The Link Between Immune System Dysregulation and Schizophrenia

October 05, 2011 | Schizophrenia [1], Amyotrophic Lateral Sclerosis [2], Bipolar Disorder [3], Paranoid Schizophrenia [4], Schizophrenia Psychotic Features [5]

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On the wide range of symptoms in schizophrenia, including alterations of the dopaminergic and/or glutamatergic systems, abnormal neurodevelopment, and the theory of immune system imbalance.

The theory of the role inflammation in the etiology of schizophrenia was formulated more than 100 years ago and has recently gained momentum with numerous new data that support this theory. For example, it is well known that the integrity of the blood-brain barrier reduces entry of inflammatory cells and antibodies into the brain. Usually only a few mononuclear cells, activated T cells, and macrophages migrate into the CNS. Comparison of cerebrospinal fluid samples from patients with schizophrenia and from control patients revealed that the proportion of mononuclear macrophages is significantly higher in patients with schizophrenia.

The importance of macrophages and T lymphocytes, and the cytokines produced by them, has been highlighted in the macrophage–T-cell theory of bipolar disorder and schizophrenia. According to this theory, chronically activated macrophages, microglia, and T cells synthesize inflammatory compounds that destabilize the brain and lead to schizophrenia. Monocytes, also known as the mononuclear phagocyte system, differentiate into macrophages or dendritic cells on activation. They originate in the bone marrow, migrate in the blood vessels, and penetrate all organs. Monocytes carrying CD54 receptors bind to intracellular adhesion molecules (ICAMs), which are important factors in the transmigration of monocytes through endothelial cells in the blood vessels. Levels of soluble ICAMs have been shown to be increased in patients who have schizophrenia.

Of great interest are findings that microglial cells—the macrophages of the brain—are activated during psychosis. Cells visualized with a positron emission tomography tracer (PK11195) that binds to peripheral benzodiazepine receptors, an indicator of microglia activation, were found to have greater receptor expression in patients with recent-onset schizophrenia. Activated microglia stimulate astrocytes to produce S100B, a marker of inflammation that is considered to be the equivalent of C-reactive protein in the brain. Serum S100B levels are elevated in patients with schizophrenia, and antipsychotics such as haloperidol and clozapine have been shown to decrease S100B release from glial cells.

Under certain environmental conditions, such as exposure to infectious agents or ischemic conditions, macrophages produce inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor α (TNF-α), IL-6, and chemokine (CC motif) ligand 2. Levels of these molecules repeatedly have been shown to be elevated in schizophrenia patients.
Mice models of immune challenge have shown that maternal viral and bacterial infections during pregnancy lead to behaviors in offspring that are considered rodent analogues of schizophrenia-like symptoms: deficits in prepulse inhibition, novelty-induced hyperactivity, and cognitive impairments.11 These behavioral alterations are thought to be caused by imbalances in proinflammatory and anti-inflammatory cytokines.11,12 Proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, can signal through the endothelial cells to cause alterations in the tight junction structure, leading to increased permeability of the blood-brain barrier and alterations in brain structure and function.13

Supporting the animal model research, studies in humans suggest that gestational exposure to infection may contribute to the etiology of schizophrenia.14 Moreover, there is extensive literature that supports the role of infectious agents in schizophrenia etiology.15,16 A very interesting review in 2008 discussed how some strong schizophrenia candidate genes, including immune system genes, play direct roles in regulating the life cycle of several pathogens and how understanding the interplay between gene function and pathogen exposure may help explain the role of gene-environment interactions in schizophrenia development.17

**Association of immune system genes with schizophrenia**

Schizophrenia is a very heterogeneous disorder with a wide array of symptoms and extraordinary variety among individuals. The impingement of different environmental factors in genetically susceptible individuals probably determines the overall expression pattern and severity of the illness. Furthermore, schizophrenia probably is not caused by mutations in just a few specific genes but rather is caused by the disruption of any number of genes involved in key developmental signaling pathways, such as the immune system pathway.

Understanding how genetic makeup, in combination with environmental stimuli, modulates expression of immune system genes and, in turn, regulates brain function and behavior, and how this could lead to the occurrence of mental disorders is an area of much research. In the past few years, several studies have demonstrated the association between genetic variants in immune system genes and schizophrenia, which further supports the hypothesis that immune system dysregulation plays an important role in the etiology of schizophrenia (Table).

Two controlled studies of patients with schizophrenia found significant associations between variants mapping to the region of chromosome 6 that forms part of the major histocompatibility complex (MHC) and increased risk of schizophrenia.18,19 The MHC has also been associated with increased risk of autoimmune disorders.20,21 A large study in Denmark found that a family history of any autoimmune disorder is associated with a 45% increased risk of schizophrenia.22

In a genome-wide association study, Lencz and colleagues23 found evidence that 2 immune system genes, colony-stimulating factor 2 receptor α and IL-3 receptor α (IL3RA), are associated with schizophrenia. Two later studies further support the finding of the association between IL3RA and schizophrenia.24,25 A single-nucleotide polymorphism in the first intron of the interferon γ gene was found to be associated with a 1.66-fold higher risk of paranoid schizophrenia in males, but not in females.26 An evaluation of genes in the IL-18 pathway revealed associations between schizophrenia and herpes simplex virus seropositivity.27 Significant differences in both genotype and allele frequencies of IL12 p40 gene promoter variants were found between patients with schizophrenia and controls.28 Evidence of an association between an IL10 gene promoter polymorphism and schizophrenia was also found.29

A haplotype in the TNF gene promoter has also been associated with schizophrenia.30 Evidence of the association between IL1 genes (IL1A, IL1B, and IL1 receptor antagonist) and susceptibility to schizophrenia has been reported recently.31 Polymorphisms in neuregulin 1 (NRG1), one of the strongest schizophrenia candidate genes currently identified, have been shown to interact synergistically with IL1B polymorphisms to increase the risk of schizophrenia.32

Our group recently reported evidence of an association between NRG1 and immune dysregulation. A valine to leucine mutation in the transmembrane region of NRG1, which was previously identified to be associated with schizophrenia, was found to be associated with higher levels of proinflammatory cytokines in plasma and increased production of proinflammatory cytokines in lymphoblastoid cell lines.33,34 This is the first report of the association between an NRG1 mutation and immune dysregulation.

**Stress, inflammation, and schizophrenia**

Stress and immune system reactivity play a major role in the development and exacerbation of psychotic symptoms in schizophrenia.35-37 First-time outbreaks of psychosis and schizophrenia are more frequent in individuals who are exposed to high levels of stress, such as newly recruited military personnel.38 Evidence suggests that with increasing life events or situational stress,
psychotic symptoms increase, possibly because of the overactivation of the immune system and overexpression of inflammatory cytokines.\textsuperscript{35,39}

Stress induces overactivation of the N-methyl-d-aspartate (NMDA) receptor, which is caused by excessive cytokine-induced glutamate release from astrocytes. Increased inflammation in the CNS also leads to impaired function of oligodendrocytes, which are damaged as a consequence of overexposure to cytokines such as TNF-\(\alpha\); this leads to impaired myelination.\textsuperscript{40} These processes have been shown to be altered in patients with schizophrenia.

Findings from these studies suggest that exposure to stress or immune challenges (either through stressful life events or infections) produces a host of biological processes that in genetically susceptible individuals can lead to the development of psychiatric disorders, such as schizophrenia.

**Implications and future research**

Levels of proinflammatory cytokines have been shown to be increased not only in patients with schizophrenia but also in patients with bipolar disorder. Overlapping but distinct gene expression patterns have been found in the monocytes of patients with schizophrenia and bipolar disorder. By performing a comprehensive analysis of inflammatory molecules involved in schizophrenia and bipolar disorder, it may become possible to identify specific disease signatures, which will provide valuable clues to understanding the progression to a particular disease. It is possible that dysregulation of a particular set of cytokines may lead to schizophrenia, while another set may lead to depression or bipolar disorder. Similar to transcriptome arrays for the analysis of inflammatory cytokines, proteomic arrays are designed to detect specific inflammatory fingerprints and may help identify psychiatric patients who will benefit from adjunctive anti-inflammatory therapy. For example, by analogy, patients treated with TNF antagonists (monoclonal antibodies against TNF) for immune diseases, such as psoriasis, Crohn disease, and rheumatoid arthritis, describe improvement not only in somatic symptoms but also in depression scores and quality of life.\textsuperscript{41}

It was recently reported that immunomodulation therapy can change aberrant monocytes that cause inflammation and the production of cytokines by restoring the monocytes/macrophages to their neuroprotective state, therefore reducing inflammation and normalizing the cellular environment of critical nerve cells.\textsuperscript{42} This approach was used in a phase 1 clinical study of the immunomodulator NP001 for the treatment of amyotrophic lateral sclerosis.\textsuperscript{42} Studies such as this are a source of optimism that immunomodulation may open up an alternative method for treatment of schizophrenia.

A number of different theories have been proposed to explain the wide range of symptoms in schizophrenia, including alterations of the dopaminergic and/or glutamatergic systems, abnormal neurodevelopment, and the theory of immune system imbalance.\textsuperscript{43-45} While all these theories are supported by a strong body of evidence, it is possible that they are not mutually exclusive and in fact may be interconnected. For example, recent studies indicate that the kynurenine pathway, by which tryptophan is metabolized into kynurenic and quinolinic acids, is activated by proinflammatory cytokines.\textsuperscript{46} It has been shown that these acids regulate NMDA receptor activity and may also be involved in dopamine regulation.\textsuperscript{46,47} Therefore, although the possibility of the interrelationship between the currently proposed schizophrenia theories remains to be demonstrated, a unifying theory that explains all the different lines of evidence may soon start to emerge.
References:
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Published on Psychiatric Times
(http://www.psychiatrictimes.com)


42. Appel SH. Of mice and men: immunomodulation as a therapy for amyotrophic lateral sclerosis. Presented at: 14th Annual Winter Conference of the Texas Neurological Society; February 25-27, 2011; Austin, TX.


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