REVIEW PAPER

The Immune Response in the Aetiology of Schizophrenia: A Review

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Abstract

Objective: To examine the evidence for immune reactions contributing to the aetiology, and clinical presentation of schizophrenia. Method: A search engine and the words “immune schizophrenia”, “genetics schizophrenia”, “immune genetic interaction” and “autoimmune encephalitis”. The extracted material was categorized under headings. Results: Information could be gathered under 8 headings: 1) autoimmune diseases, 2) autoimmune encephalitis, 3) autoimmune antibodies without encephalitis, 4) infection/inflammation in utero, 5) infection/inflammation in patients, 6) possible role for microglia 7) combined genetic and immune factors and 8) potential treatment. There is persuasive evidence that immune reactions are involved in some cases of schizophrenia, and that psychiatrists need to be keep abreast of developments in this field. Conclusion: Autoimmune antibodies occur in 6.5-8% of people with schizophrenia. An immune-genetic process features in 30-40% of people with schizophrenia.

Keywords: Schizophrenia, Immune Response, Genetics, Autoimmune Disease, Schizophrenia Treatment

Introduction

Schizophrenia is a complex and disabling disorder with a genetic basis demonstrated by high concordance between monozygotic twins¹. Genomic-wide association studies for common susceptibility variants, however, have been less successful in schizophrenia than in many other complex diseases²,³.

The lifetime expectancy for schizophrenia, when one offspring has this disorder, is higher for the dizygotic twin than for the siblings¹. This indicates that intrauterine events influence etiology.

An inflammatory basis for schizophrenia was proposed in the mid-twentieth century⁴, but until recently progress was slow⁵. Exciting, new evidence has suggested aetiological interactions between the genetic and the immune systems⁶. It is proposed that a gene-immune interaction, may be important in 40% of cases⁷. The complete pathways by which immune activation and the genes interact, and prenatal exposure to an immune reaction produces long-term...
central nervous system (CNS) changes remain to be clarified⁸.

Our aim is to examine the evidence for immune reactions contributing to the aetiology, and clinical presentation of schizophrenia; advances in genetic studies are also covered. For completeness, details of autoimmune diseases and autoimmune encephalitis are also given.

**Method**

A search was made using a literature search engine and the words “immune schizophrenia”, “genetics schizophrenia”, “immune genetic interaction” and “autoimmune encephalitis”. We focused particularly on the years 2000-2012, although older classic texts were consulted. The reference lists of the papers obtained were examined for additional leads. Extracted material was arranged under 8 headings.

**Results**

1. **Autoimmune diseases**

Autoimmune disease in individuals and their first degree relatives are associated with an increased risk for schizophrenia⁹. This was determined using a cohort of 3.7 million births, and the association holds for a range of autoimmune diseases. More specifically, schizophrenia has an increased risk of Graves’ disease, psoriasis and celiac disease and a reverse association with rheumatoid arthritis¹⁰; others also confirmed the association with autoimmune disease, and found increased risk of type 2 diabetes and a reduced risk of rheumatoid arthritis and cancer¹¹. Neuropsychiatric symptoms occur in 35-75% of people with systemic lupus erythematosus¹². Autoimmune disease increases the risk of schizophrenia by 29%¹³ and the fluctuating course of schizophrenia has been likened to that of autoimmune diseases¹⁴. In fact, any hospitalization with infection increases the risk of schizophrenia by 60%¹³. In general, autoimmune diseases involve both genetic and immune functions.

2. **Autoimmune encephalitis**

Limbic encephalitis, which is more common in women, usually presents with rapid onset of psychiatric and neurological symptoms. After a non-specific flu-like illness (sometimes un-noticed) there may be hallucinations, delusions, chaotic behavior and memory disorder, often progressing to autonomic instability, seizures and death by hypoventilation¹⁵. Many such cases can be diagnosed as paraneoplastic disorders. Antibodies are found in both serum and CSF. In a series of 100 cases, 59% had a tumor, most commonly ovarian teratoma¹⁶. Other associated tumors include thymoma, small cell lung cancer, breast cancer and testicular germ-cell tumor¹⁷.

Two sets of antibodies have been described, one directed against intracellular neuronal antigens, and the other against cell-surface antigens. Antibodies directed against neural cell-surface structures are the predominant cause of the paraneoplastic syndrome¹⁶. Complicating the picture is that antibodies against cell-surface structures can occur both in the presence and absence of neoplasia, spawning categories paraneoplastic and non-paraneoplastic autoimmune encephalitis¹⁸.

The characteristic signs and symptoms of paraneoplastic disorders depend to some extent on the nature of the neoplastic source. In a few instances psychiatric disturbance is the only set of symptoms¹⁷.

Studies of CSF in autoimmune encephalitis reveal increased lymphocytes and intrathecal
synthesis of the following antibodies; likely this list will grow with future studies.19

1. Anti-N-methyl-D-aspartate (NMDA) receptor antibodies. Some hundreds of cases have been recognized, 75% of whom initially presented to psychiatric units16. Approximately 50% of subjects do not have an identifiable neoplasm15. NMDA receptor antibodies cases preferentially develop psychiatric and amnestic symptoms, and are more common in African-American, Asian, Latinos ethnic groups.20

   Probably, glutamate opens the NMDA-receptor pore, but NMDA-receptor antibody prolongs the period of opening and additional calcium enters the cell12.

2. Voltage gated potassium channel (VGKC) antibodies. These may occur in the absence of tumor, but 20% are associated with small cell lung cancer or thymoma21.

3. Anti-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antibodies. Seven of 10 patients (70%) with this syndrome had tumor of the breast, lung or thymoma.22

4. Anti-gamma-aminobutyric acid type B (GABAB) receptor antibodies. This syndrome has been associated in about 40% of cases with small cell lung cancer.23

Magnetic resonance imaging (MRI) studies reveal in some cases transient fluid-attenuated inversion recovery (FLAIR) changes involving cortical or subcortical regions.24 In one of 4 cases with anti-NMDA receptor antibodies mild FLAIR hyperintensity was located in the medial temporal lobes. In 2 of 4 cases frontotemporal atrophy was identified during convalescence.25

3. Autoimmune antibodies without encephalitis

The studies of encephalitis detailed above involved antibodies to neuroreceptors. This raises the question of whether some cases of schizophrenia without any evidence of encephalitis may also be associated with antibodies to neuroreceptors. In one study of 46 cases of apparent first presentation schizophrenia, 4 cases featured autoimmune antibodies to receptors (3 to NMDA receptor and one to VGKC) representing 6.5% of the total.26 Referring to their own unpublished data, these authors reported no antibodies to receptors among a chronic population. In a study of 51 patients with schizophrenia and schizoaffective disorder, with no evidence of encephalitis, 4 female cases (8% of total) were identified with anti-NMDA-receptor antibody, of whom 2 were found to have ovarian tumor.27 This suggests, some individuals who appear to have schizophrenia or schizoaffective disorder, and no evidence of encephalitis, may nevertheless, be subject to the effects of autoimmune antibodies.

Moscato et al24 state that women may be asymptomatic yet carry anti-receptor antibodies, and these may access and disrupt the development of the fetal brain. Such effects on synapses and circuits may ultimately affect behavior.

4. Infection/inflammation in utero

Early attempts were made to identify the risk of schizophrenia associated with infection by studying individuals who had been in utero during influenza epidemics. Initial studies indicated an increased risk, but these were not replicated, and the
methodology lost favour\textsuperscript{28}. Subsequently, studies used birth cohorts in which prospective material provided sound evidence of infection. One study found first trimester exposure to influenza increased the risk of schizophrenia sevenfold\textsuperscript{29}. Another found in utero exposure to Toxoplasmosis gondii doubled the risk of schizophrenia\textsuperscript{30}. Thus, in utero infection with some microbial pathogens is associated with increased risk of schizophrenia.

Cytokines are key signaling molecules of the immune system, produced by both immune and non-immune cells, which co-ordinate the immune systems. They have a central role in the immune response and are ready markers of infectious and inflammatory conditions. In the brain they bind to receptors on glia cells and neurons\textsuperscript{31} and can trigger deregulations of major transmitters and development leading to psychiatric symptoms\textsuperscript{32}. They also have the ability to interfere with the metabolism of tryptophan leading to reduced synthesis of serotonin\textsuperscript{33}. A twofold increase in maternal levels of interleukin (IL)-8 has been demonstrated during the second and early third trimester among pregnancies ultimately leading to schizophrenia\textsuperscript{34}.

To study the mechanisms by which maternal infection impacts on the fetus, preclinical studies have used maternal immune activation [MIA] most often using mice. In a recent study\textsuperscript{35} pregnant dams were exposed to influenza virus, the synthetic dsRNA, poly(I:C), and IL-6. All produced gene expression changes in the embryonic brain. It was found IL-6 is necessary and sufficient for this purpose, however the different agents produced different transcriptome signatures. 256 genes were differently expressed (some upregulated, others downregulated) in the influenza model, 294 in the poly(I:C) model, and 195 genes were differently expressed in the IL-6 model. However, as a number of similar changes were produced by these different agents, it is considered that the maternal immune response has the critical impact on the offspring. The induction of maternal cytokines then alters cytokine expression in the fetal brain. The central role of IL-6 in mediating transcriptional changes has been confirmed\textsuperscript{36}. Maternal cytokine activity leads to immune activation in the fetus and amniotic fluid\textsuperscript{8}.

Hsiao and Patterson\textsuperscript{37} focused on the MIA placenta as the site of direct interaction between mother and foetus. They confirmed that IL-6 is a crucial mediator, and stated that maternal IL-6 can potentially cross the placenta and enter the foetus. They found that IL-6 impacts the placenta endocrine status, including varying growth hormone levels. They proposed that IL-6 acts directly on the brain, influencing astrogliosis, neurogenesis, microglial activation and synaptic pruning.

In a study using various agents to induce MIA\textsuperscript{35}, 12 genes were upregulated by each agent. Five of these belong to the crystalline gene family. A crystallin is a water-soluble protein found in the lens of the eye, contributing to transparency. Lens injury may promote nerve regeneration, thus crystallin has become an area of neural research. It has been demonstrated that crystallin β b2 (crybb2) may act as a neurite promoting factor.

There is an acute and transient uregulation of the alpha, beta and gamma members of the crystallin gene family\textsuperscript{35}. Crystallins have a wide functions including neuroprotection\textsuperscript{38}, however, overexpression could have detrimental effects on the developing brain\textsuperscript{39}. In schizophrenia, altered
expression of both alpha and mu crystallin have been reported in the anterior cingulate cortex and prefrontal cortex.

MIA in lab animals has long-lasting effects on behavior, CNS structure and the immune system of the offspring. It induces brain cytokine changes in the offspring that persist through development. Region and age-specific changes (frontal and cingulate cortices and hippocampus) were observed in association with 23 cytokines. In general, pro-inflammatory cytokines were elevated at birth, decreased during synaptogenesis and plasticity (day 7-14) and increased again in adult (60 day) mice. The absence of immune cell infiltration into the brain combined with little evidence of change in the blood brain barrier suggests that MIA is not associated with inflammation in the classical sense.

Some MIA studies demonstrate increased striatal release of dopamine, suggesting sensitivity of subcortical and mesolimbic dopamine pathways, which is consistent with the dopamine theory of schizophrenia, while other changes support the glutamatergic model of schizophrenia. Enlarged ventricles and Purkinje cell abnormalities have also been reported.

5. Infection/inflammation in patients

Blood

A blood study of 83 first episode patients with schizophrenia identified significantly elevated levels of IL-1beta and tumor necrosis factor (TNF) alpha. And, after 4 weeks treatment with an antipsychotic, the IL-1beta level fell. Studies of gene expression in monocytes of individuals with recent onset schizophrenia confirmed the elevated levels of IL-1beta and TNF alpha, and also elevation of additional cytokines, including IL-6. Borovacanin et al. looked at drug-naïve first episode psychosis, schizophrenia in relapse and healthy controls and found significant decreases in IL-17, increased levels of IL-4 and transforming growth factor (TGF) beta in psychosis. There is also a yet to be replicated report of different serum interleukin levels being associated with delusions and hallucinations.

In a literature review Chan et al. identified 273 potential peripheral blood markers of schizophrenia; 103 molecules were considered unique, and of these 75 were involved in the inflammatory response, suggesting an ongoing immunological inflammatory process. In addition, there were elevated cortisol levels and altered hypothalamic-pituitary-adrenal axis function among patients, suggesting an activated stress response. They found evidence of type-1 (Th1) and type-2 (Th2) immune system activation in schizophrenia. One Th2 response, with alterations in IL10 and IL5 was present in drug-naïve first onset patients, and was designated as potentially of aetiological importance. However, the authors could not determine whether the observed immunological changes were a result of persistent infection or stress, as both are able to trigger a Th2 response.

A meta-analysis of 40 blood studies found that increased IL-1beta, IL-6, and TGF beta appeared to be state markers, which normalized with antipsychotic treatment. These authors also found IL-12, interferon (IF) gamma, TNF alpha, and soluble IL-2 receptor (sIL-2R) appeared to be trait markers, remaining elevated during remission. Reservations were expressed, insofar as most studies did not control for body mass index and smoking. The sIL-6R is a normal constituent of body fluids that regulates cytokine activity in antagonistic and agonistic manners. A strong correlation exists between levels of sIL-6R and severity.
of schizophrenia, raising the possibility that this receptor may be an etiological factor.

Drexhage et al. found that monocytic gene expression signatures in schizophrenia and bipolar disorder are different, but somewhat overlapping. For example, Subset 1A, characterized by ATF3 and DUSP2 (upregulated in 67% and 51%), and Subset 1B, characterized by ERG3 and MXD1 (upregulated in 34% and 41%), were shared by those with schizophrenia and bipolar disorder. Subset 2, however, characterized by PTPN7 and NAB2, were upregulated in the monocytes of people with bipolar disorder in 62% of cases, and downregulated in the monocytes of people with schizophrenia in 48% of cases.

To date the majority of blood studies have examined acute schizophrenia. Xiu et al. found significantly higher levels of IL-18 among a group with chronic schizophrenia than among acute phase subjects, and healthy controls. In these chronic patients the level of IL-18 was positively correlated with the positive and negative symptom scale (PANSS) general psychopathology score.

Very recently, molecular profiling techniques have been used to identify a blood based biological signature for schizophrenia, and a commercially available blood test for schizophrenia has been described. These are based on the schizophrenia being a systemic disorder, with biomarkers from a range of organs and processes being incorporated. For current purposes we simply note that both included changes in several interleukin levels.

**CSF**

In a CSF screening study of 155 patients with apparent first episode schizophrenia, 5 (3.2%) patients provided results (not detailed by the authors) which changed the diagnosis and management, including two with chronic inflammation of the CNS of uncertain origin. In another study of 63 patients with affective and schizophrenia spectrum disorders, an intrathecal humoral immune reaction was detected in 9 (14%). A meta-analysis of studies of CSF revealed IL-1beta was significantly elevated in schizophrenia, compared to controls.

**Post mortem**

Neuroimaging studies of people with schizophrenia reveal grey matter grey matter loss of the dorsolateral prefrontal cortex, medial, middle frontal and superior temporal gyri, and diffuse white matter loss.

A post-mortem study of Broca’s area (BA) 9 of the prefrontal cortex of 14 schizophrenia brains compared to healthy controls found overexpression of SERPINA3, IFITM1, 2 and 3, CHI3L1, MT2A, CD14, and HSPA1A and B in the patient group. The authors speculated this was long-lasting and a signature of early environmental insult delivered during development, which contributed to prefrontal dysfunction. A post-mortem study of BA 46 of the prefrontal cortex of 12 subjects with schizophrenia showed numerous expression changes related to the neuroimmune transcriptome, including HLA-DRB1, LTB4DH, CD74, HLA-DRA, CX3CR1 and C3, strengthening the notion that neuroimmune disturbances may be central to schizophrenia pathophysiology.

Using advanced techniques Fillman et al. examined BA 46 of 20 schizophrenia brains and the controls. They detect 789 differently regulated transcripts in the schizophrenia tissue. Changes in IL-6, IL-8, IL-1beta and SERPINA3 were confirmed. The density of MHC-II-positive microglia was significantly
increased, and this correlated with IL-1beta expression.

Some evidence\textsuperscript{61} points to different patterns of lymphocytes and microglia in the hippocampus of people with residual (predominantly negative symptoms) compared to paranoid (predominantly positive symptoms) schizophrenia. Higher densities of CD3+ and CD20+ lymphocytes were located in the hippocampus of residual schizophrenia brains, while increased densities of HLA-DR+ microglia were located in the hippocampus of paranoid schizophrenia brains. This may indicate disruption of the blood brain barrier.

As mentioned above, altered expression of both alpha and mu crystallin has been reported in the anterior cingulate cortex\textsuperscript{62}, and prefrontal cortex\textsuperscript{41}.

6. Possible role of microglia
Recent research\textsuperscript{33} has focused on the potential importance of microglia on histopathological changes in schizophrenia. Microglia are the mononuclear phagocytes of the brain. They are present in the rudimentary brain and play major roles in brain development, including axon remodeling, synaptogenesis and synaptic pruning\textsuperscript{63}. They phagocytose cells programmed for death, and stimulate the proliferation of embryonic and adult progenitor cells [64]. Microglia also secrete a wide array of neurotrophic factors, chemokines and cytokines. Excessive activation of microglia disturbs normal function and is consequentially detrimental to neurogenesis and synaptogenesis\textsuperscript{65}.

Increased cytokine production in the brain is suggestive of microglial activity. A positron emission tomography (PET) study\textsuperscript{66} clearly demonstrated microglial activation in the hippocampus of people with schizophrenia. Significantly, this is a region contributing to memory\textsuperscript{67} and emotional response. Thus while concentrating on to cytokine levels, much produced by microglia, we need also to be aware of the other functions of microglia contribute to the biological response.

Frank et al\textsuperscript{68} investigated the effect of inescapable shock (IS) on the microglia of rat hippocampus. It potentiated the pro-inflammatory response when immunogens such as lipopolysaccharide are administered. That IS, a powerful stressor, sensitizes the pro-inflammatory reactivity of microglia to immunologic stimuli, this is consistent with the finding that life stressors appear to predispose to mental disorder.

7. Combined genetic and immune factors
The interactions of genes and the immune system are central to processes in autoimmune diseases. Such events as changes in serum cytokines levels are evident in people with schizophrenia, and also in their unaffected first-degree relatives\textsuperscript{62}.

Clarke et al\textsuperscript{69} have demonstrated a gene-infection interaction in schizophrenia. Offspring whose mothers had suffered pyelonephritis during pregnancy were followed up in adult life. Surprisingly, there was no significant difference in the rate of schizophrenia, when this group was compared to controls. However, when the individuals of this group with a family history of psychosis were compared to the individual with no such family history there was a remarkable difference. Those who had been exposed to infection in utero and had a family history of psychosis had a rate of schizophrenia five-fold higher than those who had been exposed to in utero infection but had no family history of psychosis. This
finding supports a gene-infection synergistic effect in schizophrenia.

A significant positive genetic association exists between certain genes which encode for the major histocompatibility complex (MHC) and schizophrenia. This is the region containing the genes for IL-1alpha, IL-1beta, and IL-1RA.6,7. Prenatal infection may modify MHC function to a greater degree among individuals who are genetically predisposed to decreased neuronal function resulting in reduced synaptic plasticity.44 The details of the gene-infection interaction are yet to be fully defined. However, evidence indicates that in schizophrenia, infection alters the effect of genes that are central to the immune response.

In addition, and complicating the picture, there is endocrine involvement. During neonatal development, cytokines produce permanent alterations of the HPA axis and the stress response.31 This modulates the susceptibility to inflammatory disease and activates transcription of hormone sensitive genes and a cascade of inflammatory responses.

Bechter14 offered an answer to the age old question, as schizophrenia is associated with low fecundity, there must be some advantage to this disorder, or it would disappear – so what could it be? The proposal is that there may be an advantage associated with an improved immune response, which acts protectively in changing environments.

8. Potential treatment
“Current treatments are ineffective at addressing the full spectrum of symptoms”7, and clinicians are desperate for new tools to manage this scourge. (The current antipsychotics have an immunomodulatory activities, which may form an important part of their antipsychotic action.)

A meta-analysis by Sommer et al71 considered 5 double-blind, randomized, placebo-controlled trials of anti-inflammatory agents, involving 264 patients. Four studies used celecoxib (400mg/day) and one used acetylsalicylic acid (1g/day). Three used PANSS and significant reductions were observed in both positive and negative symptoms. The authors suggested that acetylsalicylic acid may have the additional benefit of reducing cardiac and cancer mortality in schizophrenia.

Goldenholz et al72 observed that present treatment algorithms for autoimmune encephalitis recommend costly immune-modulating treatments. These include azathioprine and various anticytokine agents such as atilizumab, anakinra and TNF alpha blockers; and an anti-IF-gamma agent. Goldenholz et al72 report the successful treatment of a single case GABAB receptor antibody encephalitis with low-cost, oral corticosteroids. Further evidence is necessary before this approach can be recommended.

Minocycline has anti-inflammatory properties and is a microglial inhibitor which has some antidepressant properties in animal models.74 In rats infected as neonates with E Coli minocycline treatment prevented an exaggerated hippocampal IL-1beta response and impaired memory.67 In a randomized double-blind placebo-controlled clinical trial, people with recent onset schizophrenia were administered minocycline or placebo in addition to treatment as usual.75 After one year of treatment those taking minocycline demonstrated significantly less negative symptoms.
Anti-inflammatory drugs need to be fully investigated as potential agents for use in the treatment of schizophrenia.

**Discussion**

Genetic investigations have not led to a comprehensive understanding of the aetiology of schizophrenia. While clearly of major importance, as illustrated by the high concordance for schizophrenia in monozygotic twins, other factors are involved. In 30-40% of cases, immune factors have a key role, leading to a gene-immune aetiological theory.

The aetiology of autoimmune diseases is generally considered to involve genetic and immune factors, and the fluctuating course of schizophrenia is reminiscent of an autoimmune disease. The quite frequent concurrence of schizophrenia and known autoimmune diseases such as diabetes mellitus and coeliac disease suggests some common etiology.

Autoimmune encephalitis frequently presents with psychotic and disorganized symptoms. While autoimmune encephalitis is not a model for schizophrenia, it is associated with autoimmune antibodies and frequently neoplasia. It does illustrate that immune processes can underlie hallucinations, delusions and disorganized behavior. This is perhaps not surprising as the antibodies are directed at neureceptors and ion channels, and such damage would interrupt neural function. Studies show that a small percent (6.5-8) of people with apparent schizophrenia and no evidence or encephalitis do manifest these autoimmune antibodies.

The data on in utero infection leading to schizophrenia in the adult is most challenging. This is probably the route by which the immune system most commonly contributes to the etiology of schizophrenia. Brown et al found that intrauterine exposure to influenza virus increases the risk of schizophrenia by seven-fold.

The blood, CSF, and post-mortem brain studies of many people with schizophrenia demonstrate elevated cytokines and excessive gene expression. It is probable the maternal immune response impacts the foetal immune system. But the mechanisms by which this happens and how immune agents are chronically expressed in the offspring remain to be explained. Speculation by the current authors is that this may involve epigenetic processes during cortical neurogenesis.

The microglia have an important physiological role in the development and running repairs of the brain. They are also involved in the immune response, among other things, contributing to cytokine levels. It is possible that chronic immune activity may divert them from their normal maintenance activities with pathological results.

As already mentioned, the mechanisms of the gene-immune interaction remain to be clarified, but will likely involve the genes which encode for the major histocompatibility complex.

It is important to note that gene-immune interaction results in pathological changes in regions known to be dysfunctional in schizophrenia. At least 3 studies have shown abnormal gene expression in the prefrontal cortex. This is the region of the brain most concerned with executive cognitive function and known to be dysfunctional in schizophrenia. Also, excessive cytokine activity has been demonstrated in the hippocampus.
abnormal hippocampus histology has been reported. This area is important for memory and emotional integration, and again, is believed to be dysfunctional in many people with schizophrenia.

We have discussed the possibility of using anti-inflammatory drugs in the treatment of schizophrenia. Such advances are sorely needed, and all possibilities must to be explored.

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