
Ключевые слова: *интерлейкин-6; шизофрения; когнитивные симптомы*

INTRODUCTION

Schizophrenia is classified as a chronic mental disorder with a multifactorial etiology, but our understanding of its pathology remains limited [1]. Schizophrenia leads to a decrease in one's ability to function socially and an increase in the likelihood of early disability [1]. The approaches currently used to treat the disease are not pathogenetic. Moreover, they are quite limited in their ability to help shed light on the areas of negative symptoms and cognitive impairment, which are largely responsible for both the

ability of the patient to function daily and to work. Given this the effort to identify the pathological mechanisms of schizophrenia and come up with new therapeutic strategies that can attack the symptoms remains highly relevant.

Currently, much of the attention in the study of the schizophrenia etiopathogenesis centers on the role of cytokines and the immunoinflammatory hypothesis [2]. Changes in the level of interleukin-6 (IL-6), one of the key regulators of inflammatory and immune processes, are the most often mentioned [3–7]. Some authors have suggested a pathogenetic role for IL-6 in schizophrenia and concluded that therapy aimed at suppressing IL-6 activity may be useful to certain categories of patients suffering from the disorder [3, 5].

IL-6 is produced by various types of immune cells and acts as a mediator in the chain of information transmission during the immunoinflammatory response [5]. The level of IL-6 in serum increases rapidly under stressful conditions and modulates immune system activity: hematopoiesis, migration of neutrophils, the synthesis of the C-reactive protein with other elements [5]. Moreover, IL-6 can assume both pro- and anti-inflammatory properties, depending on the context. As a neurotrophic factor, it plays a crucial role in the differentiation of oligodendrocytes and the regeneration of peripheral nerves [8], but under certain conditions it can trigger and mediate various pathological conditions [9]. Despite its active role in the acute inflammatory response, in the long term, this cytokine embodies regenerative and immunosuppressive properties aimed at fighting inflammation [5]. Excess or lack of IL-6 secretion can lead to a disruption of the ratios of certain immune cells (Th17 and Treg) and lead to autoimmune and chronic inflammatory diseases. The functional dichotomy of IL-6 is underlied by its ability to perform signal transmission both through the classical binding to specific cellular receptors and through an alternative pathway via intracellular signaling molecules [9]. There is a hypothesis holding that, under conditions of oxidative stress, the disruption of the lipid-protein balance of the IL-6 receptor is one of the reasons behind the switch in the signal transmission from a classical one to an alternative pathway, which is responsible for a furthering of the pathological process.

A meta-analysis of pro-inflammatory cytokine levels in patients with schizophrenia showed an increase in IL-6 levels, along with changes in a number of other immune-response markers [3]. Miller et al. (2011) in an evaluation of 40 studies in an extensive meta-analysis, found that the levels of IL-1β, IL-6, and TGF-β were increased in the acute phase of the disease (both in patients with a relapse of schizophrenia and in the first psychotic episode, FPE) and decreased with effective treatment [2]. The level of IL-6 correlated with the overall levels of psychopathology in two of the five studies where the severity of the symptoms was assessed [2]. Other authors later also demonstrated that IL-6 is associated with symptom severity in schizophrenia [10]. It has been hypothesized that IL-6 may be a state-dependent marker of inflammation that disappears with a fading of symptoms. But in the other 3 studies included in the meta-analysis by Miller et al. (2011) association between IL-6 and symptom severity was not confirmed [2]. The results by Borovcanin et al. (2012) also failed to confirm an increase in the level of IL-6 either during the FPE or during the relapse of schizophrenia [11]. Therefore, further study of the IL-6 role in schizophrenia is needed. Moreover, elevated levels of IL-6 have been found in subjects at high risk of psychosis. Therefore, according to the authors of that study, cytokine can be used as a marker in the prodromal period [12].

At the same time, several works have reported increased levels of IL-6 in chronic schizophrenia [13]. In some of those studies, the level of IL-6 in peripheral blood showed a significant positive correlation with the duration of schizophrenia [2, 8]. This prompted a hypothesis about the effect of the therapeutic process on the secretion of IL-6. But in the systematic review and meta-analysis of 14 studies by Upthegrove et al. (2014) [14], patients (n=570) who had not been previously treated with antipsychotics (APs) also showed increased IL-6 levels. At the same time, there is evidence of a decreased IL-6 level after therapy in patients with the first episode of schizophrenia [15]. Some researchers, after *in vitro* experiments, have suggested that cytokines (including IL-6) suppress the activity of microglia, which may partially accompany the effects of some APs [16], in particular clozapine, in schizophrenia [17–19]. Khandaker et al. (2014) reported levels of IL-6 (p=0.001) and IL-13 (p=0.004) that were significantly lower after AP treatment than before the treatment in patients [10]. A meta-analysis by Miller et al. (2011) also showed that the elevated level of IL-6 during an exacerbation of psychosis and untreated FPE returns to normal after AP treatment [2]. Finally, another recent meta-analysis confirmed the drop in peripheral IL-6 levels in response to AP treatment [20]. Thus, the idea that the level of IL-6

increases in schizophrenia due to AP treatment remains unconfirmed to date.

Some studies contend that IL-6 may mediate the risk of metabolic syndrome in patients with schizophrenia [6]. Dennison et al. (2012) showed that elevated levels of IL-6, in particular, and the "pro-inflammatory phenotype", in general, in schizophrenia are closely associated with a childhood traumatic experience [21].

A number of recent studies not related to schizophrenia have shown that smoking increases IL-6 levels [22, 23]. But in patients with schizophrenia, this association is unclear. Studies focused on the association between serum IL-6 and smoking have not been published yet, although many publications have suggested that the level of inflammatory cytokines may be associated with stress, smoking, and other lifestyle factors [5]. In a meta-analysis by Goldsmith et al. (2016) [13], where smoking was considered a confounding factor potentially affecting cytokine levels in schizophrenia, the authors concluded that, due to the large heterogeneity of the studies, it was premature to draw conclusions.

The hypotheses we set out to test in this work were as follows: the presence of an association between serum IL-6 levels and different types of schizophrenia symptoms and other clinical characteristics (time of onset, duration of the disorder, etc.); treatment characteristics (generation of APs, potency, and doses); the body mass index (BMI); as well as smoking, childhood trauma, and demographic factors (gender, age).

The aim of this work was to assess the levels of serum IL-6 in patients with schizophrenia in comparison with healthy controls, as well as to study its association with clinical and socio-demographic factors.

METHODS

Study design

This is cross-sectional observational study.

Ethical approval

The study was performed according to the principles of the Helsinki Declaration of the World Medical Association. All study participants provided a written informed consent for participation and data processing. The study protocol and the informed consent were approved by Local Ethics Committee No. 1 of the of the Privolzhsky Research Medical University (the protocol No. 15 of the meeting dated October 26, 2020).

Participants

Inclusion criteria were as follows: confirmed diagnosis of schizophrenia based on the Mini International Neuropsychiatric Interview for Diagnostic and Statistical Manual, Version 5 (M.I.N.I. for DSM-5). The shared inclusion criteria for both groups were as follows: no prior history of chronic somatic and neurological conditions associated with inflammation; voluntary consent to participate in the study; and no history of intake within a month before inclusion of any synthetic vitamins, anti-inflammatory drugs or antioxidants.

Exclusion criteria for the control group were as follows: a prior history of mental illness, having undergone psychiatric consultation during one's lifetime, as well as social maladjustment and substance abuse (except for nicotine). The exclusion criteria for the entire study cohort were a refusal to participate in the study; a history with a severe mental pathology accompanied by altered consciousness or a substance use disorder (except for nicotine use); severe unstable somatic conditions that could affect the study procedures; and chronic somatic diseases and neurological disorders associated with inflammation.

The average time elapsed from the first manifestation of schizophrenia was 93.4 (119.0) months (arithmetic mean and standard deviation, further m[σ]) and 34 (15; 155) months (median and interquartile range, further Me [Q1; Q3]). Overall, 39 patients were recruited from daycare departments; 70 — from the inpatient departments; and 16 — from the outpatient treatment program.

In total, 41 patients received first-generation APs; 51 — second-generation APs; 9 — third-generation APs; 22 — a combination of first- and second-generation APs; and 2 patients did not receive APs at the time of the evaluation.

Setting

For the purposes of the study, 125 patients with schizophrenia and 95 healthy volunteers were randomly selected. All participants were residents of the Nizhny Novgorod region (European Russia). The study participants were recruited from April 2019 to February 2022.

Variables and measurement

Venous blood was drawn in the morning hours, strictly after fasting, from the cubital vein. Serum was used for biochemical studies.

Quantitative determination of IL-6 was performed by ELISA based on a three-stage "sandwich version" using mono- and polyclonal antibodies to IL-6. At the first stage of our analysis, the studied samples were incubated with immobilized monoclonal antibodies. The resulting complex interacts with human IL-6 polyclonal antibodies with biotin. At the third stage, a conjugate with streptavidin was added. The amount of conjugate bound to streptavidin was determined by the intensity of the staining, which is proportional to the content of IL-6 in the sample. The optical density was measured spectrophotometrically at a wavelength of 450 nm, and the reference wavelength was 620 nm (Sunrise, Tecan spectrophotometer, Austria). The calculation of the concentration was performed on the basis of the calibration curve. Laboratory evaluation was performed in the AVK-Med Centralized Laboratory, Nizhny Novgorod, Russia.

Patients underwent a standardized examination with the Positive and Negative Syndrome Scale (PANSS [24]), Calgary Depression Rating Scale for Schizophrenia (CDRS [25]), Snaith-Hamilton Pleasure Scale (SHAPS [26]), Bush-Francis Catatonia Rating Scale (BFCRS [27]), and the Brief Assessment of Cognition in Schizophrenia (BACS [28]). The personal and social functioning level was also assessed using the Personal and Social Performance scale (PSP [29]). The evaluation of the treatment's side effects was performed using the UKU side effect rating scale (version of "The UKUSERS-Clin" [30]) and the extrapyramidal symptoms (EPS) — using a special section "The UKUSERS-Clin", as well as the Simpson-Angus scale (SAS [31]), the Abnormal Involuntary Movement Scale (AIMS [32]), and the Barnes Akathisia Rating Scale (BARS [33]). The Childhood Trauma Questionnaire (CTQ [34]) was used to assess early traumatic experience. Information about the treatment received, the time of disease onset, education, alcohol and nicotine use, and anthropometric data (including BMI) was gathered on the basis of patient self-reporting and the analysis of medical records.

Bias

The laboratory analysis was blind to the study group status and the results of the clinical evaluation of the patients. Patient evaluation was performed by 4 specially trained raters blind to the laboratory results.

Statistical methods

The statistical analysis was performed using Statistica 6.0. According to the Shapiro-Wilk normality test, the distribution of variables deviated from the normal. So nonparametric criteria were used in our statistical analysis: the Mann-Whitney U-test (MWU-test, Z) for comparison of 2 groups, and the Kruskal-Wallis test (H) for comparison of more than 2 groups. The data were presented in the median and interquartile range (Me [Q1; Q3]), and the mean value ± standard deviation (m±σ). The spearman rank coefficient (ρ) was used for the correlation analysis. Qualitative variables were assessed using frequency tables (Chi-square with Yates correction, χ^2). P-values less than 0.05 were considered statistically significant.

RESULTS

The sociodemographic characteristics of the sample are presented in Table 1. As the samples of the patients and healthy volunteers differed statistically in age, that factor was further considered in our statistical calculations.

Table 1. Demographic characteristics of the studied cohort

Variable name	Patients, *n*=125	Healthy volunteers, *n*=95	*p*
Female/Male, abs.	62/63	60/35	χ^2=3.49; *p*=0.062
Age, years Me [Q1; Q3]/ [Min; Max]	33 [26; 43]/[18; 65]	29 [22; 38]/[19; 62]	Z=1.99; *p*=0.046
BMI, kg/m^2 Me [Q1;Q3]	23.85 [20.2; 27.6]	23.5 [21.0; 26.3]	Z=0.23; *p*=0.82
Nicotine use presence/ absence, abs.	51/74	30/65	χ^2=1.97; *p*=0.16

Note: the significance of the difference level was assessed using the Yates-adjusted chi-square test and the Mann-Whitney U-test (Z); Me [Q1; Q3] — median, interquartile range, Min — minimum value, and Max — maximum value.

Table 2. Serum IL-6 (pg/ml) in subgroups of the studied cohort

Variable name	Serum IL-6 levels (pg/ml)		MWU-test; *p*
	Patients, *n*=125	Healthy volunteers, *n*=95	
All participants: m (σ); Me [Q1; Q3]	5.6 (16.6); 1.5 [0.7; 4.9]	2.7 (3.7); 0.8 [0.3; 4.7]	z=2.58; *p*=0.0099
Women: Me [Q1; Q3]	1.73 [0.67; 8.31]	0.74 [0.29; 4.05]	z=2.89; *p*=0.0038
Men: Me [Q1; Q3]	1.41 [0.70; 2.86]	0.92 [0.41; 6.53]	z=0.51; *p*=0.61

Note: m (σ) — mean value (standard deviation); Me [Q1; Q3] — median and interquartile range; and MWU-test — Mann-Whitney U-test. Reference range of the IL-6 serum level — 0–10 pg/ml.

Table 3. Association of IL-6 with the clinical characteristics of patients

Variable name		Me [Q1; Q3]	Spearman, ρ	*P*
Age of disease manifestation, years (*n*=125)		25 [20; 32]	0.20	0.025
Daily dose of antipsychotic, chlorpromazine equivalent (*n*=125)		180 [100; 300]	0.073	0.42
Disease duration, months (*n*=125)		34 [15; 156]	0.18	0.043
Positive symptoms PANSS score (*n*=125)		12 [10; 16]	0.18	0.048
Negative symptoms PANSS score (*n*=125)		19 [15; 24]	0.17	0.07
General psychopathology PANSS score (*n*=125)		37 [31; 43]	0.19	0.038
Total symptom severity PANSS score (*n*=125)		69 [59; 82]	0.22	0.016
Level of personal and social functioning (PSP score) (*n*=125)		57 [45; 67]	−0.13	0.17
Anhedonia (SHAPS score) (*n*=117)		2 [0; 4]	0.056	0.55
Depression (CDSS score) (*n*=122)		3 [1; 7]	0.045	0.62
Adverse effects of therapy, UKU total score (*n*=125)		9 [6; 16]	−0.018	0.84
EPS (UKU-EPS score) (*n*=125)		1 [0; 3]	−0.030	0.74
EPS (SAS score) (*n*=73)		0 [0; 0]	0.15	0.22
Dyskinesia (AIMS score) (*n*=73)		1 [0; 2]	0.055	0.65
Akathisia (BARS score) (*n*=73)		0 [0;0]	0.082	0.49
Catatonia (BFCRS score) (*n*=72)		0 [0; 1]	0.053	0.66
BACS score (*n*=122)	auditory memory	36 [26; 45]	−0.31	0.00063
	working memory	15 [12; 18]	−0.25	0.0065
	motor speed	56 [46; 70]	−0.027	0.77
	verbal fluency	42 [30; 55]	−0.28	0.0019
	hand-eye coordination	36 [24; 50]	−0.29	0.0011
	problem-solving behavior, executive functions	16 [12; 18]	−0.22	0.013
Childhood trauma questionnaire (CTQ score) (*n*=113)	emotional abuse	9 [6; 13]	0.070	0.46
	physical abuse	6 [5; 8]	−0.034	0.72
	sexual abuse	5 [5; 5]	0.088	0.35
	emotional neglect	11 [8; 15]	−0.10	0.29
	physical neglect	8 [6; 10]	0.0089	0.93

Note: IL-6 — interleukin-6; PANSS — Positive and Negative Syndrome Scale; PSP — Personal and Social Performance scale; SHAPS — Snaith-Hamilton Pleasure Scale; CDSS — Calgary Depression Scale for Schizophrenia; UKU — the UKU Side Effect Rating Scale (version "The UKUSERS-Clin"); EPS — extrapyramidal symptoms; SAS — Simpson-Angus scale; AIMS — the Abnormal Involuntary Movement Scale; BARS — Barnes Akathisia Scale; BFCRS — Bush-Francis Catatonia Rating Scale; BACS — Brief Assessment of Cognition in Schizophrenia; Me [Q1; Q3] — median and interquartile range. There was a statistically significant association between the IL-6 levels and several PANSS scores: P2 (conceptual disorganization, ρ=0.31; *p*=0.00044), N5 (difficulty in abstract thinking, ρ=0.29; *p*=0.0011), N6 (lack of spontaneity and flow of conversation, ρ=0.18; *p*=0.047), G8 (uncooperativeness, ρ=0.18; *p*=0.042), G10 (disorientation, ρ=0.33; *p*=0.00019), G11 (poor attention, ρ= 0.20; *p*=0.027), and G12 (lack of judgment and insight, ρ=0.18; *p*=0.044).

Comparative analysis of IL-6 levels in patients and healthy controls

Table 2 shows that the level of IL-6 is almost twice as high in the patients compared to the volunteers. In female patients, the level of IL-6 was significantly higher than that in the healthy women. In men, it was also higher, but not as significantly. The differences in the IL-6 levels between men and women were not significant both across the entire studied sample (Z=−0.056; *p*=0.95) and separately among patients (Z=−1.45; *p*=0.15) and volunteers (Z=0.85; *p*=0.39). The lack of statistically significant differences in men was probably due to the smaller number of observations in a subgroup of healthy volunteers.

In the patients, the levels of IL-6 rather weakly correlated with age (ρ=0.21; *p*=0.016). In the healthy volunteers, however, this pattern was not found (ρ=0.029; *p*=0.78). No association between IL-6 levels and the BMI or weight was found either among the patients (ρ=−0.074; *p*=0.48

Table 4. The serum IL-6 level and daily doses of antipsychotics in patients with different clinical characteristics

Subgroup characteristic		Serum IL-6, pg/ml	H; *p*	Daily dose of APs in CPE	H; *p*	Correlation between serum IL-6 & daily dose, ρ; *p*
ICD-10 diagnosis	Paranoid schizophrenia (*n*=97)	1.55 [0.74; 5.83]	H=5.70; *p*=0.22	200 [100; 300]	H=1.89; *p*=0.76	0.09; 0.38
	Acute polymorphic psychotic disorder with symptoms of schizophrenia (*n*=17)	1.55 [0.42; 1.89]		150 [100; 280]		0.052; 0.84
	Undifferentiated schizophrenia (*n*=8)	0.95 [0.43; 1.42]		138 [68; 264]		−0.095; 0.82
	Simple schizophrenia (*n*=2)	3.36 [0.20; 6.53]		150 [70; 330]		NA
	Hebephrenic schizophrenia (*n*=1)	8.09		140		NA
Type of the disease course	Continuous (*n*=58)	1.54 [0.82; 6.53]	H=1.24; *p*=0.54	240 [135; 380]	H=2.01; *p*=0.37	0.040; 0.77
	Episodic with progressive deficit (*n*=48)	1.34 [0.50; 5.60]		150 [100; 238]		0.094; 0.53
	Course uncertain, period of observation too short (*n*=17)	1.55 [0.42; 1.89]		150 [100; 280]		0.079; 0.76
Disease duration	less than 1 year (*n*=27)	1.55 [0.50; 2.90]	H=4.60; *p*=0.10	150 [75; 250]	H=3.26; *p*=0.20	−0.052; 0.80
	1-5 years (*n*=51)	1.34 [0.67; 2.19]		160 [100; 300]		0.0061; 0.97
	over 5 years (*n*=47)	2.42 [0.74; 9.22]		230 [132; 380]		0.17; 0.25
Age of manifestation	under 30 years old (*n*=87)	1.52 [0.70; 2.86]	H=3.59; *p*=0.058	195 [100; 350]	H=1.12; *p*=0.29	0.16; 0.15
	over 30 years old (*n*=38)	2.29 [0.62; 9.22]		150 [100; 250]		−0.013; 0.94

Note: IL-6 — interleukin-6; IL-6 level displayed in Me [Q1; Q3] — median and interquartile range; H — Kruskal-Wallis test; ρ — Spearman rank coefficient; NA — not applicable; *p* — significance level of differences; AP – antipsychotic; and CPE — chlorpromazine equivalent.

and ρ=−0.11; *p*=0.26, respectively) nor among the healthy volunteers (ρ=0.17; *p*=0.10 and ρ=0.16; *p*=0.12, respectively). Moreover, in the patients treated with second-generation APs (which most significantly affect the metabolic profile), the association of IL-6 levels with BMI tended to have a weak negative correlation: ρ=−0.23; *p*=0.068.

The association of IL-6 with the clinical characteristics of patients is illustrated in Table 3. There was a statistically significant association between the IL-6 levels and several PANSS scores: P2 (conceptual disorganization, ρ=0.31; *p*=0.00044), N5 (difficulty in abstract thinking, ρ=0.29; *p*=0.0011), N6 (lack of spontaneity and flow of conversation, ρ=0.18; *p*=0.047), G8 (uncooperativeness, ρ=0.18; *p*=0.042), G10 (disorientation, ρ=0.33; *p*=0.00019), G11 (poor attention, ρ=0.20; *p*=0.027), and G12 (lack of judgment and insight, ρ=0.18; *p*=0.044).

Comparative analysis of IL-6 levels in subgroups of patients with different clinical and therapeutic characteristics

Table 4 presents a comparative characteristic of the level of serum IL-6 and daily doses of APs in patients from various clinical groups and also shows the correlation of IL-6 with doses in each subgroup. The highest doses of APs were found in the paranoid type, continuous course, and disorder duration of over 5 years (not significant); while the serum IL-6 level was highest in patients with a simple and hebephrenic form, with a disorder duration of over 5 years and onset after 30 years of age (statistically significant only in the case of onset before and after 30 years). None of the clinical subgroups showed a trend towards a correlation between IL-6 and daily doses.

The levels of IL-6 significantly differed amongst patients receiving different generations of APs (Table 5). According to pairwise comparisons, the IL-6 differences between patients treated with first- and third- generation APs were statistically significant (Z=2.12; *p*=0.034); between patients treated with first- and second-generation APs, the differences approached the level of statistical significance (Z=1.87; *p*=0.061); while between patients receiving second- and third-generation APs, they were not significant (Z=1.24; *p*=0.22). The selectivity (potency for D2 receptors)[1] of APs was not associated with the IL-6 levels (Table 5). Patients treated with combinations of APs with different selectivity showed

[1] Haloperidol, risperidone, aripiprazole, cariprazine, zuclopenthixol were included in the group of highly potent APs; olanzapine, trifluoperazine, perphenazine — in the group of medium potent APs; clozapine and quetiapine — in the group of low-potent APs; other APs were not prescribed to patients of the study sample.

Table 5. Serum IL-6 level in patients receiving different types of pharmacotherapies

Variable name		Serum IL-6, pg/ml	H; *p*/Z; *p*
APs' generation	first (*n*=41) second (*n*=51) third (*n*=10) combination of 1 and 2 (*n*=21)	1.89 [1.09; 8.09] 1.34 [0.50; 2.69] 0.86 [0.16; 1.16] 1.60 [1.20; 3.11]	6.36; 0.042
APs' selectivity[1]	highly potent (*n*=47) medium potent (*n*=31) low potent (*n*=15) combination of APs with different selectivity (*n*=30)	1.51 [0.63; 6.53] 1.38 [0.45; 2.03] 1.41 [0.95; 4.90] 1.71 [0.99; 7.00]	1.37; 0.51
Correctors of extrapyramide disorders	absent (*n*=80) present (*n*=45)	1.34 [0.62; 5.25] 1.85 [1.17; 3.87]	0.58; 0.56
not taking APs (*n*=2)		6.11 [0.74; 11.49]	NA

Note: IL-6 — interleukin-6; IL-6 level displayed in Me [Q1; Q3] — median and interquartile range; H — Kruskal-Wallis test (in case of more than 2 groups); Z — Mann-Whitney U-test (in case of 2 groups); *p* — significance level of differences; AP — antipsychotic; NA — not applicable.

Table 6. Comparative characteristics of patients receiving various types of psychiatric care

Variable name	Hospitalized patients (*n*=69)	Patients of daycare departments (*n*=39)	Outpatients (*n*=17)	H; *p*
Serum IL-6, pg/mL	2.15 [1.34; 8.09]	0.88 [0.42; 1.97]	0.91 [0.41; 1.53]	H=18.59; *p*=0.0001
Age, years	33 [26; 46]	33 [24; 40]	34 [26; 39]	H=1.51; *p*=0.47
Onset age, years	26 [20; 32]	25 [19; 31]	26 [22; 33]	H=0.51; *p*=0.77
Disease duration,months	36 [14; 190]	28 [16; 96]	34 [22; 120]	H=1.05; *p*=0.59
Positive symptoms PANSS, score	13 [10; 16]	12 [9; 14]	11.5 [10; 16]	H=2.51; *p*=0.28
Negative symptoms PANSS, score	20 [17; 27]	16 [12; 19]	20 [17; 21.5]	H=17.64; *p*=0.0001
General psychopathology PANSS, score	39 [34; 45]	33 [28; 38]	39.5 [32.5; 48]	H=12.35; *p*=0.0021
Total symptom severity PANSS, score	75 [65; 87]	62 [50; 69]	73 [60.5; 84]	H=14.89; *p*=0.0006
Daily dose of APs, CPE	200 [105; 380]	150 [100; 225]	176 [100; 225]	H=2.44; *p*=0.30
Generation of APs used: 1/2/3/combination of 1–2 (number of patients)	28/25/0/16	11/18/5/4	2/8/5/1	χ^2=25.3; *p*=0.0056
auditory memory (BACS, score)	32 [24; 40]	40 [33; 48]	42 [32.5; 51.5]	H=12.45; *p*=0.0020
working memory (BACS, score)	14 [11; 18]	16 [13; 18]	15.5 [13; 22.5]	H=4.07; *p*=0.13
motor speed (BACS, score)	51 [41; 64]	62 [54; 74]	70.5 [46; 80]	H=13.09; *p*=0.0014
verbal fluency (BACS, score)	36 [28; 47]	49 [37; 59]	51 [41.5; 58.5]	H=13.75; *p*=0.0010
hand-eye coordination (BACS, score)	27 [19; 38]	46 [38; 52]	43.5 [33; 53]	H=29.63; *p*=0.0000
problem-solving behavior (BACS, score)	14.5 [8; 18]	17 [14; 18]	18.5 [15.5; 19.5]	H=11.93; *p*=0.0026

Note: IL-6 — interleukin-6; data displayed in Me [Q1; Q3] — median and interquartile range; H — Kruskal-Wallis test; *p* — significance level of differences; PANSS — Positive and Negative Syndrome Scale; AP — antipsychotic; CPE — chlorpromazine equivalent; BACS — Brief Assessment of Cognition in Schizophrenia; χ^2 — the hi-square criterion for tables.

the highest levels of IL-6. Correctors of extrapyramidal disorders (biperiden, amantadine, trihexyphenidyl) did not affect IL-6 levels.

The comparative characteristics of patients receiving various types of psychiatric care (Table 6) showed that in hospitalized patients IL-6 levels were significantly higher compared to inpatients (Z=4.02; *p*=0.000057) and outpatients (Z=2.59; *p*=0.0097), while no significant differences were observed between inpatients and outpatients (Z=0.080; *p*=0.94).

Hospitalized patients more often were treated with first-generation APs (no one received third-generation APs, and only 25/69 received second-generation APs). Patients treated with third-generation APs were younger than patients treated with first-generation APs (Z=2.02; *p*=0.044), and those were more often treated on an outpatient basis and in daycare units. Therefore, it is likely that the lower level of IL-6 in patients treated with third-generation APs (*n*=10) has to do not with the treatment used, but with the younger age and lesser severity of the disease. There were no differences in the IL-6 levels between patients who took first- and second-generation APs in the hospital (Z=0.77; *p*=0.44). Separately, significant association between age and IL-6 level was confirmed in the subgroup of inpatients (*n*=69): ρ=0.36; and *p*=0.0018. However, in the combined subgroup of outpatients (*n*=17) and inpatients (*n*=39), there was virtually no correlation between IL-6 levels and age: ρ=−0.066; *p*=0.63.

Nicotine dependence and IL-6 levels in study participants

In patients with nicotine dependence, IL-6 levels did not differ from those of other patients (Z=0.16; *p*=0.88), and they did not tend to differ (in nicotine-dependent patients, mean IL-6 levels were lower than those in non-smokers). In the entire studied sample, IL-6 levels also did not differ between individuals with and without nicotine dependence (Z=0.19; *p*=0.84).

DISCUSSION

Our study showed statistically significant higher levels of serum IL-6 in patients with schizophrenia compared with healthy volunteers. Our results were consistent with previously published data [3–7].

Data on the IL-6 serum level association with the majority of the studied domains of cognitive function, as well as with the PANSS general psychopathology and total scores, appears to indicate that this biochemical marker could be a reflection of the severity of the schizophrenic process, the social maladaptation, as well as disability (due to cognitive impairment). This finding is further supported by the specific profile of PANSS symptoms as they show significant correlation with serum IL-6 levels (N5 — difficulty in abstract thinking, N6 — lack of spontaneity and stilted conversation, P2 — conceptual disorganization, G8 — uncooperativeness, G10 — disorientation, G11 — poor attention, G12 — lack of judgment, and insight). Our data were consistent with previously published research results. In Miller et al. meta-analysis (2011) IL-6 showed correlation with symptom severity in two of five studies [2]. Khandaker et al. (2014) [10] also demonstrated that IL-6 is associated with the severity of schizophrenia symptoms. Thus the study's results are consistent with the hypothesis that IL-6 is a state-dependent marker of inflammation. Moreover, we obtained data on a strong association between the serum IL-6 level and the cognitive functions of patients with schizophrenia. Those findings are consistent with the results of a recently published meta-analysis of the association of pro-inflammatory cytokines (including IL-6) with cognitive decline in schizophrenia [35]. Thus the heterogeneity of the clinical manifestations of schizophrenia may be associated with immunological heterogeneity, which finds indirect confirmation in the correlations identified in our study. This allows us to assign patients with the most severe symptoms of schizophrenia, especially those with severe cognitive impairment, to the category of candidates for targeted diagnostics of immune-inflammatory markers and personalized correction of immune-inflammatory dysfunctions, which requires further investigation through longitudinal studies.

Noteworthy is the weak positive correlation of IL-6 with age only in patients, but not in healthy volunteers. The correlation of cytokine levels with the duration of the disease in patients is consistent with the results of other studies in which the peripheral blood IL-6 level had a significant, positive correlation with the duration of schizophrenia [2, 8]. The association of IL-6 with the duration of the disease may be indication of an increase in the role of the immune response with the course of the disease, which does not exclude a secondary role for this pathogenetic process in relation to the other pathogenetic mechanisms studied in schizophrenia. In addition, patients with a longer duration of the disorder could hypothetically experience an earlier onset of schizophrenia and, thus,

a greater severity of the symptoms. However, this contradicts our data pointing to a direct IL-6 correlation with the age of manifestation of the disease. This discrepancy may have something to do with a later entry date into the psychiatric care system for some patients and a longer duration of untreated psychosis in the subgroup of patients with a later age of manifestation of the disease.

We have not been able to find studies on the association of IL-6 and other immunoinflammatory markers with a later manifestation of schizophrenia. However, some studies showed that late-onset psychoses are often secondary in up to 60% of cases and require a more thorough differential diagnosis and the exclusion of somatogenic causes for the psychosis, also using autoimmune panels [36, 37].

More pronounced differences in the level of IL-6 between patients and volunteers in women compared with men were consistent with data on a higher incidence of autoimmune encephalitis in women [38]. Anti-NMDA receptor encephalitis can phenotypically manifest as a symptomatic psychosis that meets the diagnostic criteria for schizophrenia; according to a systematic review by Al-Diwani et al. (2019) 32% of cases of NMDAR-antibody encephalitis are associated with ovarian teratoma [38, 39]. Thus, the gender differences in immuno-inflammatory disruptions in schizophrenia may be of interest for further study.

The association of serum IL-6 levels with smoking, identified in a pilot study [40], was not confirmed in this work. The association of IL-6 levels with different EPS subtypes obtained in the same pilot study [40] was also not confirmed in this work.

The differences in the IL-6 levels of patients receiving antipsychotics of different generations merit close attention. Patients who received first-generation APs, as well as combinations of APs of different generations, had a significantly higher level of IL-6 (Table 5). However, as shown in Table 6, inpatients received them significantly more often, therefore, they also had more pronounced symptoms that were associated with the level of IL-6. At the same time, within the subgroup of inpatients, there were no differences in the level of IL-6 between patients treated with first- and second-generation APs. In addition, there was no association between IL-6 levels and AP doses in CPE. We can assume that the therapy applied does not have a significant effect on the level of serum IL-6, the latter being more closely associated with the symptoms of the disease and cognitive functions. This is consistent with data obtained earlier by other researchers [2, 10, 14, 15].

Fang et al. (2019) obtained data on the association of IL-6 levels with the metabolic syndrome in patients treated with second-generation AP [6]. According to them, this association may be due to the fact that second-generation APs activate the pro-inflammatory molecular mechanisms involved in the metabolic syndrome pathology. This hypothesis was also not confirmed in our study. There was a tendency to a weak negative correlation between the level of IL-6 and BMI in patients treated with second-generation APs. This may be due to the use of different drugs within the second-generation APs group, which requires additional analysis. Patients in our sample who received the most BMI-affecting drugs (clozapine *n*=11, olanzapine *n*=18) had a lower BMI and IL-6 than other patients (not significantly). That could be due to recent prescription of these drugs (which was not evaluated), as well as to the personalized selection of therapy (considering the initial data on BMI and the exclusion of clozapine and olanzapine use in the risk group with an initially high BMI). Given that IL-6 in patients treated with clozapine was lower than in the other patients in our sample (not significantly), and in alignment with data in the literature [15–17], and considering the data in a large body of studies pointing to a decrease in the level of IL-6 during AP treatment [2, 10], further study into the effects of AP on the immune-inflammatory profile is called for.

Strengths and limitations of the study

Strengths of the study: In-depth phenotyping of patients was conducted using standardized validated psychometric instruments and laboratory studies were blind to the participant group, and clinical examination was blind to laboratory results.

Limitations of the study: A cross-sectional design did not allow one to draw conclusions on any causal relationship between IL-6 and clinical characteristics. The duration of AP intake before inclusion was not analyzed in patients, which may have Interfered with the analysis of the APs effect on the IL-6 levels.

The severity of schizophrenia symptoms, especially cognitive symptoms, a late-onset of the disorder, and the female gender can serve as clues in targeted diagnostics and personalized approach to the mitigation of disruptions caused by immune inflammations. This requires a more thorough differential diagnosis and the exclusion of somatogenic causes of psychosis.

CONCLUSION

Our study highlights an association between serum IL-6 levels and schizophrenia, patient age, duration of the disease and a later onset, various clinical variables in schizophrenia patients (cognitive impairment, severity of the PANSS general psychopathology subscale, as well as the total PANSS score). Considering that IL-6 is associated with a wide range of symptoms that are poorly controlled by APs and affect the daily activities of patients, this biochemical marker needs to be considered for association with an unfavorable course of schizophrenia, which requires further prospective studies. The results obtained here point to the pressing need for further investigation of inflammatory markers among patients with schizophrenia in order to isolate the data with a bearing on their causality in the disease's pathogenesis.

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