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The role of autoimmune processes in the course of mental illness - a review of the most important immunological markers and therapeutic perspectives

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Abstract

Background A growing body of research indicates that autoimmune processes may play a significant role in the etiopathogenesis of mental disorders common worldwide, including schizophrenia, affective disorders, and depression. Abnormal immune system activation, including elevated levels of proinflammatory cytokines and the presence of autoantibodies, is associated with exacerbated psychopathological symptoms and cognitive decline in some patients. At the same time, research results remain inconclusive due to factors such as the heterogeneity of clinical populations, differences in disease progression, the impact of pharmacological treatment, and varying methods for measuring immune markers. Despite these limitations, autoimmune phenomena represent a promising direction for the search for biomarkers and new therapeutic approaches.

Aim This study aims to review the current state of knowledge on the impact of autoimmune processes on the development of psychiatric conditions. This knowledge may aid in the future diagnosis and treatment of patients, especially in cases resistant to standard therapeutic methods.
Materials and Methods The review includes 27 studies published primarily between 2015 and 2025, selected for their number and relevance to current medical knowledge.
Results Research indicates that disturbances in the proper functioning of the immune system, including elevated levels of proinflammatory cytokines, microglial activation, and the presence of autoantibodies, can affect neuronal function, synaptic plasticity, and the integrity of the blood-brain barrier. Although the results of some studies remain uncertain due to methodological differences and clinical heterogeneity, a growing body of evidence suggests that immunological mechanisms may play a significant role in the pathogenesis of mental illness.
Conclusions A growing body of research shows that autoimmune processes may influence the development of certain mental illnesses through immune system dysfunction and the resulting inflammation in the central nervous system.

Keywords: autoimmunity, depression, schizophrenia.

Introduction

Recent years have seen a dynamic development in research on the etiopathogenesis of psychiatric illnesses. The prevailing theories of these conditions have focused on neurotransmitter imbalances (e.g., monoamines, glutamate, GABA) and neuroanatomy. However, a growing number of scientific articles indicate that these illnesses may have a more complex basis, including inflammatory and autoimmune processes. As this concept has developed, numerous immunological markers have been discovered that play a significant role in the development of these illnesses [2]. A significant example confirming this hypothesis is not only the description of inflammation in neurological disorders (e.g., autoimmune encephalitis), but also data indicating that antibodies directed against neuronal antigens or other immunological markers can be detected in patients with common psychiatric disorders. [1]

Overview of Immunological Processes

Prolonged elevated levels of proinflammatory cytokines activate inflammatory pathways in the brain, which can disrupt neurotransmitter balance and impair neurogenesis and neuroplasticity due to, among other things, reduced levels of Brain-Derived Neurotrophic Factor (BDNF) [3]. A study by JC Felger and FE Lotrich demonstrated that increased proinflammatory cytokine activity correlates with activation of the enzyme indoleamine-2,3-dioxygenase (IDO), which shifts tryptophan metabolism to the kynurenine pathway, leading to products such as kynurenine and quinolinic acid instead of serotonin synthesis. They also damage glutamatergic and dopaminergic synapses [4]. Another mechanism by which proinflammatory cytokines can impair dopamine synthesis involves limiting the activity of the coenzyme tetrahydrobiopterin (BH4), which is essential for dopamine synthesis. [5] Additionally, autoimmunity can lead to the development of autoantibodies against NMDARs. This leads to a reduction in NMDAR receptors in synapses, which in turn disrupts glutamatergic function.

In clinical settings, this can cause psychotic disorders and cognitive impairment. [6] Another article discusses that patients with rheumatic (autoimmune) diseases often demonstrate an impaired HPA axis response to inflammatory stimuli. This means that the production of endogenous glucocorticoids (e.g., cortisol) is insufficient to limit the inflammatory process. This prolongs the inflammatory state, which can translate into chronic symptoms and psychiatric disorders (e.g., chronic stress, fatigue, and depression). [7] However, the review "Autoimmune Diseases and Psychotic Disorders" demonstrates that autoimmunity and psychiatric disorders may share a common genetic basis. This may mean that some people are at greater risk of developing psychiatric disorders with autoimmunity, not because of a causal chain between the two phenomena, but because both may share a common genetic basis.[8]

Depressive Disorders

The study involved 60 women with primary Sjögren's syndrome. Of these, 39 had depression, and 34 had anxiety. Inflammatory biomarkers such as IL-6 were measured, and the severity of depression and anxiety was assessed simultaneously. It was found that patients with depression/anxiety had significantly elevated IL-6 levels, and IL-6 was a significant predictor of depression in this group (OR ≈ 3.23) [9].

Forty patients with first-episode depression (FDD) were examined before and after treatment, as well as 40 controls. Before treatment, patients with FDD had elevated IL-6 and IL-17 compared to controls. After treatment with an SSRI, IL-17 levels decreased, and this decrease correlated with a decrease in the HAMD (Hazardous Depression Scale) score [10].In another study of 82 patients with depression, proinflammatory cytokine levels were measured. Higher concentrations of IL-1β and TNF-α, among others, were associated with a more severe course of the disease and greater suicidal ideation [11]. A meta-analysis of 19 studies, including 21 independent trials, with a total of 36,174 participants (35,168 with depression and 34,094 with anxiety), shows a particularly strong association of these conditions with thyroid and skin autoimmunity, which may indicate that even autoimmune processes outside the CNS can affect mental health. [12] In a study involving 190 individuals with recurrent depression (and 100 healthy controls), the levels of cytokines associated with autoimmunity, such as IL-17, IL-21, IL-23, IL-35, and Foxp3, were measured. Significant disturbances in these immune mediators were found in depression compared to controls.[15]

One study of treatment-resistant depression observed an increased risk of subsequent development of autoimmune diseases, which may suggest that in some patients chronic depression accompanies autoimmunity.[13] However, research also indicates a possible bidirectional relationship between autoimmunity and depression.[14]

Psychotic Disorders

In a study involving 54 patients with schizophrenia and 118 healthy controls, 15 cytokines were measured. Compared to controls, patients had increased levels of CCL11, MIP-1α, sTNF-R1, and sTNF-R2, and decreased levels of IP-10, TNF-α, IL-2, and IL-4. The combination of five biomarkers, sTNF-R1, sTNF-R2, CCL11, IP-10, and IL-4, predicted the diagnosis of schizophrenia with a sensitivity of ~70% and a specificity of ~89%. Furthermore, patients with drug resistance had elevated levels of sTNF-R1, sTNF-R2, and MCP-1. This suggests that some

inflammatory markers may potentially be useful in clinical diagnosis and may also indicate patients with drug resistance. [16]
Another study included 71 patients with acute schizophrenia without pharmacotherapy for a minimum of 4 weeks and 55 healthy controls. Symptoms were assessed using the PANSS (Positive and Negative Syndrome Scale). During this time, levels of TNF-α, IL-8, and IL-18 were measured. The authors demonstrated associations between the levels of these cytokines and the severity of clinical symptoms during an episode of acute psychosis. [17]
An analysis of 25 studies, with a total of 2,398 patients with schizophrenia, also demonstrated a correlation between inflammation and cognitive deficits in patients with schizophrenia. [18] [19] However, a small study of 30 patients with schizophrenia and 30 healthy controls matched for gender and age, found no statistically significant differences in TNF-α and IL-6. This may indicate the influence of metabolic factors such as body weight on the results of immunological-psychiatric correlation [21].

Can markers aid diagnosis?
A comprehensive analysis encompassing 43 meta-analyses and 44 different inflammatory markers across eight major mental disorders revealed that 30 of the 44 markers demonstrated significant differences between individuals with schizophrenia and healthy controls. However, only a fraction of these markers were specific to a disorder. This suggests that inflammatory markers have some diagnostic power, but their low specificity limits their diagnostic utility. [22] A meta-analysis encompassing 25 studies, including a total of 2,398 patients with schizophrenia, examined the associations between levels of proinflammatory markers (IL-6, IL-1β, TNF-α, CRP) and cognitive functioning. Higher levels of these markers correlated with poorer performance on neuropsychological tests in both patients and controls. This suggests that inflammatory markers may have prognostic significance and indicate the risk of cognitive deficits.[23] A recent study (2025) reached similar conclusions, suggesting that elevated levels of certain inflammatory markers, such as hs-CRP, may predict the risk of developing mental disorders. In the future, inflammatory markers may be used as screening tools in individuals at increased risk of mental disorders. [24]

Immunomodulatory Treatment Prospects
A randomized, double-blind, 8-week study included 27 patients with schizophrenia or schizoaffective disorder with elevated inflammatory markers (IL-1β, IL-6, hsCRP, and/or elevated NLR). Canakinumab 150 mg (single subcutaneous injection) was administered versus placebo. A single administration of canakinumab reduces CRP and may improve positive symptoms in a subgroup of patients with increased inflammation, but larger and longer studies are needed to assess the efficacy of this treatment. However, no significant changes in negative symptoms or cognitive function were observed [25]. The randomized, double-blind, placebo-controlled study included 80 patients with chronic schizophrenia.
Treatment lasted for 8 weeks and included risperidone + fingolimod 0.5 mg/day or placebo.
Seventy patients completed the study (35 in each group). According to the authors, fingolimod as an adjunct to an antipsychotic drug could improve negative symptoms in patients with chronic schizophrenia, while maintaining good treatment tolerance. [26]

In another study, nine patients with refractory schizophrenia (SSD) and 10 with OCD received a single dose of 1000 mg of rituximab while continuing standard treatment. After a one-year follow-up, clinical results (SSD): 7 of the nine patients with SSD achieved ≥40% reduction in symptoms (PANSS) at week 12. In one patient, the reduction was maintained for approximately 3 years with rituximab administered every 6 months. In schizophrenia cases, an increase in gray matter volume (GMV) was observed in some brain regions (including the right insula and cortex), as well as increased functional connectivity (rs-FC) between brain structures. The results indicate that B-cell depletion may have therapeutic value in the treatment of refractory schizophrenia; however, further research is needed in this direction. [27] A study examining the mechanism of action of ECT (Electroconvulsive Therapy) included 8 patients with refractory schizophrenia and 13 controls. After ECT, a decrease in pro-inflammatory IL-6 and IL-12 and a decrease in anti-inflammatory IL-10 were observed, along with a concomitant reduction in symptoms (PANSS). This may indicate that the effect on the immune system is one of the mechanisms of ECT's therapeutic action. [20]

Discussion

Autoimmune processes may influence the development and course of mental disorders through inflammation and proinflammatory cytokines. In some patients, this is associated with symptom exacerbation, cognitive deficits, and changes in brain function. However, study results may prove unreliable due to differences in patient selection, overlapping conditions, disease stage, treatment, methods of measuring immunological markers, and genetic predisposition.

The use of immunological markers may find applications in future diagnostics and treatment selection, but further, larger, and more controlled studies are needed to better understand the mechanisms, identify specific patient groups, and confirm the safety and effectiveness of immunomodulatory therapies.

Conclusions

Research indicates that disturbances in the proper functioning of the immune system, including elevated levels of proinflammatory cytokines, microglial activation, and the presence of autoantibodies, can affect neuronal function, synaptic plasticity, and the integrity of the blood-brain barrier. Although the results of some studies remain uncertain due to methodological differences and clinical heterogeneity, a growing body of evidence suggests that immunological mechanisms may play a significant role in the pathogenesis of mental
illness.

DISCLOSURE

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