An Abbreviated Review of Immune Abnormalities in Schizophrenia

By Mark H. Rapaport, MD, and Katia K. Delrahim

ABSTRACT

Initial investigations of the possible interaction between schizophrenia and the immune system began in the early 1900s and have proceeded in a rather halting fashion because of the methodological challenges faced by investigators. However, a confluence of recent data suggests that activation of the inflammatory response system, the cellular immune system, and the humoral immune system may be present in some patients with schizophrenia. Some of the most compelling data support the hypothesis that minor levels of immune activation may be associated with acute psychotic exacerbations. However, a second body of evidence suggests that some individuals with schizophrenia may have chronic, evolving autoimmune processes. This article is an overview of the history, rationale, and some of the recent findings on the interaction between schizophrenia and the immune system.

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INTRODUCTION

Initial investigations of the relationship between immune dysfunction and psychosis were published in the early 1900s.[1-3] These investigators reported either a lymphocytosis or the presence of autoantibodies in institutionalized patients with psychosis. In the 1960s, a series of studies suggested that there might be an autoimmune-mediated process involved in the etiology of schizophrenia.[4,5] With the advent of antipsychotics, the majority of investigations about the etiology of schizophrenia became focused on the link between dopamine and psychosis.[6] It was not until the 1980s that there was a reemergence of interest in studying the relationship between the immune system and schizophrenia. Several lines of evidence stimulated this renaissance of interest, including observations that autoimmune disorders such as systemic lupus erythematosus had significant neuropsychiatric consequences.[7,8] There was also an increased understanding that infectious processes such as the human immunodeficiency virus (HIV) can cause significant neuropsychiatric sequelae.[9,10] This led a number of international groups of investigators to explore different aspects of the immune system, including cellular immune system function, autoantibodies, lymphocyte morphology and trafficking, and viral antigens.[11-15]

THE CHALLENGES FACED BY IMMUNOLOGY AND PSYCHIATRY

Research focusing on the potential relationship between immune function and psychosis has faced a number of significant challenges. First, it must be recognized that work in this area encompasses an interface between two rapidly evolving fields—immunology and psychiatry. Since both of these fields are changing quickly, it is challenging to develop consistent methodology to identify, replicate, and move forward findings at this interface. Some of the methodological constraints have included:

(1) Differences in techniques in assessing immune function in schizophrenia;
(2) Constraints caused by sampling problems—often the cohorts used in these studies have been small samples of convenience;
(3) Limitations caused by the statistical approaches used to evaluate results; and
(4) Studies that had not been controlled for the myriad of confounding variables that complicate work in this field, such as medication, treatment of nosocomial infections, diagnostic heterogeneity, drinking, smoking, and drug abuse.

Despite these limitations, there have been a variety of replicated findings, including changes in cytokine and cytokine receptor levels in the serum and cerebrospinal fluid (CSF), the identification of putative autoantibodies, the presence of alterations in the levels of adhesion molecules, and the presence of unusual phenotypes of circulating lymphocytes.

These findings can be conceptualized as falling into two possibly related formulations. The first is a commonly accepted postulate that acute psychosis may be associated with diffuse, yet relatively minor, levels of immune activation. The second hypothesis is that there may be a small group of individuals with schizophrenia who manifest an autoimmune-mediated disorder. These individuals have consistent elevation of immune parameters and seem to be less responsive to traditional treatments.[16,17] Current data support competing, but not necessarily mutually exclusive, hypotheses suggesting that some patients with schizophre-

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nia have more chronic immune dysregulation characterized by T-helper cell type 1 (TH-1) activation while others may present with signs more consistent with T-helper cell type 2 (TH-2) activation.

CURRENT HYPOTHESES AND RESEARCH

Cytokines communicate information between various types of cells, including those of the central nervous system (CNS) and immune system. The most relevant activating cytokines known to act on the CNS are interleukin (IL)-1, IL-2, IL-6, and tumor necrosis factor alpha (TNF-α).[17] Recent findings show that these cytokines can modulate neurotransmitter function and, therefore, may play a role in either the pathogenesis or mediation of psychiatric disorders.

In order to demonstrate that cytokines play a significant role in the activation of the CNS, one needs to prove that the following minimal requirements are met. First, support for the presence of cytokines in the CNS should be examined. It has been demonstrated that some cytokines can enter the CNS through active transport mechanisms: IL-1, IL-2, and TNF-α can be transported into the CNS across the blood-brain barrier.[18-20] In addition, recent studies show that neurotransmitters stimulate the *de novo* synthesis of certain cytokines in the CNS.[21,22] For example, noradrenaline stimulates the synthesis and release of IL-6 from astrocytes. Since IL-6 can stimulate and modulate other cytokines—IL-1, IL-2, and TNF-α—it has been postulated that the release of IL-6 can activate a cascade of cytokine synthesis in the CNS.[21,22]

We can use IL-2 as a model for how cytokines might influence CNS function. As discussed previously, one of the first things that needs to be demonstrated is its presence in the CNS. The hippocampus is the site of the highest concentration of both IL-2 messenger ribonucleic acid and IL-2 receptors.[23] Second, we need to show that IL-2 can modulate CNS activity. IL-2 is a profound positive modulator of dopaminergic neurotransmission.[24-26] Third, we need to demonstrate that IL-2 affects behavior. When IL-2 is employed in cancer chemotherapy, a significant number of patients develop either acute psychosis or depression.[27] This suggests a possible mechanism by which infectious and autoimmune disorders or processes that stimulate IL-2 production might cause neuropsychiatric sequelae.[17]

In the rest of this section, we will review some of the data addressing the correlations between immune dysfunction and schizophrenia. These studies include those purported to investigate the relationship between acute (or an exacerbation of) psychosis and immune system stimulation, as well as studies investigating immune activation in stable schizophrenia patients.

In vitro studies involving schizophrenia patients have demonstrated a decrease in mitogen-stimulated IL-2 production[12,28-31] that has been postulated to be the result of tonically activated lymphocytes. It is hypothesized that those activated lymphocytes are too spent to mount a brisk response to an additional exogenous stimulator.[32] A number of investigators report that the greatest suppression of mitogen-stimulated IL-2 production is in acutely ill patients.[12,29,33] A second line of studies has investigated mitogen-stimulated production of interferon-γ (IFN-γ). They report that IFN-γ production is also suppressed in acutely ill patients with schizophrenia. Several groups have reported that these decreases in mitogen-stimulated cytokine responsivity can be remediated by neuroleptic treatment.[29,34,35] These data have been interpreted as supporting the postulate that acute psychiatric symptomatology is associated with diffuse activation of the immune system.[16,17]

Immune abnormalities in schizophrenia also include elevated levels of serum IL-6, a pleiotropic cytokine released from macrophages, lymphocytes, and astrocytes.[36,37] Several studies report a significant correlation between increased serum IL-6 levels and clinical features such as duration of illness[36] and treatment resistance.[38] There is also one exciting study claiming a positive correlation between elevated soluble interleukin-6 receptor (sIL-6R) levels in both serum and CSF and the paranoid-hallucinatory symptoms of patients with schizophrenia.[32] These data, again, support the hypothesis that the exacerbation of psychosis may be associated with activation of the inflammatory immune response system.

Schizophrenia patients also have been found to have increased serum sIL-2R levels, a marker of immune activation.[39] Increased sIL-2Rs have been reported in a variety of conditions where there is immune activation, including transplant rejection, acute infection, and during the active phase of autoimmune diseases.[14,28,40] In 1989, several groups

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reported that patients with schizophrenia had a significant increase in serum sIL-2Rs.[14,28] Our group was intrigued by the observation that a significant group of patients had serum sIL-2R levels greater than two standard deviations beyond the mean of matched normal volunteer levels. Similar findings of increased serum sIL-2Rs have been reported by a variety of international groups, and this is the most commonly replicated finding in the field.[15,39,41-43] Increased serum sIL-2R levels have been correlated, in some studies, with acute exacerbation of schizophrenia, as well as high levels of nicotine ingestion; however, in other studies, increased serum sIL-2R levels seem to be autonomous from the states of illness of the patient.[44,45]

SUPPORT FOR AN AUTOIMMUNE HYPOTHESIS FOR SCHIZOPHRENIA

We have attempted to characterize this increase in sIL-2Rs by performing a series of experiments. In a replication study, we measured serum sIL-2R levels in monozygotic twins who were both concordant and discordant for schizophrenia. We demonstrated that twins with schizophrenia, in general, have increased serum sIL-2Rs compared with discordant well twins and normal control twin pairs.[44] In an experiment performed in collaboration with Professor Kim,[46] we demonstrated that this finding is present across both Caucasian and Korean ethnic groups. In the same paper, we also reported that patients who had been medication free (for several weeks to many months) had increased serum sIL-2Rs. In an attempt to further investigate the role of antipsychotic medications in modulating serum sIL-2Rs, we investigated serum sIL-2R levels in antipsychotic naive schizophrenia patients and determined that a subset of these patients had markedly elevated serum sIL-2R levels.[45] Work from these earlier studies suggested that there might be an association between serum sIL-2Rs and movement disorders. We have investigated the potential relationship between very high levels of sIL-2Rs and tardive dyskinesia by employing both subjective ratings (the Abnormal Involuntary Movement Scale) and objective ratings (electromechanical measurement of tremor). We observed a positive correlation between serum sIL-2Rs in both subjective and objective measurements of hyperkinesia.[45,47]

In a more recently published work, we investigated the relationship between increased serum sIL-2R levels, mitogen-stimulated cytokine production, and the presence of autoantibodies. We identified two different subgroups of patients. One subgroup had marked elevations in serum sIL-2Rs and mitogen-stimulated cytokine responses (IL-2, alpha interferon) consistent with TH-1 activation. The second subgroup had an increased presence of antibodies directed against thyroid microsomal antigens and did not manifest signs of TH-1 activation.[48] In summary, these findings suggest that there may be three different types of immune dysregulation: (1) diffuse, nonspecific enhancement of the inflammatory response system related to psychosis, (2) TH-1–mediated immune activation, and (3) TH-2–mediated immune activation.

SUPPORT FOR TH-2 ACTIVATION

There are a small number of reports suggesting that there might be increased serum levels of IL-10,[31] CSF levels of IL-10,[49] and CSF levels of IL-4[50] in schizophrenia subjects. These cytokines are associated with TH-2 activation. The TH-2 arm of the immune system modulates β-lymphocyte activity and antibody synthesis, and can be activated by helmeth infections. These results, taken together with recent data reporting decreased levels of soluble intercellular adhesion molecule-1 (sICAM-1) in the serum of patients with schizophrenia, suggest that some patients may have a TH-2–mediated response.[51] (Since ICAM-1 is a molecule that frequently is expressed in large quantities during TH-1 activation, its diminished activity can be interpreted as a shift toward TH-2 balance.) Other inferential data that support the hypothesis that some patients with schizophrenia have a TH-2 response include studies of lymphocyte morphology describing the presence of activated β-cells (CD5+, CD19+) in the serum of schizophrenia patients.[11,41,52] The data, again, may be coupled with the rather complex and inconclusive studies investigating autoantibodies and schizophrenia.

The majority of older studies do not report either increased serum immunoglobulins or increased viral-specific antibodies in the serum or CSF of patients with schizophrenia.[16] However, there have been some recent reports suggesting an association between immunoglobulin G antibodies in the CSF and the presence of predominately negative symptoms of schizophrenia.[53] There also have

been some intriguing studies suggesting that there may be an increased prevalence of antibodies directed against heat shock protein-60 (HSP-60) in some patients with schizophrenia.[54-56] (It has been postulated that these antibodies might block the protective benefits of HSP-60 on immune dysregulation.) The confluence of evidence—cytokine dysregulation, shifts in lymphocyte subpopulations, and increased antibodies directed against common antigens—suggest that a second subpopulation of patients with schizophrenia might have TH-2 activation.

THE EFFECTS OF MEDICATION ON IMMUNE FUNCTION

Initial studies designed to look at the effects of antipsychotics on mitogen-stimulated *ex vivo* levels of lymphocyte proliferation and lymphocyte morphology did not demonstrate profound modulation by phenothiazines or haloperidol.[57,58] However, studies investigating the *in vivo* effects of phenothiazines on immune function demonstrated that phenothiazines, as a class, can stimulate the production of autoantibodies in some individuals and cause the production of a typical morphology of lymphocytes.[59,60] Data also demonstrate that phenothiazines might have significant immunosuppressant effects that could potentially be of theoretical value in understanding sepsis.[61-64] These studies led to a series of observational experiments where individuals with acute exacerbation of psychosis were studied before and after treatment with antipsychotics. The majority of these short-term treatment trials, which attempted to correlate immune function with antipsychotic treatment, reported that patients in an acute exacerbation of schizophrenia had elevations of a variety of immune activation markers, and that these elevations were ameliorated by antipsychotic treatment.[65-67] However, it is interesting to note that clozapine, a very effective but atypical antipsychotic, was associated with *ex vivo* stimulation of serum sIL-2Rs and other immune parameters typically seen with TH-1 activation, but *in vivo* immune suppression.[68-70] Again, these data could be interpreted as suggesting that the immune system is intimately linked to psychosis. The data support both the hypothesis that generalized immune activation is a sequelae of psychotic exacerbation and that immune activation might be intrinsic to the etiology of psychosis in certain individuals.

CONCLUSIONS

This review of immune abnormalities in schizophrenia is not meant to be exhaustive. The intention is to demonstrate to the reader that there is data available that support the generation of three working hypothesis: (1) immune activation is associated with acute psychosis, (2) immune activation may reflect TH-1 activation in some patients, and (3) immune activation may reflect TH-2 activation in some patients. The presence of such data is exciting because it suggests clear directions for future experiments. More work is necessary in order to determine which, if any, of these possible hypotheses may correctly describe some patients with schizophrenia. CNS

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