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SCHIZOPHRENIA AND NEUROINFLAMMATION: PATHOGENETIC AND THERAPEUTIC ASPECTS

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Introduction. Schizophrenia is a complex mental disorder with heterogeneous symptoms, including psychotic, negative, cognitive, affective, and psychomotor symptoms. Although the pathogenesis of schizophrenia is mainly associated with neurotransmitter imbalance, recent studies have suggested the importance of neuroinflammation in the pathogenesis of this disease.

Objective. To study the involvement of neuroinflammation in the pathogenesis of schizophrenia and a prognostic assessment of the potential anti-inflammatory effect of antipsychotic medications.

Discussion. Current data indicate a significant role of neuroinflammation in the development and course of schizophrenia. At the initial stages of its development, the number of lymphocytes and the level of some proinflammatory cytokines (IL-1, IL-6, TNF-α, IL-1β) increase, which can be decreased by antipsychotic therapy. Studies involving experimental models of maternal immune activation (MIA) and data obtained by immunohistochemical and PET studies confirm an abnormal activation of microglia, indicating the involvement of innate immune cells. Adaptive immune response cells can also play a significant role in the development of neuroinflammation in schizophrenia. Thus, an increased level of Th17 cells and an increase in the production of proinflammatory cytokines, correlating with the disease severity, were revealed. The role of neurotransmitters in modulating the immune-inflammatory response is discussed. Available data suggest that the participation of dopamine in the schizophrenia pathogenesis can be mediated by its immunomodulatory effect. The role of neuroinflammation in schizophrenia is also indicated by the clinical effectiveness of anti-inflammatory treatment in this disease. On the other hand, the immunomodulatory effect of antipsychotics has been established, which, at least in part, may mediate their clinical effectiveness in schizophrenia.

Conclusions. Given the importance of neuroinflammation in the schizophrenia pathogenesis, further studies into both the anti-inflammatory properties of antipsychotics and the effects of anti-inflammatory drugs in schizophrenia are promising in order to further optimize the treatment of this disease.

Keywords: schizophrenia; inflammation; neuroimmune interactions; antipsychotics; neuroleptics; dopamine

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ШИЗОФРЕНИЯ И НЕЙРОВОСПАЛЕНИЕ: ПАТОГЕНЕТИЧЕСКИЕ И ТЕРАПЕВТИЧЕСКИЕ АСПЕКТЫ

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Введение. Шизофрения — это сложное психическое расстройство с гетерогенной симптоматикой, включающей в себя психотические, негативные, когнитивные, аффективные и психомоторные симптомы. Несмотря на то что патогенез шизофрении главным образом связывают с дисбалансом нейротрансмиттеров, исследования последних лет указывают на большое значение нейровоспаления в патогенезе этого заболевания.

Цель. Изучение роли нейровоспаления в патогенезе шизофрении с оценкой вовлечения клеток врожденного, адаптивного иммунного ответа и функционирования гематоэнцефалического барьера (ГЭБ) в возникновении заболевания, а также прогностическая оценка противовоспалительного эффекта антипсихотических средств при шизофрении.

Обсуждение. Современные данные свидетельствуют о значительной роли нейровоспаления в развитии и течении шизофрении. На начальных этапах заболевания повышается количество лимфоцитов, а также уровень нескольких провоспалительных цитокинов (ИЛ-1, ИЛ-6, ФНО-α, ИЛ-1β), которые могут снижаться на фоне антипсихотической терапии. Исследования на экспериментальной модели материнской иммунной активации (МИА) и данные иммуногистохимических и ПЭТ-исследований подтверждают аномальную активацию микроглии, что указывает на вовлечение клеток врожденного иммунитета. Клетки адаптивного иммунного ответа также могут играть существенную роль в развитии нейровоспаления при шизофрении (выявлено повышенное содержание Th17-клеток и увеличение продукции провоспалительных цитокинов, коррелирующих с тяжестью заболевания). Обсуждается роль нейромедиаторов в модуляции иммуновоспалительного ответа. Существующие данные позволяют предположить, что участие дофамина в патогенезе шизофрении может быть опосредовано его иммуномодулирующим эффектом. На роль нейровоспаления при шизофрении также указывает клиническая эффективность применения противовоспалительного лечения при данном заболевании. С другой стороны, установлен иммуномодулирующий эффект антипсихотиков, который, по крайней мере частично, может опосредовать их клиническую эффективность при шизофрении.

Выводы. Ввиду значимости нейровоспаления в патогенезе шизофрении перспективны дальнейшие исследования как противовоспалительных свойств антипсихотиков, так и клинической эффективности противовоспалительных препаратов при шизофрении с целью дальнейшей рационализации терапии данного заболевания.

Ключевые слова: шизофрения; воспаление; нейроиммунные взаимодействия; антипсихотики; нейролептики; дофамин

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INTRODUCTION

Schizophrenia is a progressive mental illness with heterogeneous symptoms, including productive, negative, affective, cognitive, and psychomotor symptoms. This disease has a continuous or paroxysmal course, leading to specific personality changes in the form of mental disintegration, autism, thinking disorders, emotional-volitional and cognitive decline [1].

Schizophrenia is the most complex and socially significant problem in modern psychiatry, which is determined by its widespread prevalence, constant tendency to disease progression, and, in the absence of adequate treatment, severe disability of patients, mainly young people who are active in social and labor activities [2]. According to the World Health Organization, in the 15–44 age group, schizophrenia ranks eights among the leading causes of disability worldwide. At the same time, patients with schizophrenia lose an average of 15 years of their life expectancy, mainly due to suicide (suicide risk from 5 to 10%), as well as due to the presence of concomitant diseases, including substance abuse with a prevalence rate of up to 41% [3]. In addition, disordered lifestyle, unhealthy diet, lack of physical activity, and side effects of antipsychotic therapy contribute to an increase in the incidence of metabolic syndrome, as well as cardiovascular and pulmonary diseases [4]. Among mental disorders, schizophrenia is the largest socioeconomic burden, accounting for about 54.5% of the total number of mental disorders, with this number having doubled in recent years [5]. Thus, the treatment of patients with schizophrenia is one of the most urgent tasks of practical psychiatry.

According to the classical understanding, the pathogenesis of schizophrenia is based on a disorder of the metabolism of biogenic amines, especially dopamine, whose receptors are a key target for drugs of pathogenetic therapy of the disease (antipsychotics). In particular, most antipsychotics used in the treatment of schizophrenia are predominantly antagonists of dopamine receptors of the D2 group (D2-, D3-, D4-receptors). However, despite the relief of a number of clinical symptoms, antipsychotic drugs are not capable of significantly slowing down the progression of the disease, which suggests additional pathogenetic mechanisms of schizophrenia [6].

Thus, recent studies have shown that along with impaired functioning of neurotransmitters, neuroinflammation can also be an essential factor in the schizophrenia pathogenesis [6, 7]. It has been shown that at the initial stages of schizophrenia, the number of lymphocytes and the level of certain pro-inflammatory cytokines increases: interleukin-1 (IL-1), IL-6, tumor necrosis factor α (TNF-α) and others, which may decrease against the background of antipsychotic therapy [8]. The higher incidence of autoimmune diseases of the central nervous system (CNS) in patients with schizophrenia also supports the involvement of neuroinflammation in the pathogenesis of schizophrenia [9, 10]. Common mechanisms for these diseases include activation of microglia, increased production of pro-inflammatory cytokines, and disruption of the blood–brain barrier (BBB) [10].

In this article, we study the role of neuroinflammation in the schizophrenia pathogenesis with an assessment of the involvement of cells of the innate, adaptive immune response and functioning of the BBB in the disease development, as well as a prognostic assessment of the anti-inflammatory effect of antipsychotics in schizophrenia.

MATERIALS AND METHODS

The search for relevant scientific publications was conducted in electronic bibliographic databases in both the Russian (eLibrary, CyberLeninka) and English (Web of Science, Scopus, PubMed) languages. The search queries included the words: schizophrenia, inflammation, neuroimmune interactions, antipsychotics, antipsychotics, dopamine. The search depth was 10 years. The inclusion criteria were the availability of data on the results of cohort studies, randomized controlled trials, and preclinical studies.

RESULTS AND DISCUSSION

Role of innate immune response in the development of neuroinflammation in schizophrenia

For a long time, the development of an immune response in the CNS was considered unlikely, which was associated with the isolation of the CNS from the immune system through the BBB, as well as the lack of lymphatic drainage and other mechanisms of natural immunological tolerance (the “immunoprivileged” status of the CNS) [11]. However, recent knowledge indicates the presence of resident immune cells in the CNS, as well as the ways in which the CNS communicates with the deep cervical lymph nodes through the lymph vessels of the dura mater and the lymphatic system. In addition, the ability of cells of both the innate and adaptive immune responses to migrate to the CNS from the periphery has been established. Therefore, research into the role of neuroinflammation in

the pathogenesis of various diseases of the CNS is increasingly attracting attention [12].

Among the cells of the innate immune response in the context of neuroinflammation, microglia — resident macrophages of the CNS — attract the most attention. It has been shown that microglia are able to participate both in the development of neuroinflammation by producing pro-inflammatory cytokines and inducing Th17 and Th1 immune responses (M1 microglia), and maintaining immunological tolerance by producing anti-inflammatory factors and inducing regulatory T cells (Treg) (M2 microglia) [6].

Microglial changes in schizophrenia have been described mainly on experimental models of schizophrenia in animals, MIA, which are reproduced by injecting pregnant rodents with agonists of the innate immune response receptors (in particular, toll-like receptors — TLR-3 and TLR-4). Adult offspring of such rodents develop neuroanatomical, neurochemical, and behavioral changes, some of which correspond to those in schizophrenia (hyperactivity of the dopaminergic system, enlargement of the ventricles of the brain, behavioral and cognitive impairments) [13,14].

In particular, an increase in mobility, density, and the ability of microglia to produce cytokines in MIA induced by the TLR-4 lipopolysaccharide (LPS) agonist has been shown [13]. In addition, the pro-inflammatory functions of microglia in MIA are increased when MIA is induced by the administration of a TLR-3 agonist (polyinosinic:polycytidylic (PolyI:C) [14]. The results of research studies obtained thus far indicate the pro-inflammatory profile of microglia in adolescence with MIA.

In addition, the involvement of microglia in the pathogenesis of schizophrenia is evidenced by the association between suppression of its functions and a decrease in the severity of symptoms of the disease in the setting of anti-inflammatory therapy, in particular minocycline, which has a modulating effect on microglia [15].

Data on abnormal microglial activation, shown in several postmortem immunohistochemical studies and *in vivo* positron emission tomography (PET) studies in patients with schizophrenia, are contradictory [16, 17]. Additional ambiguity during postmortem immunohistochemical examination may be caused by the actual effect of long-term antipsychotic therapy on microglial activation, which is confirmed by PET data [18,19]. At the same time, PET studies in people with an ultra-high risk of developing schizophrenia or in patients with schizophrenia who have not received pathogenetic therapy still remain ambiguous. Thus, according to some studies, a decrease or absence of an increase in the binding of the translocator protein (TSPO, a marker of microglial activation in vivo) has been shown, which indicates a decrease in microglial activation [20, 21]. However, some studies have indicated, on the contrary, an increase in the binding of this ligand throughout the gray matter [22].

The first psychotic episode of schizophrenia is associated with a decrease in the concentration of IL-10 and IL-4 anti-inflammatory cytokines; conversely, the concentration of pro-inflammatory cytokines such as IL-6 and TNF-α, increases [23, 24]. According to Halstead et al., the concentrations of IL-1β, IL-1 receptor antagonist (IL-1RA), soluble IL-2 receptor (sIL-2R), IL-6, IL-8, IL-10, TNF-α, and C-reactive protein increased in peripheral blood (plasma/serum) of schizophrenia patients compared to the control group. The levels of IL-2 and interferon-γ (IFN-γ) were significantly higher in the acute episode of schizophrenia, whereas, in the chronic form, the levels of IL-4, IL-12, and IFN-γ were significantly reduced [25]. A meta-analysis of studies into the cytokine level in cerebrospinal fluid showed similar data, i.e., an increase in IL-1β, IL-6, and IL-8 in patients with schizophrenia [26].

In addition, increased production of IL-8 and IL-1β by LPS-stimulated peripheral blood mononuclear cells (PBMCs) in patients with schizophrenia was observed, confirming the role of innate immune response cells in the pathogenesis of schizophrenia [27]. These data are also consistent with the assessment of mRNA expression levels of proinflammatory cytokines (IL-6, IL-8, and TNF-α) in the PBMCs of patients with schizophrenia [28]. In addition, it was found that the blood serum of patients with schizophrenia who did not receive pathogenetic therapy is able to activate microglia in vitro [29].

The potential role of perivascular macrophages in the pathogenesis of schizophrenia has been reported. In particular, immunohistochemical staining of the frontal lobe of the brain of patients with schizophrenia revealed an increased level of $CD163^+$-macrophages [30, 31].

In addition, patients with schizophrenia have an increased number of M1- and M2-monocytes circulating in the peripheral blood, which have pro- and anti-inflammatory functions, respectively. It is important that, along with disease progression, the ratio of such functional types of monocytes may change. Thus, the predominance of M1 monocytes at an early stage of the disease is replaced by the predominance of M2 monocytes at a later stage [32]. The involvement of proinflammatory M1 monocytes in the pathogenesis of schizophrenia was confirmed by data from other studies [33]. Moreover, an increase in the level of soluble CD14 (a marker of monocytes) in the blood of people who subsequently developed schizophrenia has been reported; this suggests activation of monocytes as an early predictor of the disease [34].

Along with the abovementioned, an increase in the production of IL-1β, IL-6, and TNF-α by stimulated monocytes of patients with schizophrenia was found in comparison with healthy donors *in vitro* [35, 36]. In addition, an increase in the level of chemokines (CL2, CCL4, CL22) necessary for the migration of monocytes, including through endothelial barriers, including the BBB, was found in the blood serum of patients with schizophrenia [37].

Role of the adaptive immune response in the development of neuroinflammation in schizophrenia

Recent studies have shown that along with the innate immune response, adaptive immune response cells can also play a significant role in the development of neuroinflammation in schizophrenia. It was found that during an acute episode of schizophrenia, the number of activated T cells in the central nervous system increases. The relationship between the risk of developing schizophrenia and the level of NK cells, T helper cells ($CD4^+$ T cells), and B lymphocytes was also discussed [38].

Among the cells of the adaptive immune response, presumably involved in the pathogenesis of schizophrenia, type 17 T helper cells (Th17 cells) attract particular attention. Th17 cells differentiate from naive T cells or memory T cells with the participation of IL-6 cytokines, transforming growth factor-β (TRF-β), IL-1β, and IL-23. Th17 cells produce proinflammatory IL-17, IL-21, IL-22 cytokines, granulocytic and granulocyte-macrophage colony stimulating factors (G-CSF or GM-CSF). As a rule, the Th17-type immune response is of a pronounced inflammatory nature. The involvement of these cells in the pathogenesis of autoimmune and neuroinflammatory diseases was emphasized in [39]. The importance of Th17 cells in the development of neuroinflammation is mainly attributed to their ability to migrate to the CNS through the BBB. It was established that C-C chemokine receptor 6 (CCR6; CD196) is a distinctive receptor of Th17 cells, due to which Th17 cells are able to penetrate the BBB. The CCR6 chemokine receptor binds to the corresponding CCL20 ligand, which is expressed on endothelial barriers, including the BBB. An additional factor contributing to the migration of Th17 cells to the CNS may be the destabilizing effect of IL-17 (a key product of Th17 cells) on the BBB permeability. The role of neuroinflammation and Th17 cells in the pathogenesis of schizophrenia has become a focus of research relatively recently. It is believed that the immunopathogenesis of schizophrenia may be based on a chronic inflammatory process supported by the interaction of Th17 cells and microglia activated by IL-17 [39].

A number of studies have found that patients with schizophrenia have a higher level of circulating Th17 cells, as well as IL-17-producing $CD4^+$ T cells, compared with the group of healthy donors [40]. Zheng et al. showed that the number of $CD4^+$ T lymphocytes in the peripheral blood of patients with schizophrenia in the acute phase in the absence of pathogenetic therapy is higher than in the control group [41]. Activation of Th17 cells in patients with the first episode of schizophrenia was also reported. In addition, BBB disorders, brain infiltration by T cells, and activation of microglia were shown in such patients. During the first episode of schizophrenia, changes in the distribution of T-cell subpopulations in the cerebrospinal fluid (CSF) and higher T-lymphocyte densities in the hippocampus of patients were noted [42]. Having penetrated into the CNS, Th17 cells produce pro-inflammatory IL-17 and IL-22 cytokines, leading to neuroinflammation and neurodegeneration [39]. These data are also consistent with the observed increased concentrations of IL-17, IL-22, IL-6, and IL-23 in the blood plasma of patients with schizophrenia compared with the group of healthy donors [43]. Elevated plasma levels of IL-17, TRF-β, and IL-23 (cytokines necessary for Th17 cell differentiation) in patients with schizophrenia correlate with the severity of the disease, aggressive behavior, and apathy [44]. In addition, increased production of IL-6, IL-17A, TNF-α was found in the culture of peripheral blood mononuclear cells (PBMCs) of patients with schizophrenia compared with healthy donors [45].

The malfunction of T-regulatory cells (Treg) that have an anti-inflammatory effect and prevent autoimmune neuroinflammation was revealed. In the absence of pathogenetic treatment, patients with schizophrenia showed a decrease in the number of circulating Tregs, as well as a decrease in the expression of the *Foxp3* gene in these cells, which determines their suppressive properties [45].

Immunomodulatory effects of biogenic amines and antipsychotics in schizophrenia

The leading theory behind the pathogenesis of schizophrenia is associated with a metabolism disorder of biogenic amines, dopamine in particular, whose receptors are one of the key targets for pathogenetic therapy of this disease. Due to the growing interest in the role of neuroinflammation in the schizophrenia pathogenesis, dopamine involvement in neuroimmunomodulation is attracting particular attention. It has become common knowledge that biogenic amines, whose receptors are expressed by cells of both the nervous and immune systems, are direct mediators of neuroimmune interaction. Drugs acting on these receptors are considered as potential neuroimmunomodulators [46, 47].

Dopamine is among the most studied neurotransmitters with immune effects. It can be assumed that dopamine involvement in the schizophrenia pathogenesis, at least partially, may be mediated by its immunomodulatory effect. Dopamine receptors are known to be expressed by T and B lymphocytes, macrophages, monocytes, eosinophils, neutrophils, dendritic cells, NK cells, and microglia.

Research found that the percentage of $CD8^+$ T cells expressing the D2-dopamine receptor ($CD8^+D2R^+$ T cells) is increased in patients with schizophrenia compared to that in healthy donors, while the percentage of $CD4^+D2R^+$ T cells, on the contrary, is reduced. In addition, a positive relationship was revealed between the scores on the BPRS (Brief Psychiatric Rating Scale) and PANSS (Positive and Negative Syndrome Scale) scales with the number of $CD8^+D2R^+$ T cells [48].

The effect of pathogenetic therapy drugs on immune cell functions in schizophrenia has also been shown. Thus, the patients with schizophrenia with a metabolic syndrome treated with second-generation antipsychotics (SGAs) (risperidone, olanzapine, quetiapine, and aripiprazole) demonstrated an increase in the levels of a number of pro-inflammatory cytokines, such as IFN-α2, IL-1α and IL-7, after six weeks of therapy. At the same time, IFN-γ, IL-1β, IL-12p40, IL-17A, IL-6, and TNF-α levels were reduced in patients without a metabolic syndrome [49].

A 28-day treatment of schizophrenia with aripiprazole revealed a significant decrease in the levels of C-reactive protein, insulin, IL-1β, IL-6, TNF-α, sTNF-R1, IL-12, IL-23, IL-1RA, TRF-β1, IL-4, IFN-γ, as well as a significant increase in IL-10 [50].

Of the individual drugs used as monotherapy in patients with the first episode of psychosis, risperidone was associated with statistically significant activation of 11 immune system genes, including cytokines and cytokine receptors, pattern-recognizing receptors (TLR-1, TLR-2, TLR-6) and molecules involved in apoptosis (FAS). It should be noted that risperidone exhibited strong immunomodulatory properties, affecting mainly the components of innate immunity in this category of patients, whereas the observed effects of quetiapine and olanzapine were only insignificant [51].

SGA risperidone has also been shown to reduce the level of the chemotactic cytokine monocyte chemotactic protein-1 (MCP-1), which may indicate some anti-inflammatory effect [52]. A detailed literature review of the immune effects of SGA provides evidence that most of these drugs cause leukopenia, lymphopenia, neutropenia, thrombocytopenia, and agranulocytosis, while reducing the levels of pro-inflammatory cytokines (TNF-α, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IL-21, IL-23) and C-reactive protein in patients with schizophrenic spectrum disorders [53].

Regarding the possibility of chronic inflammation in patients with schizophrenia, it is worth noting that plasma levels of IL-6 and its soluble receptor (IL-6R) are significantly higher in patients with schizophrenia, although decreasing after treatment with antipsychotics [54]. All first-generation antipsychotics (FGAs), especially chlorpromazine and haloperidol, reduce IL-6 and IL-6R levels in patients with schizophrenia. A meta-analysis of the use of antipsychotics in the treatment of the first psychotic episode in schizophrenia showed antipsychotic therapy to be associated with a decrease in the concentration of proinflammatory IL-1β, IL-6, IFN-γ, TNF-α cytokines, as well as anti-inflammatory IL-4, IL-10 cytokines. On the other hand, the levels of pro-inflammatory IL-2 and IL-17 remain unchanged [55].

In patients with schizophrenia, all antipsychotics show a clear effect on Treg. Tregs are elevated in the blood of patients with schizophrenia who receive stable therapy. At the same time, a negative correlation was found between Treg cells and negative symptoms [56]. A decrease in the level of Th17 cells was shown in the group of patients with the first episode of schizophrenia after a four-week course of treatment with risperidone. In addition, a significant positive relationship was found between the rate of changes in the total PANSS score and those in the percentage of Th17 cells. However, it remains unclear whether these results were related to risperidone treatment or the natural course of the disease, since the study did not include a placebo control group [40]. However, in a later study, in 113 patients who had not previously taken antipsychotics (or had taken them for less than two weeks in their entire lives), and who had had symptoms of schizophrenia no more than five years prior to the study, risperidone therapy did not cause significant changes in IL-17 in the blood [57].

In another study, the effect of antipsychotic drugs on the expression of *STAT3* and *RORC* genes involved in the development and differentiation of Th17 cells was studied in 27 patients with schizophrenia who had not previously taken antipsychotics. In addition, the effect of antipsychotic drugs in plasma was evaluated at the level of five cytokines associated with Th17 cells. A significant decrease in *STAT3* gene expression and levels of IL-1β, IL-6, and IL-17A in blood plasma was found after three months of taking antipsychotic drugs [58].

Concerning the use of SGA in other diseases, in particular in multiple sclerosis, all studies agree on the effectiveness of SGA in reducing the severity of symptoms in animal models of multiple sclerosis and experimental autoimmune encephalomyelitis (EAE), delaying the disease onset at the same time as suppressing the production of various pro-inflammatory cytokines. Clozapine demonstrated a similar and even a more intense effect than risperidone, quetiapine, and olanzapine, significantly reducing $CD4^+$ T cell infiltration and activation of myeloid cells, while increasing Treg levels. Clozapine also reduced the level of chemokines responsible for the migration of immune cells to the CNS and caused an increase in the level of dopamine receptors in the brains of mice with EAE [59].

At the same time, it has been reported that antipsychotics are capable of increasing IL-17 levels in in vitro experiments (in stimulated blood samples of healthy women) [60].

An experimental model of schizophrenia has shown an inhibitory effect of many FGAs and SGAs (risperidone, aripiprazole, quetiapine, ziprasidone) on IFN-γ-induced microglial activation in the mouse microglial cell line [61].

Feng et al. studied the possible correlation between the level of inflammatory markers in the blood of patients with schizophrenia and the level of their psychopathological symptoms. Markers of inflammation and psychopathological symptoms were studied in patients with schizophrenia after 3, 6, and 12 months of antipsychotic therapy. A significant decrease in monocyte levels, intercellular adhesion molecules, and adiponectin levels between baseline and 12 months of age was observed. A higher baseline level of IL-6 in the blood predicted a greater decrease in the overall PANSS score after 3 and 6 months, as well as the PANSS subscale for negative symptoms after three months. A higher baseline level of leptin in the blood predicted a greater decrease in the overall score and score on the subscale of negative symptoms of PANSS after six months. During the post-hoc analysis, the associations between baseline IL-6 levels and symptom reduction were strongest in patients receiving SGA ziprasidone or quetiapine. The results obtained provide additional evidence that measuring inflammatory markers in the blood may be important for the clinical management of patients with schizophrenia. In particular, these markers can be helpful in selecting antipsychotic therapy for a more personalized approach to the treatment of patients with schizophrenia [62].

It seems interesting that, due to the established role of neuroinflammation in the pathogenesis of schizophrenia in addition to the immunomodulatory effect of antipsychotics, the potential therapeutic effect of anti-inflammatory drugs in schizophrenia is also being discussed. Jeppesen et al. presented a meta-analysis, according to which the addition of anti-inflammatory drugs to basic antipsychotic therapy reduces the clinical manifestations of schizophrenia (according to the PANSS scale) [55].

CONCLUSION

The data accumulated to date indicate the important role of inflammation in the pathogenesis of schizophrenia. Moreover, the reviewed literature data allow us to assume that in some cases, chronic inflammation, both at the systemic and central nervous system levels, is not only a pathogenetic, but also an etiological factor in schizophrenia. In this regard, anti-inflammatory therapy can be an important component in the management of patients with schizophrenic spectrum disorders. It seems also relevant to analyze the existing classical antipsychotic therapy for its anti-inflammatory effects.

Numerous studies that have studied the effects of first- and second-generation antipsychotics on different groups of patients indicate mainly a common anti-inflammatory vector of action of these drugs. However, there is a significant amount of ambiguous and contradictory data. Hence, further research is needed to elucidate the anti-inflammatory effects of antipsychotics, which may lead to the discovery of new mechanisms of action to affect neuroinflammation by using these drugs more efficiently for therapeutic purposes.

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