Review article
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The importance of immune biomarkers in predicting therapeutic response in schizophrenia

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Schizophrenia is a chronic, severe, and often highly disabling neurodegenerative disorder affecting 1% of the global population. To this day, the pathogenesis of schizophrenia remains insufficiently understood; however, there is increasing evidence pointing to the role of the immune system in the development of all psychotic disorders, including schizophrenia. Despite the discovery of newer generations of antipsychotic medications, a significant percentage of therapy-resistant schizophrenia persists, with about one-third of patients affected by this form of schizophrenia. As recent emphasis is placed on prevention, early detection of the disease, and the development of personalized treatment approaches, there is a growing need to identify new markers to facilitate this process. Immune biomarkers such as interleukins and C-reactive protein, which can be rapidly measured from easily accessible bodily fluids, are emerging as potential biomarkers for schizophrenia. Their use could facilitate diagnosis, monitoring of disease progression and prognosis, as well as tracking response to antipsychotic therapy.

Keywords: schizophrenia, biomarkers, interleukins, C-reactive protein

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Značaj imunskih biomarkera u predviđanju terapijskog odgovora kod shizofrenije

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Shizofrenija je hronični, teški i često visoko onesposobljavajući neurodegenerativni poremećaj koji pogađa oko 1% svetske populacije. Do danas patogeneza shizofrenije nije u potpunosti razjašnjena; međutim, sve je više dokaza koji ukazuju na ulogu imunskog sistema u razvoju svih psihotičnih poremećaja, uključujući i shizofreniju. Uprkos razvoju novijih generacija antipsihotika, značajan procenat terapijski rezistentne shizofrenije i dalje postoji, pri čemu je oko jedne trećine pacijenata pogođeno ovim oblikom bolesti. Kako se savremeni fokus sve više usmerava na prevenciju, rano otkrivanje bolesti i razvoj personalizovanih terapijskih pristupa, javlja se rastuća potreba za identifikacijom novih markera koji bi olakšali ovaj proces. Imunski biomarkeri, poput interleukina i C-reaktivnog proteina, koji se mogu brzo odrediti iz lako dostupnih telesnih tečnosti, nameću se kao potencijalni biomarkeri shizofrenije. Njihova primena mogla bi doprineti dijagnostici, praćenju progresije bolesti i prognoze, kao i proceni odgovora na antipsihotičku terapiju.

Ključne reči: shizofrenija, biomarkeri, interleukini, C-reaktivni protein

Introduction

Schizophrenia is a chronic, hereditary, and disabling neurodegenerative brain disease with a heterogeneous genetic and neurobiological background. Symptoms of schizophrenia include positive, negative, and cognitive symptoms, as well as mood changes. Hallucinations, delusions, and disorganized speech and behavior are considered as positive symptoms, whereas emotional passivity, social dysfunction, poverty of speech, and loss of interest and motivation belong to negative ones. Cognitive symptoms include deficits in working memory, attention, and executive functions, such as the ability to organize and abstract thinking. It is estimated that schizophrenia affects 1% of the population worldwide (1-3). According to the World Health Organization, psychotic disorders, including schizophrenia, are the eighth leading global cause of disability for individuals aged 15 to 44, ranked above violence, hearing loss, and disability resulting from war injuries (4).

The etiopathogenesis of schizophrenia is far from clear. The earliest proposed pathogenic mechanism of schizophrenia relies on dopamine hypothesis, where changes in dopamine neurotransmission are considered responsible for positive and negative symptoms (5). There is a consensus that psychotic disorders are heterogeneous, in many cases with a complex multifactorial etiology.

Among other, family, twin, and adoption studies suggest a significant role of genetic factors in its etiology. Genetic factors could be associated with susceptibility to the disorder (i.e., they represent risk factors) in the presence of negative environmental influences, and it has been proposed to be referred as plasticity variants, as they modulate sensitivity to both negative and positive environmental influences (1). However, in recent years, there has been increasing discussion about the role of adaptive and innate immune processes in the etiology of psychotic disorders (6). Recent genome-wide association studies (GWAS) suggest a link between schizophrenia and genes involved in immune function, such as the major histocompatibility complex (MHC) locus (7) and complement genes (8). Several studies have found that adjuvant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with improvements in psychopathology in some patients with schizophrenia (9, 10), and that baseline levels of inflammatory biomarkers in the blood may predict the response to these agents (11, 12). Epidemiological studies have also confirmed the association between psychotic disorders and autoimmune diseases. The rates of autoimmune disorders such as celiac disease, Graves' disease, systemic lupus erythematosus (SLE), multiple sclerosis, autoimmune hepatitis, and psoriasis are

higher in individuals with schizophrenia (13). Peripheral inflammation could enhance the permeability of the blood-brain barrier, leading to a cerebral inflammation (6). Possible mechanisms of immune-mediated psychosis is presented in Figure 1.

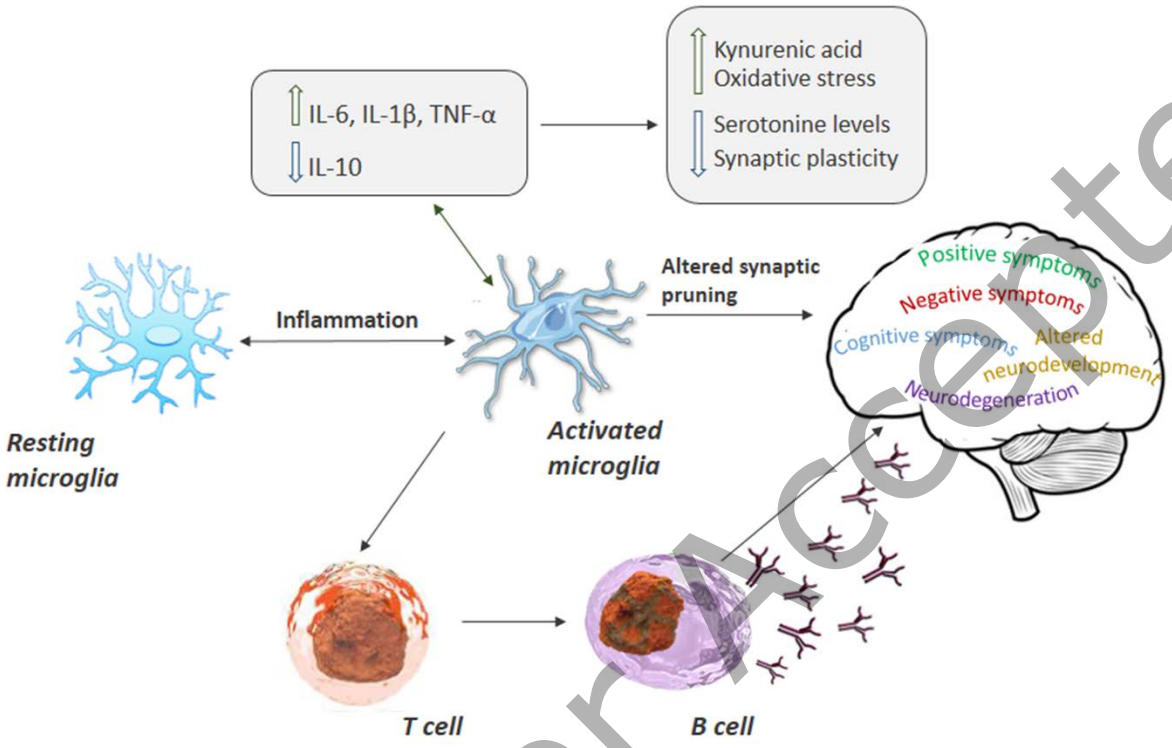

Figure 1. Illustrative representation of possible mechanisms of immunologically induced psychosis. Modified from Khandaker et al., 2015. (6)

Several systematic reviews and meta-analyses provide evidence of altered cytokine levels in the peripheral blood of patients with first-episode psychosis or schizophrenia, further indicating increased immune activation (14-25). Miller et al. demonstrated that patients with an acute relapse of schizophrenia express elevated levels of peripheral interleukins (IL), including IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and reduced levels of IL-10 compared to healthy controls (18). Two post-mortem studies showed that markers of microglial activation, IFN-γ, and TNF-α were also elevated in post-mortem brain tissue in these patients (26, 27). All these studies suggest increased peripheral and central inflammation in patients with established schizophrenia and its association with treatment response.

Antipsychotics in the treatment of schizophrenia

Antipsychotic medications have been the cornerstone of schizophrenia treatment since the 1950s, when first-generation antipsychotics (FGAs) were introduced and shown to alleviate positive symptoms of the disorder (26). Despite decades of therapeutic use, the treatment of schizophrenia remains a considerable clinical challenge, as current antipsychotics are not uniformly effective across the full spectrum of symptoms. All available antipsychotic drugs primarily exert their effects through modulation of the dopamine D2 receptor. FGAs and second-generation antipsychotics (SGAs) function as D2 receptor antagonists, whereas third-generation antipsychotics act as partial agonists or ligands at this receptor, and some also target related dopamine receptor subtypes (e.g., D3, D4, D5) (27).

Chlorpromazine, a prototypical FGA, exerts its antipsychotic action by blocking D2 receptors in the brain. However, this mechanism is associated with a broad range of adverse effects, including extrapyramidal symptoms, tardive dyskinesia, and dystonia. In contrast, clozapine, an SGA, primarily acts as an antagonist of serotonin 5-HT2A receptors and presents a lower risk of motor side effects. Nevertheless, clozapine use is frequently accompanied by metabolic disturbances, including a high prevalence of metabolic syndrome (28, 29). Aripiprazole, representative of the third generation of antipsychotics, differs fundamentally from previous agents in that it acts as a partial agonist at D2 receptors. Rather than completely blocking dopamine activity, it modulates dopamine transmission, helping to stabilize dopamine levels within a physiologically optimal range. This pharmacological profile has earned aripiprazole the designation of a “dopamine stabilizer” (28).

Approximately one-third of patients with schizophrenia meet the criteria for treatment-resistant schizophrenia (TRS) (30). The biological mechanisms behind the lack of response to antipsychotics are still unclear (31), but there is increasing evidence that excessive immune system activity may be of importance (15, 32, 33). There are two leading theories on TRS: one suggests normal dopamine function but with dysregulation of serotonergic, glutamatergic, or inflammatory pathways, while the second theory proposes that dopaminergic supersensitivity leads to TRS over time (34).

All of the above highlights need to consider newer treatment options, more frequent use of personalized treatments, as well as finding objective biomarkers for easier and earlier diagnosis, monitoring, and prediction of disease progression, as well as markers for assessing treatment response. Immune biomarkers are increasingly being used as markers for numerous physical

conditions because they can be quickly measured from easily accessible bodily fluids such as plasma/serum, urine, and cerebrospinal fluid (CSF), and as such, they impose themselves as potential biomarkers for schizophrenia (35, 36, 37).

Therefore, in this review we sumarized the most common immune biomarkers that could be of help in predicting therapeutic response in schizophrenia.

Immunological biomarkers as predictors of treatment response in schizophrenia

Immunological biomarkers are widely utilized in the diagnosis and monitoring of numerous physical illnesses, including both systemic conditions and those confined to the central nervous system (CNS). Given the growing recognition of the immune system's involvement in psychotic disorders, it is increasingly likely that immunological biomarkers will assume a significant role in the field of biological psychiatry in the future (38). A substantial body of evidence supports the role of inflammation as a contributing factor in the pathophysiology of schizophrenia. Studies have identified associations between elevated levels of specific perinatal inflammatory cytokines (IL-6, IL-1β, TNF-α, IL-8, IFN-γ) and an increased risk of developing schizophrenia later in life (39). Additionally, epidemiological data indicate that a history of severe infections or autoimmune diseases is associated with a heightened risk of schizophrenia (40).

C-reactive protein and schizophrenia

C-reactive protein (CRP), as a marker of the acute phase of inflammation, is one of the most sensitive biological markers of peripheral inflammation applied in clinical practice. Its synthesis in hepatocytes in the liver dramatically increases in response to any type of inflammation, and it particularly reacts to stimulation by IL-6 or TNF-α (41). The role of CRP in schizophrenia is well-documented (42, 43). Namely, higher CRP levels have been confirmed in the peripheral blood of individuals with schizophrenia compared to healthy controls (44-47). These elevated CRP levels correlate with more severe symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS), aggression and agitation, comorbid depression and suicidal risk, cognitive decline, and treatment resistance (48-54).

Few studies have assessed the intensity of inflammation according to different phases of the disease. One longitudinal study (55) has found that CRP levels were significantly elevated during the acute phases of the illness, continuing even after 8 weeks of treatment, suggesting CRP as a "marker of characteristics" rather than a "marker of state." However, four meta-analyses failed to find such an association when comparing patients before and after antipsychotic treatment (45) or patients with their first episode of schizophrenia who had not used medication compared to controls (23, 56, 57). A meta-analysis that included 50 studies with patients at different stages of the disease, found that individuals with schizophrenia had higher CRP levels compared to controls in both acute and stable phases of the disease (58). Additionally, they found that patients with an acute exacerbation of the disease had higher CRP levels than stable patients, but this difference was not maintained when considering patients who were taking antipsychotics in both phases (58). Research has also been conducted to monitor CRP levels after the administration of specific antipsychotic medications. For example, Baptista et al. measured CRP levels in patients with chronic schizophrenia treated with different types of antipsychotics, and then switched to monotherapy with olanzapine. Increase of serum CRP levels were observed after 8 weeks of treatment with olanzapine (59).

A recent meta-analysis involving 2398 patients found an inverse relationship between CRP levels, as well as IL-6, IL-1β, and TNF-α in the plasma of schizophrenia patients, and the cognitive functioning of these patients across five cognitive domains (attention-processing speed, executive function, working memory, verbal and visual learning, and memory). The results of the meta-analysis indicated a significant decline in cognitive performance with higher inflammatory markers (60).

Interleukin-6 and schizophrenia

Interleukin-6 (IL-6) is an immune biomarker synthesized by macrophages, T and B lymphocytes, or by CNS microglia. Multiple functions of IL-6 include regulation of neurodevelopment, altering synaptic plasticity, regulation of various behaviors related to nutrition, sleep, and stress, and release of growth hormone (GHRH) and thyroid-stimulating hormone (TSH) (61, 62). Evidence from animal studies suggests that IL-6 may convert tryptophan into quinolinic acid by activating indoleamine 2,3-dioxygenase, and then into an NMDA antagonist in the central nervous system, which may activate schizophrenia symptoms (63).

Meta-analysis of Zhou et al. showed that the IL-6 serum level in schizophrenia patients was higher than in healthy controls (64). Furthermore, the IL-6 serum levels remained elevated even after treatment, as compared to healthy controls, suggesting important role of IL-6 in the pathogenesis of schizophrenia (64). Another study demonstrated positive correlation of IL-6 with the dose of applied antipsychotics, and negative correlation to general cognitive performance (65). Additionally, in patients with the first episode of psychosis, severe inflammation partially impaired the effectiveness of antipsychotics, with higher levels of IL-6 and IFN-γ associated with a poor response to antipsychotic therapy (15). Similarly, Song et al. (66) monitored IL-6, IL-1β and TNF-α levels in the serum during six months of risperidone therapy in patients with first-episode psychosis who had not been previously treated. They observed that IL-6 and IL-1β levels decreased during the first months but gradually returned to baseline levels by the 6-month period. In contrast, TNF-α levels continued to increase over time. Another study included 14 patients with first-episode schizophrenia who had not previously used medication. Biomarker levels before and after eight weeks of monotherapy with olanzapine were monitored. It was found that negative symptoms on the PANSS scale positively correlated with initial IL-6 levels, as well as with IL-27 levels (67).

Furthermore, a positive correlation was found between IL-6 levels and PANSS general psychopathological subscales in patients with TRS, thus providing evidence of IL-6 as a TRS predictor (68).

CRP and IL-6 as markers of metabolic syndrome induced by the use of SGA

It is well-established that second-generation antipsychotics (SGAs) can contribute to the development of metabolic syndrome (MetS), a major risk factor for cardiovascular disease (69). Existing literature indicates that immune dysregulation may play a role in the onset of chronic metabolic conditions (70), and abnormal levels of inflammatory biomarkers have been observed in individuals with schizophrenia undergoing treatment with SGAs (71). This suggests that chronic low-grade inflammation may be a contributing factor in the pathogenesis of MetS in patients with schizophrenia.

Moreover, research has demonstrated a link between MetS and its individual components with cognitive decline and an increased risk of dementia (72, 73). A preliminary study by Zhang et al. found that patients with schizophrenia and comorbid MetS exhibited more severe cognitive impairments than those without MetS, with inflammation potentially playing a central role in this

association (74). Among SGAs, clozapine and olanzapine have been most strongly associated with obesity, further contributing to MetS risk. Patients diagnosed with MetS have been found to exhibit significantly elevated plasma levels of interleukin-6 (IL-6), suggesting a heightened inflammatory state in individuals with both schizophrenia and MetS (75).

Early studies have also proposed that inflammation may be a primary mechanism underlying clozapine-induced MetS. Evidence indicates that clozapine may stimulate IL-6 secretion in insulin-responsive and obesity-related cell types (76). Additional correlation analyses have identified IL-6 as being significantly inversely related to high-density lipoprotein (HDL) levels, suggesting that higher IL-6 concentrations are associated with lower HDL levels (77). Notably, elevated IL-6 levels were detected only in male patients with MetS, and a significant correlation between IL-6 and HDL was found in men, but not in women (77).

Despite the limited number of studies systematically examining sex differences in the inflammatory characteristics of MetS in schizophrenia, existing evidence does suggest gender-specific variations (78–80). Some studies have reported higher metabolic risk and reduced antioxidant enzyme activity in men with schizophrenia compared to women (79–81). These differences may be attributed to the protective effects of female sex hormones against oxidative stress and immune-mediated inflammation (82). Consequently, men may be more vulnerable to the effects of immune activation and IL-6 elevation, potentially making them more prone to developing MetS.

Interleukin-2 and schizophrenia

Interleukin-2 (IL-2) is a cytokine that functions primarily as a growth factor regulating the autocrine secretion of T lymphocytes. To a lesser extent, IL-2 is also produced by monocytes, macrophages, and endothelial cells. IL-2 may play a role in various pathological processes implicated in the pathophysiology of schizophrenia, including disturbances in neurotransmitter systems (83).

In particular, IL-2 has been shown to influence dopamine metabolism (22, 84, 85). Given that dopaminergic hypersensitivity is one of the most widely accepted hypotheses explaining the pathogenesis of schizophrenia, several researchers have proposed a potential link between IL-2 levels and the clinical manifestations of the disorder. This includes possible associations with tardive dyskinesia (TD) (86, 87), as well as the negative and cognitive symptoms characteristic of schizophrenia. Asevedo and colleagues investigated the correlation between peripheral IL-2 levels,

symptom severity, and cognitive performance in patients with schizophrenia (88). In a comparative study involving 29 outpatients receiving long-term antipsychotic therapy and 26 healthy controls, they found that IL-2 levels were negatively correlated with the severity of negative symptoms and impairments in language function (88). Furthermore, experimental data suggest that clozapine may modulate IL-2 levels, exerting anti-inflammatory effects through inhibition of NLRP3 inflammasome expression, as demonstrated by Giridharan et al. (89). Several human studies have also reported changes in IL-2 concentrations following antipsychotic treatment. A meta-analysis indicated a general decrease in IL-2 levels among schizophrenia patients treated with antipsychotics (90). In a study by Yuan et al., IL-2 levels in patients with treatment-resistant schizophrenia were found to be positively correlated with clozapine dosage—but notably, this association was observed only in female patients (91).

Additionally, a comprehensive meta-analysis of 23 studies reported an increase in IL-2 levels and a decrease in IL-1β and IFN-γ levels following antipsychotic treatment, supporting the notion that antipsychotics exert anti-inflammatory effects in schizophrenia (92). Despite a substantial body of research, findings regarding IL-2 levels in schizophrenia remain inconsistent. Some studies have reported elevated IL-2 levels (93–95), others have documented reductions (88, 96), while some have found no significant differences compared to controls (97). These discrepancies may be attributable to variations in factors such as ethnicity, illness duration, stage of disease progression, symptom severity, and methodological differences in control group selection.

Interleukin-1α and schizophrenia

Interleukin-1α (IL-1α) is a pro-inflammatory cytokine that exerts its effects not only through binding to cell surface receptors but also via translocation into the cell nucleus, where it may influence gene expression (98). It is primarily secreted by activated microglia, macrophages, and lymphocytes. IL-1α promotes mast cell maturation and the subsequent release of various inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-4 (99). Emerging evidence suggests that IL-1α may play a role in the development and maturation of the nervous system. Early studies demonstrated that microglia-derived IL-1α contributes to both neurodegenerative processes and neuroprotection by regulating synaptic plasticity (100). Furthermore, IL-1α has been shown to exert trophic effects on dopaminergic neurons in both *in vivo* and *in vitro* models—mechanisms closely linked to the neurobiology of schizophrenia (101). However, findings on IL-1α levels in plasma and cerebrospinal fluid of individuals with schizophrenia

have been inconsistent (102–104). These discrepancies may be related to the stage of illness. For instance, one study reported no significant changes in IL-1α levels following pharmacological treatment or modified electroconvulsive therapy (105). Additionally, changes in IL-1α were not correlated with reductions in symptom severity, as measured by the Positive and Negative Syndrome Scale (PANSS).

Conversely, elevated IL-1α levels have been observed in schizophrenia patients with co-occurring metabolic syndrome, even after six weeks of treatment with atypical antipsychotics (106). In another study, decreased IL-1α expression was found in conjunction with reduced levels of interferon-gamma-inducible protein 10 (IP-10) in patients with schizophrenia (107). These findings have led to the hypothesis that a suppressed upstream signaling pathway may be involved in the altered inflammatory response observed in schizophrenia.

Conclusion

Since psychotic disorders, including schizophrenia, are among the most common causes of global disability, the identification of new forms of therapy and reliable biomarkers for assessing treatment response is of significant importance. As the etiopathogenesis of schizophrenia remains insufficiently understood, the role of immune mechanisms in the development of psychiatric disorders is gaining increasing attention. Numerous studies from the past century have confirmed this role and suggest that immune biomarkers, such as CRP and interleukins, could serve as additional diagnostic tools, prognostic markers, and indicators of response to antipsychotic therapy. However, the data obtained from current studies are heterogeneous, so further research should focus on further clarifying the already known immune mechanisms in the pathogenesis of schizophrenia, as well as proving the role of biomarkers in these processes in larger samples.

Future research could explore the effectiveness of incorporating immunological therapy, with mechanisms of action based on suppressing the overactive immune response in these patients. Immunological therapy could become an integral part of schizophrenia treatment in the future, reducing the occurrence of therapy-resistant schizophrenia and improving the quality of life for patients.

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References

1. Halldorsdottir T, Binder EB. Gene × Environment Interactions: From Molecular Mechanisms to Behavior. Annu Rev Psychol. 2017; 68: 215-241.

2. Kahn RS, Sommer IE, Murray RM, et al. Schizophrenia. Nat Rev Dis Primers. 2015; 1: 15067.

3. Chan MK, Krebs MO, Cox D, et al. Development of a blood-based molecular biomarker test for identification of schizophrenia before disease onset. Transl Psychiatry. 2015; 5 (7): e601.

4. Rangaswamy Srinivasa Murthy JMB, Epping-Jordan J, Funk M, Thomson Prentice BS, Saxena S.. The World Health Report: 2001. Geneva: World Health Organization; 2001.

5. Stępnicki P, Kondej M, Kaczor AA. Current concepts and treatments of schizophrenia. Molecules. 2018; 23(8): 2087.

6. Khandaker GM, Cousins L, Deakin J, et al. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry. 2015; 2 (3): 258-270.

7. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. Nat Genet. 2011;4 3 (10): 969-976.

8. Sekar A, Bialas AR, de Rivera H, et al. Author Correction: Schizophrenia risk from complex variation of complement component 4. Nature. 2022; 601 (7892): E4-E5.

9. Nitta M, Kishimoto T, Müller N, et al. Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. Schizophr Bull. 2013; 39 (6): 1230-1241.

10. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. Schizophr Bull. 2014; 40 (1): 181-191.

11. Laan W, Grobbee DE, Selten JP, et al. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010; 71 (5): 520-527.

12. Müller N, Ulmschneider M, Scheppach C, et al. COX-2 inhibition as a treatment approach in schizophrenia: immunological considerations and clinical effects of celecoxib add-on therapy. Eur Arch Psychiatry Clin Neurosci. 2004; 254 (1): 14-22.

13. Benros ME, Eaton WW, Mortensen PB. The epidemiologic evidence linking autoimmune diseases and psychosis. Biol Psychiatry. 2014; 75 (4): 300-306.

14. Perkins DO, Jeffries CD, Addington J, et al. Towards a psychosis risk blood diagnostic for persons experiencing high-risk symptoms: preliminary results from the NAPLS project. Schizophr Bull. 2015; 41 (2): 419-428.

15. Mondelli V, Ciufolini S, Belvederi Murri M, et al. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. Schizophr Bull. 2015; 41 (5): 1162-1170.

16. Goldsmith DR, Rapaport MH, Miller B.J. A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. Mol. Psychiatry. 2016; 21: 1696–1709.

17. Wang AK, Miller BJ. Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. Schizophr. Bull. 2018; 44: 75–83.

18. Miller BJ, Buckley P, Seabolt W, et al. Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects. Biol. Psychiatry. 2011; 70: 663–671.

19. Gallego JA, Blanco EA, Husain-Krautter S, et al. Cytokines in cerebrospinal fluid of patients with schizophrenia spectrum disorders: New data and an updated meta-analysis. Schizophr. Res. 2018; 202: 64–71.

20. Frydecka D, Krzystek-Korpacka M, Lubeiro A, et al. Profiling inflammatory signatures of schizophrenia: A cross-sectional and meta-analysis study. Brain Behav Immun. 2018; 71: 28-36.

21. Pillinger T, Osimo EF, Brugger S, et al. A meta-analysis of immune parameters, variability, and assessment of modal distribution in psychosis and test of the immune subgroup hypothesis. Schizophr Bull. 2019; 45 (5): 1120-1133.

22. Potvin S, Stip E, Sepehry AA, et al. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry. 2008; 63 (8): 801-808.

23. Zajkowska Z, Mondelli V. First-episode psychosis: an inflammatory state? Neuroimmunomodulation. 2014; 21 (2-3): 102-108.

24. Mondelli V, Vernon AC, Turkheimer F, et al. Brain microglia in psychiatric disorders. Lancet Psychiatry. 2017; 4 (7): 563-572.

25. Trépanier MO, Hopperton KE, Mizrahi R, et al. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol Psychiatry. 2016; 21 (8): 1009-1026.

26. Zhang C, Li Z, Shao Y, et al. Association study of tryptophan hydroxylase-2 gene in schizophrenia and its clinical features in Chinese Han population. J Mol Neurosci. 2011; 43: 406–411.

27. Luedtke R, Rangel-Barajas C, Malik M, et al. Bitropic D3 dopamine receptor selective compounds s potential antipsychotics. Curr. Pharm. Des. 2015; 21: 3700–3724.
28. Mailman, R.B.; Vishakantha, M. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? Curr. Pharm. Des. 2010; 16: 488–501.

29. Hirsch L, Yang J, Bresee L, et al. Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies. Drug Saf. 2017; 40: 771–781.

30. Meltzer HY. Treatment-resistant schizophrenia--the role of clozapine. Curr Med Res Opin. 1997; 14 (1): 1-20.

31. Gillespie AL, Samanaite R, Mill J, Egerton A, MacCabe JH. Is treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? a systematic review. BMC Psychiatry. 2017; 17 (1): 12.

32. Zhang XY, Zhou DF, Cao LY, et al. Changes in serum interleukin-2, -6, and -8 levels before and during treatment with risperidone and haloperidol: relationship to outcome in schizophrenia. The Journal of Clinical Psychiatr. 2004; 65: 940-947.

33. Miller BJ, Goldsmith DR. Towards an immunophenotype of schizophrenia: progress, potential mechanisms and future directions. Neuropsychopharmacol. 2017; 42 (1): 299-317.

34. Potkin SG, Kane JM, Correll CU, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. NPJ Schizophr. 2020; 6(1): 1.

35. Demjaha A, Lappin JM, Stahl D, et al. Antipsychotic treatment resistance in first-episode psychosis: Prevalence, subtypes and predictors. Psychol. Med. 2017; 47: 1981–1989.

36. Levine SZ, Rabinowitz J, Faries D, et al. Treatment response trajectories and antipsychotic medications: Examination of up to 18months of treatment in the CATIE chronic schizophrenia trial. Schizophr. Res. 2012; 137: 141–146.

37. Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: A systematic review and network meta-analysis. Lancet. 2022; 399: 824–836.

38. Perkovic MN, Erjavec GN, Strac DS, Uzun S, Kozumplik O, Pivac N. Theranostic biomarkers for schizophrenia. Int J Mol Sci. 2017;18(4):733.

39. Fineberg AM, Ellman LM. Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. Biol Psychiatry. 2013; 73 (10): 951-966.
40. Benros ME, Nielsen PR, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am J Psychiatry. 2011; 168 (12): 1303-1310.

41. Castell JV, Gómez-Lechón MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. Hepatology. 1990;12(5):1179-1186.

42. Jiwan G,Chamlagai D,Bera NR, et al. Elevated levels of C-reactive Protein and IL-6 among the antipsychotic medicating schizophrenia patients of Siliguri, West Bengal, India. Nord J Psychiat. 2018;72 (4): 311-17.

43. Fond G, Resseguier N, Schürhoff F, et al. Relationships between low-grade peripheral inflammation and psychotropic drugs in schizophrenia: Results from the National FACE-SZ Cohort. Eur Arch Psy Clin N. 2018; 268 (6): 541-53.

44. Miller BJ, Culpepper N, Rapaport MH. C-reactive protein levels in schizophrenia: a review and meta-analysis. Clin Schizophr Relat Psychoses. 2014; 7 (4): 223-230.

45. Fernandes BS, Steiner J, Bernstein HG, et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry. 2016; 21 (4): 554-564.

46. Wang Z, Li P, Chi D, et al. Association between C-reactive protein and risk of schizophrenia: An updated meta-analysis. Oncotarget. 2017; 8 (43): 75445-75454.

47. Dickerson F, Stallings C, Origoni A, et al. C-reactive protein is elevated in schizophrenia. Schizophr Res. 2013; 143 (1): 198-202.

48. Dimitrov DH, Lee S, Yantis J, et al. Elevated serum levels of high-sensitivity C-reactive proteins are associated with severe delusional symptoms in a subgroup of patients with schizophrenia. J Clin Psychiatry. 2016; 77 (1): 131-132.

49. Bolu A, Aydın MS, Akgün A, et al. Serum levels of high sensitivity C-reactive protein in drug-naïve first-episode psychosis and acute exacerbation of schizophrenia. Clin Psychopharmacol Neurosci. 2019; 17 (2): 244-249.

50. Boozalis T, Teixeira AL, Cho RY, Okusaga O. C-reactive protein correlates with negative symptoms in patients with schizophrenia. Front Public Health. 2018; 5: 360.

51. Barzilay R, Lobel T, Krivoy A, et al. Elevated C-reactive protein levels in schizophrenia inpatients is associated with aggressive behavior. Eur Psychiatry. 2016; 31: 8-12.

52. Kachouchi A,Sebbani M, Akammar S, et al. C-reactive protein and agitation in patients with schizophrenia: A cohort study with a control group. Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique.2020; 46 (4): 264-68
53. Bora E. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. 2021; 51 (9): 1589.

54. Faugere M, Micoulaud-Franchi JA, Faget-Agius C, Lançon C, Cermolacce M, Richieri R. High C-reactive protein levels are associated with depressive symptoms in schizophrenia. J Affect Disord. 2018; 225: 671-675.

55. De Picker L, Fransen E, Coppens V, et al. Immune and neuroendocrine trait and state markers in psychotic illness: decreased kynurenines marking psychotic exacerbations. Front Immunol. 2020; 10: 2971.

56. Çakici N, Sutterland AL, Penninx BWJH, et al. Altered peripheral blood compounds in drug-naïve first-episode patients with either schizophrenia or major depressive disorder: a meta-analysis. Brain Behav Immun. 2020; 88: 547-558.

57. Fraguas D, Díaz-Caneja CM, Ayora M, et al. Oxidative stress and inflammation in first-episode psychosis: A systematic review and meta-analysis. Schizophr Bull. 2019; 45 (4): 742-751.

58. Lestra V, Romeo B, Martelli C, et al. Could CRP be a differential biomarker of illness stages in schizophrenia? A systematic review and meta-analysis. Schizophr Res. 2022; 246: 175-186.

59. Baptista T, Dávila A, El Fakih Y, et al. Similar frequency of abnormal correlation between serum leptin levels and BMI before and after olanzapine treatment in schizophrenia. Int Clin Psychopharmacol. 2007; 22 (4): 205-211.

60. Patlola SR, Donohoe G, McKernan DP. The relationship between inflammatory biomarkers and cognitive dysfunction in patients with schizophrenia: A systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2023; 121:110668.

61. Bauer S, Kerr BJ, Patterson PH. The neuropoietic cytokine family in development, plasticity, disease and injury. Nat Rev Neurosci. 2007; 8 (3): 221-232.

62. Spangelo BL, Judd AM, Isakson PC, MacLeod RM. Interleukin-6 stimulates anterior pituitary hormone release in vitro. Endocrinology. 1989; 125 (1): 575-577.

63. Walker AK, Budac DP, Bisulco S, et al. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. Neuropsychopharmacol. 2013; 38 (9): 1609-1616.

64. Zhou X, Tian B, Han HB. Serum interleukin-6 in schizophrenia: A system review and meta-analysis. Cytokine. 2021; 141: 155441.

65. Ribeiro-Santos R, de Campos-Carli SM, Ferretjans R, et al. The association of cognitive performance and IL-6 levels in schizophrenia is influenced by age and antipsychotic treatment. Nord J Psychiatry. 2020; 74 (3): 187-193.

66. Song X, Fan X, Li X, et al. Changes in pro-inflammatory cytokines and body weight during 6-month risperidone treatment in drug naïve, first-episode schizophrenia. Psychopharmacology (Berl). 2014; 231 (2): 319-325.

67. Hatziagelaki E, Tsiavou A, Gerasimou C, et al. Effects of olanzapine on cytokine profile and brain-derived neurotrophic factor in drug-naive subjects with first-episode psychosis. Exp Ther Med. 2019; 17 (4): 3071-3076.

68. Yang H, Zhang J, Yang M, et al. Catalase and interleukin-6 serum elevation in a prediction of treatment-resistance in male schizophrenia patients. Asian J Psychiatr. 2023; 79: 103400.

69. Lone S, Lone K, Khan S, et al. Assessment of metabolic syndrome in Kashmiri population with type 2 diabetes employing the standard criteria's given by WHO, NCEPATP III and IDF. J Epidemiol Glob Health. 2017; 7: 235–239.

70. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444 (7121): 860-867.

71. Beumer W, Drexhage RC, De Wit H, et al. Increased level of serum cytokines, chemokines and adipokines in patients with schizophrenia is associated with disease and metabolic syndrome. Psychoneuroendocrinology. 2012; 37: 1901–1911.

72. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. Nat Rev Cardiol. 2015; 12: 267–277.

73. Kaffashian S, Dugravot A, Elbaz A, et al. Predicting cognitive decline: a dementia risk score vs. the Framingham vascular risk scores. Neurology. 2013; 80: 1300–1306.

74. Zhang C, Fang X, Yao P, et al. Metabolic adverse effects of olanzapine on cognitive dysfunction: a possible relationship between BDNF and TNF-alpha. Psychoneuroendocrino. 2017 ;81: 138–143.

75. Zhang C, Wu Z, Zhao G, Wang F, Fang Y. Identification of IL6 as a susceptibility gene for major depressive disorder. Sci Rep. 2016; 6: 31264

76. Contreras-Shannon V, Heart DL, Paredes RM, et al. Clozapine-induced mitochondria alterations and inflammation in brain and insulin-responsive cells. PLoS One. 2013; 8: e59012.

77. Fang X, Wang Y, Chen Y, Ren J, Zhang C. Association between IL-6 and metabolic syndrome in schizophrenia patients treated with second-generation antipsychotics. Neuropsychiatr Dis Treat. 2019; 15: 2161-2170.

78. Zhang Y, Chen M, Wu Z, et al. Association study of Val66Met polymorphism in brain-derived neurotrophic factor gene with clozapine-induced metabolic syndrome: preliminary results. PLoS One. 2013;8:e72652.

79. Chen S, Broqueres-You D, Yang G, et al. Male sex may be associated with higher metabolic risk in first-episode schizophrenia patients: a preliminary study. Asian J Psychiatr. 2016; 21: 25–30.

80. Kraemer S, Minarzyk A, Forst T, et al. Prevalence of metabolic syndrome in patients with schizophrenia, and metabolic changes after 3 months of treatment with antipsychotics – results from a German observational study. BMC Psychiatry. 2011; 11: 173.

81. Pepe H, Balci SS, Revan S, et al. Comparison of oxidative stress and antioxidant capacity before and after running exercises in both sexes. Gend Med. 2009;6:587–595.

82. Harish G, Venkateshappa C, Mahadevan A, Pruthi N, Srinivas Bharath MM, Shankar SK. Glutathione metabolism is modulated by postmortem interval, gender difference and agonal state in postmortem human brains. Neurochem Int. 2011; 59: 1029–1042.

83. Huang Y, Zhang X, Zhou N. The Interrelation between Interleukin-2 and Schizophrenia. Brain Sci. 2022; 12 (9): 1154.

84. Meyer U, Feldon J, Schedlowski M, Yee BK. Immunological stress at the maternal-foetal interface: a link between neurodevelopment and adult psychopathology. Brain Behav Immun. 2006; 20 (4): 378-388.

85. Rankin JS, Zalcman SS, Zhu Y, Siegel A. Short- and long-term effects of interleukin-2 treatment on the sensitivity of periadolescent female mice to interleukin-2 and dopamine uptake inhibitor. PLoS One. 2013; 8 (5): e64473.

86. Rapaport MH, Lohr JB. Serum-soluble interleukin-2 receptors in neuroleptic-naive schizophrenic subjects and in medicated schizophrenic subjects with and without tardive dyskinesia. Acta Psychiatr Scand. 1994;90 (5) :311-315.

87. Liu H, Kang Y, Liang, J, et al. Lower serum interleukin-2 levels in schizophrenic patients with tardive dyskinesia. Psychiatry Res. 2012;198 (2):329–331.

88. Asevedo E, Rizzo LB, Gadelha A, et al. Peripheral interleukin-2 level is associated with negative symptoms and cognitive performance in schizophrenia. Physiol Behav. 2014; 129: 194-198.

89. Giridharan VV, Scaini G, Colpo GD, et al. Clozapine prevents Poly (I:C) induced inflammation by modulating Nlrp3 pathway in microglial cells. Cells. 2020; 9: 577.

90. Capuzzi E, Bartoli F, Crocamo C, et al. Acute variations of cytokine levels after antipsychotic treatment in drug-naïve subjects with a first-episode psychosis: A meta-analysis. Neurosci Biobehav Rev. 2017; 77: 122-128.

91. Yuan X, Wang S, Shi Y, et al. Pro-inflammatory cytokine levels are elevated in female patients with schizophrenia treated with clozapine. Psychopharmacology (Berl). 2022; 239 (3): 765-771.

92. Tourjman V, Kouassi É, Koué MÈ, et al. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. Schizophr Res. 2013; 151 (1-3): 43-47.

93. Ebrinc S, Top C, Öncül O, et al.. Serum Interleukin 1α and Interleukin 2 Levels in Patients with Schizophrenia. J. Int. Med. Res. 2002; 30: 314–317.

94. McAllister CG, van Kammen DP, Rehn TJ, et al. Increases in CSF levels of interleukin-2 in schizophrenia: effects of recurrence of psychosis and medication status. Am J Psychiatry. 1995; 152 (9): 1291-1297.

95. Chen L, Zheng WH, Du Y, et al. Altered peripheral immune profiles in first-episode, drug-free patients with schizophrenia: response to antipsychotic medications. Front Med (Lausanne). 2021; 8: 757655.

96. Zhang XY, Zhou DF, Cao LY, et al. Decreased production of interleukin-2 (IL-2), IL-2 secreting cells and CD4+ cells in medication-free patients with schizophrenia. J Psychiatr Res. 2002; 36 (5): 331-336.

97. Rapaport MH, McAllister CG, Pickar D, Tamarkin L, Kirch DG, Paul SM. CSF IL-1 and IL-2 in medicated schizophrenic patients and normal volunteers. Schizophr Res. 1997; 25 (2): 123-129.

98. Cohen I, Rider P, Carmi Y, et al. Differential release of chromatin-bound IL-1alpha discriminates between necrotic and apoptotic cell death by the ability to induce sterile inflammation. Proc Natl Acad Sci U S A. 2010; 107 (6): 2574-2579.

99. Arend WP, Palmer G, Gabay C. IL-1, IL-18, and IL-33 families of cytokines. Immunol Rev. 2008; 223: 20-38.

100. Ma H, Cheng N, Zhang C. Schizophrenia and Alarmins. Medicina (Kaunas). 2022 May 24;58(6):694.

101. Wang J, Bankiewicz KS, Plunkett RJ, Oldfield EH. Intrastriatal implantation of interleukin-1. Reduction of parkinsonism in rats by enhancing neuronal sprouting from residual dopaminergic neurons in the ventral tegmental area of the midbrain. J Neurosurg. 1994; 80 (3): 484-490.

102. Dawidowski B, Górniak A, Podwalski P, Lebiecka Z, Misiak B, Samochowiec J. The Role of Cytokines in the Pathogenesis of Schizophrenia. J Clin Med. 2021; 10 (17): 3849.

103. Zhou Y, Peng W, Wang J, et al. Plasma levels of IL-1Ra are associated with schizophrenia. Psychiatry Clin Neurosci. 2019; 73 (3): 109-115.

104. Balõtšev R, Koido K, Vasar V, et al. Inflammatory, cardio-metabolic and diabetic profiling of chronic schizophrenia. Eur Psychiatry. 2017; 39: 1-10.

105. Guo YF, Fu HB, Liu ZY, et al. Effects of the modified electric convulsive treatment (MECT) on cell factors of schizophrenia. Exp Ther Med. 2017; 13 (3): 873-876.

106. Boiko AS, Mednova IA, Kornetova EG, et al. Cytokine level changes in schizophrenia patients with and without metabolic syndrome treated with atypical antipsychotics. Pharmaceuticals (Basel). 2021; 14 (5): 446.

107. Izumi R, Hino M, Wada A, et al. Detailed postmortem profiling of inflammatory mediators expression revealed post-inflammatory alternation in the superior temporal gyrus of schizophrenia. Front Psychiatry. 2021; 12: 653821.