

Role of Inflammatory Cytokines in Schizophrenia

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Abstract. Schizophrenia is a complex psychological disorder with a prevalence rate that ranges from 0.16% to 1.21%. It affects individuals of different ages and genders, although the first onset of symptoms typically occurs during adolescence or young adulthood. Patients with schizophrenia often demonstrate impairments in cognition, emotion, and behavior, which can hinder their ability to interact with their surroundings. While the disease is persistent and chronic, most patients do not experience intellectual disabilities. Furthermore, schizophrenia places a heavy burden on society and the economy. As a result, there is a pressing need for extensive research on its etiology and pathogenesis, making it a prominent topic in psychiatric research. The neurotransmitter hypothesis, which suggests that schizophrenia may be associated with dysfunction in the dopamine system, has been widely utilized to study the pathogenesis of the disorder. Genetics, neuropathology, and neurotransmitter hypotheses provide important insights into the understanding of schizophrenia. However, further research is necessary to uncover the underlying causes and mechanisms of the disease fully. This review aims to provide a systematic introduction to the current understanding of schizophrenia, discuss the various hypotheses and findings related to its etiology and pathogenesis, and emphasize the role of the immune system in this disorder, thus improving the diagnosis, treatment, and prevention of schizophrenia. By exploring the immune system's involvement in schizophrenia, researchers can gain a more comprehensive understanding of the disease and develop novel interventions and treatments.

Keywords: Innate immunity, schizophrenia, psychotic disorder.

1. Introduction

Schizophrenia is a serious mental illness, in which patients often experience hallucinations, delusions, mental disorders, and abnormal emotions and behaviors. This disease brings a huge burden to patients, family members, and the entire society. The etiology and pathogenesis of schizophrenia have not yet been fully understood. However, research has confirmed that gene transfer between parents, surrounding environmental factors and neurochemical factors have a significant influence in its development. Understanding and exploring these factors is of great significance for us to gain a deeper understanding of schizophrenia and better manage and treat the disease.

In many recent studies, specialized scholars have begun to focus on immune dysfunction, and in particular, its impact on the onset and progression of schizophrenia has attracted the interest of researchers [1]. The immune system is closely related to the body's immune response, which protects the entirety of the body from everything that is harmful to us from invading the body and jeopardizing our health. Some studies have found that patients with schizophrenia have some abnormalities in immune function, including changes in immune cell activity and cytokine production. This indicates that schizophrenia may be related to immune dysfunction. Round et al. found that *Bacteroides fragilis* can induce Immune tolerance of intestinal microorganisms by producing polysaccharide A, thereby promoting the function of Foxp3+regulatory T cells (Tregs). The study also found that *Clostridium* (especially the IV and XIV system clusters) were more effective in inducing Tregs cell differentiation than *Lactobacillus* and *Bacteroides*. Romijn et al. proposed the concept of the brain-gut axis in 2008, which integrates neural conduction, endocrine, nutritional, and immunological signal transmission between CNS & gastrointestinal tract. There are strong links between our gut microbes and the CNS, and these studies reveal the extent to which these links are important and suggest a new term called the microbiota gut-brain axis.

The purpose of this review is to explore the immune dysfunction in schizophrenia and its impact on the occurrence and development of the disease. Specifically, this review focuses on the abnormal cytokines and changes in immune cell activity in patients with schizophrenia, as well as their association with disease symptoms and development. By gaining insight into what the immune system can specifically do about schizophrenia, it will allow researchers to better understand the pathophysiological mechanisms of the disease and has important implications for further research and for the benefit of people with mental illness.

2. Cytokines as key mediators of immune response

2.1. Definition and Function of Cytokines

Cytokines are a class of small molecule peptides that transmit information between cells and can be regulated accordingly in the human immune process, enabling us to better maintain the physiological balance of the organism [2]. Cytokines can be produced by various cells, including immune cells, inflammatory cells, neural cells, and other cells. These molecules can be secreted, cleaved, and released outside the cell, and then bind to adjacent cells through specific receptors, triggering a series of biological reactions. It does a wide range of work on the many reactions of cytokines in the body. For example, it is linked to the body's immune response, inflammation, cell growth and apoptosis.

The functions of cytokines are diverse, including promoting or inhibiting cell proliferation, regulating cell differentiation and function, regulating immune response, mediating inflammatory response, and regulating cell survival and apoptosis [3]. The diversity of cytokines enables them to play different roles in different cell types and pathological environments. The same cytokine may have different functions in different cell types, depending on the expression of Cell surface receptor, as well as the synergy with other cytokines and Signaling molecule.

Cytokines can be divided into multiple families, such as interleukins, tumor necrosis factors, interferons, and chemokines [4]. These family members play specific regulatory roles in different immune and inflammatory processes. For example, the cytokine family of interleukins is involved in the development and activation of immune cells, regulating the occurrence and severity of immune responses. The tumor necrosis factor family of cytokines plays an important role in tumor cell apoptosis and immune antigen-mediated cytotoxicity. Interferons are involved in cellular antiviral and anti-tumor immune responses. Chemokines mediate the chemotaxis and activation of immune cells, participating in the regulation of inflammation and immune responses.

2.2. The role of cytokines in inflammation and immune processes

Cytokines play a crucial regulatory role in inflammation and immune processes. When tissues are stimulated or damaged, immune cells and inflammatory cells release cytokines, triggering an inflammatory response. Inflammatory response is a self-protection mechanism of the body aimed at clearing the source of infection, repairing damaged tissue, and restoring normal physiological state.

In the process of inflammation, cytokines mediate the transmission of inflammatory signals and intercellular interactions. They can recruit and activate immune cells, such as Monocyte, macrophages and neutrophils, to clear infected and damaged tissues. Cytokines can also promote an increase in vascular permeability, making it easier for immune cells and hemolytic molecules to enter injured tissues. Cytokines can also activate and regulate immune cells of the body, such as lymphocytes and Natural killer cell, to play its role in killing and regulating immune response.

In the immune process, cytokines play a positive and negative regulatory role. They can promote or inhibit the proliferation, differentiation, and activation of immune cells to control and regulate the intensity and duration of immune responses. Cytokines can also regulate the function of immune cells and cell death to ensure the balance and effectiveness of immune responses.

Cytokines, as key mediators of immune response, play important regulatory roles in inflammation and immune processes. By regulating the function of immune cells and the intensity of immune

responses, cytokines are involved in clearing infection sources, repairing damaged tissues, and maintaining normal physiological states. An in-depth study of how cytokines function in the human body and how they help humans regulate the corresponding physiological activities is important for understanding the onset and progression of immune and inflammation-related diseases.

3. Evidence for changes in cytokines at different stages of schizophrenia

3.1. Cytokine changes in the stage of drug-induced juvenile psychosis

In the stage of drug infantile psychosis, the use of antipsychotics may have an impact on immune and cytokine levels [5]. Previous studies have shown that anti sperm drugs may interfere with immune cell function, and this effect typically occurs within the time after initial contact with the drug. However, there are differences between different studies. Some studies have shown that antipsychotic drugs may stimulate the activity of immune cells, while other studies have shown that they may inhibit the activity of cytokines mediated Microglia.

Researchers called more than five hundred patients to participate in the experiment in order to explore how patients who had never taken psychotropic drugs would react to their first exposure to such products [6]. The results showed that among the patients taking antipsychotic drugs for the first time, IL-16, IL-6, sIL2r and TNF- α These cytokine levels significantly increased compared to the control group. This increase is not related to medication. However, due to the small sample size and limited number of studies, the results of these cytokine measurements lack statistical significance. Therefore, more research is still needed to further confirm these findings and understand the impact of antipsychotic drugs on the immune system.

Previous studies have found that antipsychotic drugs may affect immune cells. For example, one study found that antipsychotic drugs can inhibit the activity of immune cells and reduce their production of cytokines [7]. This may work by inhibiting inflammatory reactions and regulating the function of the immune system. Another study shows that antipsychotic drugs can also reduce the migration of immune cells, thus regulating the inflammatory response. These results suggest that antipsychotic drugs may interfere with the normal function of the immune system.

Some studies have also shown that antipsychotic drugs may stimulate the activity of immune cells [8]. A study found that antipsychotic drugs can increase the level of cytokines produced by immune cells, thereby promoting the function of the immune system. This stimulating effect may be achieved by inhibiting inflammatory reactions and increasing the activity of immune cells. Another study also showed that antipsychotic drugs can increase the migration of immune cells and regulate inflammatory reaction. These findings suggest that antipsychotic drugs may have a positive impact on the function of the immune system.

Despite the differences between these research results, a meta-analysis study provides some new insights. This study included 14 studies and observed 570 first-time patients [9]. The results showed that indices such as IL-16, IL-6, sIL2r and TNF- α were significantly elevated in these patients who participated in the experiment. There were no significant changes in these indices in the control group of this experiment. This change was not related to medication and may be due to the effect of infantile psychosis itself.

Although these results provide valuable clues for further understanding the impact of antipsychotic drugs on the immune system, there are also research limitations. Firstly, some research samples are small, and the number of studies is limited, which may lead to a lack of statistical significance in the measurement results of these cytokines. Secondly, this meta-analysis study only focuses on patients who take antipsychotic drugs for the first time, but it is not clear about the impact of long-term use of antipsychotic drugs, drug dose and course of treatment. In addition, these studies did not delve into the specific mechanism, and could not provide a detailed understanding of antipsychotic drugs on immune cell function.

Future research still needs to further explore the impact of antipsychotics on the immune system [10]. These studies can expand the sample size and increase the number of studies to ensure that the

results are statistically significant. At the same time, it is also possible to consider expanding the research object to patients who have been taking long-term medication to understand the potential impact of different doses and treatment courses on the immune system. In addition, through in-depth study of specific mechanisms, we can further reveal the impact of antipsychotics on immune cell function and provide better guidance for future clinical treatment.

3.2. Changes in cytokines during acute psychiatric attacks

According to a comprehensive meta-analysis study conducted in 2011, Miller et al. found that patients with schizophrenia had higher levels of cytokines in the acute phase of the disease, whether they were recurrent or first-episode psychiatric patients. Specifically, cytokines such as IL-16, IL-6, and TGF- β significantly increase in the acute phase but decrease after successful treatment [11]. In addition, the study found that approximately two-fifths of studies showed a correlation between IL-6 and overall levels of psychiatric pathology. These changes in cytokine levels may be regarded as state dependent inflammatory markers and correspond to the reduction of disease symptoms.

In addition, some studies also focused on the relationship between mental illness and BDNF. In Mondelli et al.'s study, they found that compared with the healthy control group, BDNF gene expression was reduced in patients with schizophrenia, while IL-6 and a were increased. In addition, the study also pointed out that childhood trauma experiences in childhood are closely related to changes in these cytokines. Four population-based longitudinal and Gregor Mendel randomized studies examined causality. Studies have found that high levels of IL-6 and ESR in childhood may make it more likely to experience psychiatric symptoms or be diagnosed with schizophrenia in adulthood. In addition, high CRP levels in adolescence may increase the likelihood of hospitalization and predispose to an earlier age of onset of schizophrenia. Another longitudinal study found that high ESR levels may influence the likelihood of developing schizophrenia in early adulthood. These research results indicate that the inflammatory response of the immune system may be related to the occurrence and development of mental illness. These research results emphasize the importance of the immune system in mental illness, providing clues for further research and understanding of the pathogenesis of mental illness.

To explore more deeply the relationship between psychiatric disorders and cytokines, future research needs to further explore the potential mechanisms between these cytokines and diseases. Research can further expand the sample size and adopt stricter research designs to increase statistical support for the results. In addition, researchers can also consider observing patients with long-term medication to understand the impact of treatment on cytokine levels. Future researchers can build on this foundation to explore and determine whether elevated cytokines in the early stages of psychiatric disorders can serve as potential markers for early diagnosis and prevention, and to investigate their relationship to childhood abuse experiences.

In addition to antipsychotics, there are other treatments that have caused some concern about the impact on the immune system and cytokine levels. For example, comprehensive treatment methods such as psychotherapy, exercise, and nutritional intervention have been widely studied to explore their regulatory effects on immune system function and changes in cytokine levels. These treatment methods may work by reducing inflammatory reactions, promoting the release of neuroprotective factors, and improving the overall health of patients. Future research can further explore the potential role of these comprehensive treatment methods in improving immune system function and cytokine levels in patients with mental illness.

Existing research suggests that the levels of cytokines in patients with mental illness may be closely related to the occurrence and development of the disease. Cytokines such as IL-6, TNF- α , and BDNF may play important roles in the pathophysiological processes of mental illness, and the levels of these cytokines may be influenced by early environmental factors, stages of mental illness, and treatment. However, current research still has some limitations and requires more large-scale and long-term research to validate these findings and delve deeper into the exact mechanism between

cytokines and mental illness. These further studies will help reveal the pathophysiological processes of mental illness and provide better guidance for the prevention and treatment of mental illness.

3.3. Changes in cytokines during the stage of chronic schizophrenia

In patients with chronic schizophrenia, studies have found an increasing trend in cytokine levels. Including TNF- α , IL-12, INF- γ the levels of cytokines such as sIL2r and sIL2r have been reported to be elevated. IL-6 is significantly elevated in chronic patients with this disorder, but the index of IL-6 is not elevated in emotionally stable conditions, such as major depressive disorder. This suggests a correlation between IL-6 and the pathogenesis of chronic schizophrenia.

In addition to IL-6, studies have also found significant increases in levels of cytokines such as IL-1 and sIL2r in patients with chronic schizophrenia and positive bipolar disorder. In addition, the inflammatory marker TNF- α It is considered a characteristic marker of neuroinflammation. These research results suggest that the pathological and physiological processes of chronic schizophrenia may be related to sustained neuroinflammation.

The meta-analysis study also found that approximately 28% of chronic schizophrenia patients have elevated levels of C-reactive protein (CRP). Another large sample study found that even after adjusting for other influencing factors, the CRP levels in patients with schizophrenia still significantly increased. In addition, the study also found a correlation between CRP levels and cognitive function in patients with chronic schizophrenia, and high CRP levels may be associated with poor cognitive function. These results further support the importance of inflammation in chronic schizophrenia.

Despite these research findings, the exact mechanism of cytokine action in chronic schizophrenia is still not fully understood and further research is needed to explore. At the same time, it is also necessary to study the correlation between cytokines and disease development, severity, as well as patients' cognitive function and other symptoms. Future research can also explore the impact of treatment methods that regulate cytokine levels on the efficacy and prognosis of patients with chronic schizophrenia.

The current research results suggest that cytokine levels may increase in patients with chronic schizophrenia. The changes in these cytokines are related to the development and severity of the disease, as well as to the patient's cognitive function and other symptoms [12]. However, the exact mechanism of action of cytokines in chronic schizophrenia is still unclear and further research is needed to explore. Future research can also explore the impact of treatment methods that regulate cytokine levels on the efficacy and prognosis of patients with chronic schizophrenia.

4. Role of cytokines in patients with schizophrenia

4.1. The association between elevated early inflammatory markers and the risk of schizophrenia

Schizophrenia is a complex and common mental illness, and its pathogenesis is still not fully understood. Recent research suggests that some unusual activities and inflammatory responses of the immune system may be correlated with the pathogenesis of psychiatric disorders, especially schizophrenia. By observing the changes in cytokines in early stages of schizophrenia patients, we can understand the correlation between increased early inflammatory markers and the risk of schizophrenia.

The increase in early inflammatory markers refers to indicators of abnormal immune system responses observed in studies conducted several years before the onset of mental illness [13]. Inflammatory markers mainly include a series of protein molecules, such as Interleukin 6 (IL-6) and tumor necrosis factor- α (TNF- α) And C-reactive protein (CRP), etc. The increase in these indicators may reflect abnormal activation of the immune system and may be related to the pathogenesis of schizophrenia.

A study suggests that an increase in IL-6 levels in childhood is associated with symptoms of schizophrenia in early adulthood. IL-6 is a cytokine produced by immune cells and has pro-inflammatory effects [14]. Its elevation may reflect abnormal reactions in the body's immune system, thereby increasing the risk of developing schizophrenia. The data from these studies could suggest that we can assess the risk of patients by detecting early markers of inflammation prior to the onset of schizophrenia, thus offering the possibility of early intervention and the provision of more effective treatment.

Other studies also support the association between increased early inflammatory markers and increased risk of schizophrenia. For example, a study on young patients found that an increase in CRP levels is associated with early manifestations and severity of schizophrenia. CRP is an early inflammatory marker, and its elevation may reflect the degree of inflammatory response in the body, further affecting the development and condition of schizophrenia.

The results of these studies indicate that abnormal activation of the immune system and inflammatory response may be important factors in the development of schizophrenia. Abnormal activation of the immune system may lead to an exacerbation of inflammatory reactions in the body, ultimately affecting the function of the nervous system. This impact may be closely related to the symptoms and pathogenesis of schizophrenia.

Although these studies provide important clues for us to understand the development mechanism of schizophrenia, there are still many issues that need further research. The current research mainly explores the relationship between inflammatory response and schizophrenia by observing changes in inflammatory markers, and further in-depth understanding of specific inflammatory pathways and the mechanisms of immune system abnormal activation is needed. Further research also needs to consider the impact of other potential factors, such as environmental and genetic factors.

The association between elevated early inflammatory markers and the risk of schizophrenia has been a research hotspot in the field of psychiatry in recent years. These research results provide new ideas for early intervention and treatment of schizophrenia, with the potential to improve the prognosis and quality of life of patients. With the deepening and progress of relevant research, we can better understand the pathogenesis of schizophrenia and provide more effective treatment strategies for patients.

4.2. The relationship between cytokines and disease severity

Abnormal activation of the immune system may be a critical point in the development of schizophrenia. By comparing schizophrenic patients with healthy controls, researchers found that schizophrenic patients had significantly elevated cytokine levels during the acute phase of the illness. This abnormal level was positively correlated with the severity of the illness, i.e. the more severe the illness, the higher the cytokine levels.

Some studies have shown that IL-6 and TNF- α The elevated levels of cytokines are associated with the overall pathological level of schizophrenia. IL-6 is a pro-inflammatory cytokine, and its elevation may reflect abnormal activation of the immune system. And TNF- α It is an early inflammatory marker, and its elevation may reflect the level of inflammatory response in the body [15]. The increase of these cytokines is related to the severity of the condition, which may represent the intensity of inflammatory response and the progression of schizophrenia.

In addition, some studies have found that changes in cytokines may be related to specific symptoms of schizophrenia. For example, IL-6 and IL-1 β The increase in cognitive impairment and emotional symptoms is related to schizophrenia. This means that different cytokines may be associated with different symptoms and manifestations of schizophrenia.

If future researchers focus on examining the relationship between cytokines and other clinical features, such as disease course, treatment response, and prognosis, then we can gain a deeper understanding of what kind of contribution cytokines can have in psychiatric disorders. This could both aid research in psychiatry and provide hope for more people with schizophrenia. This study helps to reveal the relationship between cytokines and the pathogenesis of schizophrenia, providing

new clues for the diagnosis, treatment, and prevention of schizophrenia. In addition, cytokine based disease severity assessment may contribute to the development of personalized treatment plans, improving the treatment effectiveness and prognosis of patients.

4.3. The potential significance of cytokines in the treatment of schizophrenia

The treatment of schizophrenia usually includes comprehensive treatment methods such as medication and psychotherapy. In recent years, some research evidence suggests that cytokines may have potential significance in the treatment of schizophrenia.

The study found that antipsychotic drugs may have a regulatory effect on the level of cytokines. Some antipsychotics, such as chloramphenicol and Olanzapine, have been found to reduce the levels of inflammatory markers, such as IL-6 and TNF- α . This means that these drugs may treat schizophrenia by inhibiting inflammatory reactions and affecting the immune function of patients with schizophrenia.

Some comprehensive treatment methods have also been studied to regulate cytokine levels. For example, psychological intervention methods such as psychotherapy and Cognitive behavioral therapy have been found to reduce the level of inflammatory markers in patients with schizophrenia. In addition, moderate exercise and nutritional interventions can also improve immune system function and regulate the production of cytokines. These comprehensive treatment methods may alleviate inflammatory reactions by improving lifestyle and promoting overall health, and play a role in the treatment of schizophrenia.

Cytokines may play an important role in the development, severity, and treatment of schizophrenia. By further studying the relationship between cytokines and schizophrenia, we can better understand the pathophysiological mechanisms of schizophrenia and provide more effective guidance for the treatment of schizophrenia. Therefore, conducting in-depth research on the mechanism of cytokines in schizophrenia and evaluating the impact of different treatment methods on cytokine levels has important clinical and research significance.

5. Conclusion

Schizophrenia is a common and serious mental disease whose etiology has not yet been fully defined [16]. Its high incidence rate and long course of disease bring heavy burden to patients and their families. Although schizophrenia has been studied for decades, its specific Pathophysiology mechanism has not yet been fully clarified. However, increasing evidence suggests that the development of schizophrenia is related to the interaction between genes and environmental factors, forming a neurodevelopmental model. Schizophrenic patients have a shorter life expectancy, and they are more likely to suffer from cardiovascular disease, obesity, diabetes, hypertension, metabolic syndrome and other diseases. These observations may be related to abnormalities in immunity, metabolism, and central nervous system function. More and more studies have shown that immune abnormalities play an important role in the development of schizophrenia. Research has found that the concentration of inflammatory factors in the serum of patients with schizophrenia increases, which supports the viewpoint of the cytokine hypothesis. In addition, some studies have found that adjuvant use of anti-inflammatory drugs may help improve clinical symptoms in patients with schizophrenia, thus providing the possibility of a new treatment method.

Although the exact cause of schizophrenia is not yet fully understood, studies have shown that dysfunction of the immune system may be a key factor [17]. Studies have shown that patients with schizophrenia have abnormalities in the immune system, including abnormal activity of immune cells, elevated levels of pro-inflammatory factors, and disturbances in immune regulation. This may lead to chronic inflammatory reactions and neurological disorders, leading to the development and worsening of symptoms in schizophrenia. Some studies have found that the serum proinflammatory factors in schizophrenia patients, such as Interleukin 6 (IL-6), tumor necrosis factor- α (TNF- α) And interleukin-1 β (IL-1 β) The level of increase [18]. Overactivation of these cytokines may lead to

disturbances in neurotransmitters, affecting neuronal communication and regulation. In addition, the study also found that the immune cells of schizophrenic patients, such as Monocyte and T cells, have abnormal functions, which are manifested by abnormal cytokine production and cell activity. Further research has found that immune dysfunction is closely related to the onset and course of schizophrenia. People with schizophrenia may be more likely to suffer from other immune related diseases, such as autoimmune diseases and cardiovascular diseases. In addition, immune dysfunction is also related to the severity of symptoms and prognosis of schizophrenia. The immune dysfunction of patients with schizophrenia may be related to inflammatory reactions and neurological disorders. This suggests that the immune system may play an important role in the development of schizophrenia. Researchers have proposed the "cytokine hypothesis", which states that immune dysfunction leads to excessive inflammatory responses that affect neural function, thereby exacerbating the symptoms of schizophrenia. The significance of immune dysfunction in the treatment and prevention of schizophrenia is obvious. Some studies have shown that anti-inflammatory drugs and immune modulators may have certain effects on alleviating symptoms of schizophrenia. For example, Nonsteroidal anti-inflammatory drug and antioxidants can reduce levels of inflammatory factors and alleviate symptoms. In addition, immunomodulators, such as the antiepileptic drug valproate used by schizophrenic patients, may also have a positive impact on the treatment of schizophrenia.

In recent years, research has found that the gut microbiota composition of patients with schizophrenia may be related to the development of the disease [19]. This echoes the theory of immune abnormalities, as gut microbiota can affect the function of the immune system. By improving the balance of gut microbiota, it may help alleviate the inflammatory response and neurological dysfunction in patients with schizophrenia, thereby improving their psychological state and quality of life. Therefore, the relationship between gut microbiota and schizophrenia has become a new research field, providing possibilities for finding new treatment methods and prevention strategies. For example, methods that regulate the composition of gut microbiota, such as the use of probiotics and prebiotics, may help improve immune and neurological function in patients with schizophrenia. This study provides a new direction for the treatment of schizophrenia and may provide a basis for future individualized treatment.

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