



Cytokines in Schizophrenia: Predisposing Factors and Inflammatory Responses

Mohammad Javad Azmand¹, Reza Divanbeigi², Marziyeh Hajati Pirabas^{3*}

¹Department of Physiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

²Islamic Azad University, Qeshm Medical Branch, Qeshm, Iran.

³General Psychology, Islamic Azad University of Semnan, Semnan, Iran.

Abstract

Schizophrenia is a multifactorial disease that may be triggered by environmental disorders, mental stress, or physical illness in a person who is genetically predisposed to it. Recent research has extremely evaluated the role of inflammatory cytokines in schizophrenia. The current study attempted to find any association between cytokines and schizophrenia. This narrative study was conducted through a literature review in Scopus, PubMed, and Web of Science databases using keywords related to schizophrenia and cytokines without any time limitation. This review focused on discussing the relationship between various symptoms of disease and cytokine levels. Environmental factors such as embryonal infections were found to be associated with alternations in mothers' blood cytokines and further effects on schizophrenia probability in children. Heritable factors including disrupted-in-schizophrenia 1 (DISC1) and neuregulin 1 (NRG1) genes were shown to be linked with immunological responses, as well as Toll-like receptors or AKT1/p13k activation and following alternations in the cytokine profile. Based on the findings, the cytokines and inflammatory responses of the body were reported to be involved in many psychological disorders and schizophrenia. Various interleukins (ILs), as well as IL-6, IL-8, and IL-2R are known to be associated with the severity of schizophrenia symptoms. Although various data exist regarding different cytokines and their association with schizophrenia, no study has so far formulated research fields on specific types of cytokines that have the potential to be further studied for therapeutic hope.

Keywords: Schizophrenia, Cytokines, Inflammation, DISC1, Neuregulin 1

*Correspondence to

Marziyeh Hajati Pirabas,
General Psychology, Islamic
Azad University of Semnan,
Semnan, Iran.
Tel: +98 912 395 5198
Email: mhajatip2019@
gmail.com



Received: July 18, 2021, Accepted: November 1, 2021, ePublished: January 1, 2022

Introduction

Schizophrenia is a psychiatric disorder that often manifests as an abnormal individual and social behavior and is associated with a patient's lack of proper recognition of reality. Despite affecting a small percentage of the population, schizophrenia causes extreme damage to individuals and society and is a severe mental illness that affects, on average, nearly 1% of the world's population (1,2). Schizophrenia is the most severe mental disorder starting before 25 years old and usually lasting until the end of life (1). The lifetime prevalence of schizophrenia is approximately 1% and equally affects men and women. This disorder is associated with a greater burden of chronic disability compared to any other mental illness (1, 2). Schizophrenia is one of the disorders that can cause a decrease in IQ and mental abilities (3) and is diagnosed through interviews and repeated encounters with subjects experiencing hallucinations, delusions, and other mental disorders (2, 3). Diagnostic and Statistical Manual of Mental Disorders is still used as one of the most reliable systems and, in many cases, as a basis for

assessing the validity and reliability of other systems. In addition, it is divided into positive, negative, and mixed subsets (3). According to evidence, the current conclusions and inferences about the specific symptoms of schizophrenia are highly complex and controversial. All offered theories about the diagnosis of schizophrenia are directly related to questions about the boundary between schizophrenia and other psychotic disorders, as well as the feasibility of the classified definitions of schizophrenia (4). This disease is characterized by positive and negative symptoms. Positive signs include hallucinations, delusions, unorganized thoughts, and negative signs are loss of emotion, inability to speak, communicate and interact with others, and impaired perception and cognition (5). Our previous study on the murine models of neurological impairment indicated potential inflammatory responses that persuaded us to review these topics for further studies (6). Schizophrenia is a heterogeneous disease, which has not been thoroughly detected by any of the laboratory diagnostic tests yet. Considering that there have been multiple studies on the

effect of the inflammatory mechanism on the development and progression of schizophrenia, there is a need for conclusive review studies to specify the achievements and shortcomings of the research field. Accordingly, the current study seeks to find any association of cytokines with schizophrenia as the cytokines and inflammatory responses of the body are found to be involved in many psychological disorders.

Literature Review

This was a narrative review study through a literature review in Scopus, PubMed, and Web of Science databases using some keywords such as “schizophrenia”, “inflammation”, “interleukin” (IL), and “cytokines” without any publication date limitation. All included papers were hand-searched in references for potentially relevant papers. Two independent researchers conducted the literature review, thus duplicated papers were removed at the end of the first stage of the online database search. Then, all types of original studies, as well as the experimental and clinical studies were included if having the inclusion criteria regarding investigating the association of cytokine with various aspects of the disease. On the other hand, review studies, letters to editor papers, and any type of study not reporting research data were excluded from our primary search list. The final list of the included articles was full texts that were reviewed and discussed between our study authors.

Symptomology and Cytokines

Schizophrenia has positive and negative symptoms. The first group includes hallucinations, delusions, disturbed speech, disturbing behaviors, and thought disorders. On the other hand, the affected social function, lack of pleasure sense, motivation, and social withdrawal are among the negative symptoms. It can be argued that negative symptoms are extremely important in schizophrenia since they are the best predictor of future schizophrenia disability and its progression (7, 8). Dahan et al showed that elevated levels of IL-6, IL-8, and IL-2R proteins are linked to the severity of both negative and positive symptoms in schizophrenia patients (9). Similarly, Na et al (10) indicated that elevated monocytic cytokines and reduced Th1 and Th2 biased immune responses can be associated with acute psychotic schizophrenia symptoms. Nonetheless, Th2-biased immune responses are of more interest to researchers (11). Tseng et al (12) compared Th1 versus Th2 immune responses in schizophrenia patients and found that individuals with schizophrenia had higher levels of Th2 cytokine (IL-10) and Th17 cytokine (IL17) in their serum while having lower levels of Th1 cytokine (IFN-).

Inflammatory Responses as Risk Factors

Schizophrenia is a multifactorial disease, meaning that

it can be triggered via environmental disorders, mental stress, or physical illness in a person who is genetically predisposed to the disease (13). According to evidence, the hereditary characteristic of schizophrenia, among others, is highly significant, and genetic factors account for about 80% of the causes of this disease (13).

Genetic and environmental factors cause schizophrenia. The risk factors are divided into several categories including demographic (e.g., age, gender, race, and social class), accelerating (e.g., life events and migration occurring before schizophrenia, and genetic factors. Numerous human epidemiological studies have shown that the presence of environmental factors (including exposure to viral and bacterial ophthalmic agents during pregnancy) increases the risk of psychiatric illness and neurological disorders in newborns (13, 14).

Environmental Factors and Cytokines

A systematic review and meta-analysis study by Taghipour et al (15) demonstrated that the *Toxocara* infection had a higher pooled seroprevalence in schizophrenia patients (15%) compared to healthy controls (3.3%), indicating a significant connection in this regard (odds ratio: 4.06). Likewise, Bransfield (16) showed that *Toxoplasma gondii* infection in children, due to infection of the nucleus accumbens, thalamus, and subthalamus, leads to varying degrees of gray matter inflammation of the brain. The findings of one study revealed that sudden autistic-like behaviors were found in infants and toddlers with herpes encephalitis infections (17, 18). Moreover, having viral illnesses such as chickenpox, fever of no specific origin, and middle ear infection can increase the risk of schizophrenia (18). According to another study, a significant relationship was observed between *Toxoplasma* and testosterone levels. In fact, the increase in testosterone in infected people is due to the increase in dopamine in the brain. The unbalanced secretion of this hormone by *Toxoplasma* causes inflammation in the brain and release of cytokines and affects the hypothalamic-pituitary-adrenal axis (19, 20). In toxoplasmosis, the protective response by cellular immunity is performed by CD4+ and CD8+ T lymphocytes. The findings of Allswede et al (21) indicated that early embryological exposure to elevated maternal proinflammatory cytokine concentrations may play a role in psychosis.

Vitamin D could also be considered as an environmental factor, and its values are determined by dietary variables or sun exposure (22). In recent years, studies have confirmed the role of vitamin D and its deficiency in most people with this disorder and the relationship with the positive, negative, and cognitive symptoms of this disorder. It seems that vitamin D, in addition to calcium homeostasis and bone health, is essential for brain growth and function through immune responses (22). In clinical studies, low serum levels of 25(OH)D, which is a form of

vitamin D storage in the body, have been reported with psychiatric symptoms such as anxiety, depression, and decreased cognitive function (22). In schizophrenia, low levels of serum vitamin D are linked with higher IL-6 levels and subsequent poor disease progression (22).

Genetic Factors Causing Cytokine Release

Similar to other multifactorial and complex diseases, genetic factors are involved in schizophrenia, including disease-prone genes, epigenetics, and polymorphic factors. Family studies, especially the study of twins, have also shown the role of genetic factors in the development of this disease, as well as several high-risk genes that are associated with schizophrenia. Extensive research has approved that dysbindin, neuregulin 1 (NRG1), and disrupted-in-schizophrenia 1 (DISC1) are the most important genes (23). DISC1 was first identified in a large Scottish family in 1990 with multiple bipolar disorder and recurrent depression cases in its members. Several accompanying studies of this gene were performed in Finnish, Taiwanese, and British populations and confirmed its link with schizophrenia (24). Chen et al (24) showed that a novel Toll-like receptor (TLR) 3 mechanism regulates dendritic morphology by schizophrenia gene DISC1 down-regulation. The TLR is responsible for identifying pathogenic patterns, and its activation induces immune responses including the production of type I interferons (α and β) and proinflammatory cytokines, limiting the replication of the pathogen, as well as initiating immune responses (25). Further, the TLR plays an important role in controlling innate immune responses, and its stimulation promotes dendritic cell maturation and increases the antigen delivery capacity of antigen-presenting cells to initiate and expand responses (25). It should be noted that the expression of TLRs in peripheral blood mononuclear cells is altered in schizophrenia (25).

The NRG1 gene has various roles in the central nervous system and schizophrenia-related processes such as neuronalization, neuronal elasticity. It extends between neurons involved in the gamma-aminobutyric acid (GABA) system and between dopamine receptors, serotonin, and monoamine transporters (26). NRG1 and its receptor (Erb4) are associated with schizophrenia. In the study by Aureli et al (27), IL-1 β and NRG-1 were reported to be essential in the activity-dependent growth of neuronal structures and functional plasticity. The genetic functional dysregulations of IL-1 β and NRG-1 can disrupt

neuronal processes that influence cognitive growth and have a variety of neurological consequences. Based on previous evidence, NRG1 and DISC1 are directly linked to a common pathway mediated by Erb receptors and the AKT1/p13k pathway (28). The activation of AKT1/p13k pathway receptors (including tyrosine kinase receptors or G-protein-coupled receptors) by the activation of ligands such as growth factor-1 can cause consequent alternations in cytokine expression levels which might be effective in schizophrenia pathophysiology (29).

A summary of the most important predisposing factors is suggested in Table 1. To our current knowledge, other cytokines mostly contribute to Schizophrenia development following the change in these factors.

Pathophysiology

Obviously, the biological processes underlying the disease are diagnosed to exist for years when mental illness is observed in people with schizophrenia. The pathophysiology of schizophrenia is multifactorial. Dopamine is a neurotransmitter or chemical that carries a cellular message from one brain to another. Schizophrenia is the over-activation of central nervous system pathways in the brain by which dopamine interference works, and this extreme activity is somehow related to the symptoms of the disease. Increased dopamine secretion from striatal branches is a sign before diagnosis and begins at the time of exposure and increases during the course of the disease. Lower N-methyl-D-aspartate (NMDA) receptor activity or mild inflammation of the brain, probably due to increased dopamine secretion over the years, are correlated with cognitive or social disorders in schizophrenia patients (30). T-cells, microglial cells, and peripheral monocytes are immune cells that have been indicated to lead to cognitive functions, and dopamine can play a role in their activity, migration, differentiation, and proliferation. As a result, changes in dopamine levels linked to schizophrenia can affect immune cell inflammatory responses and certain behavioral functions (30).

At the time of diagnosis, patients with schizophrenia show a decrease in the cranial volume compared to normal individuals. The brain of people with schizophrenia has stopped before this age, and the smaller volume of the brain represents the lower amount of both white and gray parts of the brain (31). The frontal lobe is one of the centers of dysfunction in schizophrenia (32, 33). It is believed

Table 1. Most Important Cytokines of Schizophrenia Development

Factor	Gene	Role	Schizophrenia-related Effect	Evidence
DISC1	Chromosome 1q42.1	Neural development and brain maturation	Increased expression in schizophrenia patients	(23, 24)
TLR3	Chromosome 4: 186.07–186.09 Mb	Innate immunity	Altered expression in schizophrenia patients in comparison of controls	(25)
NRG1	Chromosome 8: 31.64–32.86 Mb	Synaptic plasticity and increasing myelination	Decreased expression in schizophrenia	(26-29)
IL-1 β	Chromosome 2: 112.83–112.84 Mb	Inflammatory mediator	Causing neural inflammation	(28)

Note. DISC1, disrupted-in-schizophrenia 1; TLR: Toll-like receptor; NRG1: neuregulin 1; IL: interleukin.

that different types of schizophrenia may be associated with damage to various areas of the brain and thus have a variety of clinical manifestations due to damage to different areas and nerve pathways. Abnormalities in dopamine and glutamate levels have been reported in the peripheral cortex of patients with schizophrenia (34). NMDA receptors are involved in the release of dopamine into the striatum and frontal cortex of these patients. Unlike dopamine receptors, glutamate receptors are found in the cortical and subcortical regions of the brain (35). Dopamine activity is regulated by the GABA neurotransmitters and glutamate. Furthermore, high levels of glutamate are observed in people with schizophrenia. Dopamine disorder in the basal nuclei of schizophrenic patients is one of the features of impairments associated with the analysis of their cognitive abilities (36). On the other hand, glutamate abnormalities in the peripheral cortex and hippocampus cause dopamine secretion into the striatum, and these changes occur as a result of genetic abnormalities in these people (37).

Schizophrenia includes the contribution of NMDA channel inhibitors that mimic the effects of psychosis. Additionally, it is hypothesized that decreased performance NMDA in schizophrenia can lead to decreased stimulation of the GABA neuronal cell, thus the release of glutamate into the synapses increases, causing nerve cells to die following the release of cytokines. This is primarily mediated by glutamate NMDA receptors (38). Neuronal damage caused by neuronal cell death plays a vital role in the pathology of schizophrenia and is essentially associated with negative and positive symptoms, as well as cognitive symptoms caused by inflammatory cytokines in patients (39).

We were currently working on the murine models of memory impairments from a biochemistry perspective to obtain more information about possible models to study the role of inflammatory processes in the brain (6) although COVID-19 has led to a pause in research.

Conclusion

Many neurological conditions (e.g., schizophrenia) are linked to cytokines and inflammatory reactions in the body. Behavioral, neurological, neural imaging, and animal research must be thoroughly pooled and analyzed to explain the inflammatory pathways that are involved in the complex illness of schizophrenia. †

Acknowledgments

None.

Author's Contributions

MJA designed the study. In addition, RD and MHP conducted the literature review. The manuscript was drafted by MJA, RD, and MHP.

Conflict of Interest Disclosures

None.

Ethical Statement

Not applicable.

Funding/Support

None.

Informed Consent

Not applicable.

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