



# Inflammation-Schizophrenia: A Bidirectional Causal Association Mediated by Cytokines

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Psychotic disorders, a group of heterogeneous syndromes, are the loss of contact with reality and failure to recognize what is real, and have several types; the most common one is schizophrenia. Schizophrenia is manifested by hallucinations, delusions, disorganized speech and behavior, and negative, cognitive, and mood symptoms and may lead to serious adverse outcomes. Schizophrenia has a lifetime prevalence of 1%, and its onset usually occurs before middle age, which imposes a significant burden and costs <sup>1-3</sup>. A better understanding of the neuropathophysiology of the disorder seems to be a proper solution for the lack of complete knowledge of the etiology, the diagnosis being absolutely clinical, and the incomplete effectiveness and side effects of the current treatments. Mainly, genetic predisposition, perinatal complications, brain structural problems, neurotransmitter function abnormalities, infections, and, recently, abnormal activation of the immune system have been implicated in the pathophysiological causes of psychosis <sup>4</sup>. Increasing evidence has suggested the role of the immune system in schizophrenia, so that changes in blood levels of cytokines as the main mediators of the immune response and C-Reactive Protein (CRP) have been reported. It seems that this low-grade inflammation has a causal relationship with schizophrenia and also causes resistance to antipsychotic treatment <sup>5</sup>.

Dysregulation of pro-inflammatory immunity in patients with medication-naïve first-episode schizophrenia has been shown by observing increased levels of Interleukin (IL)-1 $\beta$ , soluble IL-2 receptor (sIL-2R), IL-6, IL-12, and Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) but not of Interferon-gamma (IFN- $\gamma$ ) <sup>4</sup>. On the contrary, a recent study suggested an increase in cytokines IFN- $\gamma$ , IL-6, and IL-12. This study showed a positive relationship between IL-1 $\beta$ , IL-2, IL-6, IL-10, and TNF- $\alpha$  and negative symptoms and a negative relationship between IL-10 and these symptoms <sup>6</sup>. The particular importance of this stage is to have less of a confounding factor.

An increase in the blood levels of IL-1 $\beta$ , IL-6, and Transforming Growth Factor-beta (TGF- $\beta$ ) was observed in the next stage to consider, acute relapse of established schizophrenia, whose levels decreased after successful treatment. In contrast, the levels of IL-12, IFN- $\gamma$ , TNF- $\alpha$ , and sIL-2R did not decrease after treatment <sup>7</sup>. In the next stage, in stable outpatients with chronic schizophrenia, IL-1 $\beta$ , IL-6, IL-12, TNF- $\alpha$ , INF- $\gamma$ , and sIL-2R were increased <sup>8</sup>. Also, increase in CRP has been observed in the first episode, acute psychosis and chronic schizophrenia in many studies, which has been associated with positive, negative, and cognitive symptoms in different studies <sup>4,9</sup>.

Even before the onset of schizophrenia, *i.e.*, before the mentioned stages, there is evidence of alteration of inflammatory factors. A study reported that IL-6 blood levels were higher and IL-1 $\beta$  lower in subjects at increased risk for psychosis compared to controls <sup>10</sup>. Changes in the levels of cytokines in Cerebrospinal Fluid (CSF) were also reported, many of which were concordant with those in peripheral blood. IL-1 $\beta$ , IL-6, and IL-8 were increased in the CSF of patients with schizophrenia in previous studies <sup>5,11</sup>.

Moreover, evidence of the effectiveness of anti-inflammatory agents on psychotic disorders reinforces the above-mentioned evidence. Resveratrol adjunct to risperidone has been shown to outperform placebo in treating negative symptoms. This agent has inhibitory effects on the production of IL-12, TNF- $\alpha$ , and INF- $\gamma$  <sup>2</sup>. Another example is pioglitazone, which attenuates the expression of IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , and as an adjunct to risperidone, it outperformed placebo in treating schizophrenia <sup>3</sup>. There are other examples; however, these agents may have exerted their effects from other pathways. Although schizophrenia is a clinical diagnosis and is not associated with specific laboratory findings, it may be possible to aid in [early] diagnosis and especially predict prognosis using inflammatory items. It has been suggested that IL-1 $\beta$ , IL-6, and TGF- $\beta$  may be markers of acute exacerbation <sup>7</sup>, and IL-12, IFN- $\gamma$ , TNF- $\alpha$ , and sIL-2R may be trait markers that do not decrease with treatment <sup>7,8</sup>. Some of these alterations may have occurred as a result of other factors, such as comorbid disorders and medication use. Clarity will become available following high-

quality large-sample longitudinal studies on participants at various stages of psychosis. Also, the possibility of differences in the levels of peripheral cytokines compared to cytokines operating in the brain should be considered<sup>12,13</sup>.

**Keywords:** Immune response, Mental disorder, Neuroimmunomodulation, Pathophysiology, Psychiatry, Psychotic disorder, Refractory schizophrenia, Schizophrenic disorder

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### Conflict of Interest

The authors had no competing interests.

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