Viral Infections as Etiological Factors of Schizophrenia

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Schizophrenia is a major psychiatric disorder with different clinical subtypes. However, the etiological factors and pathogenetic mechanisms involved in the development of schizophrenia remain obscure. The discrepancies among the findings of previous genetic studies of schizophrenia that have taken place over several decades may have resulted from the failure of these studies to account for environmental risk factors. Epidemiological studies have indicated viral infection as one of the environmental risk factors of schizophrenia. Prenatal and perinatal infections may affect the immune reaction or neuronal development and result in schizophrenia in genetically susceptible individuals. Viral infections during development may be a source of the differences in the subgroups of patients with schizophrenia. Several putative viral infectious agents have been suggested as potential risk factors for schizophrenia. Although there are some constraints on the investigation of infectious agents in patients with schizophrenia, viral infection as an etiologic factor involved in the development of schizophrenia should be a primary focus of future studies.

KEY WORDS: Schizophrenia, Etiology, Pathogenesis, Virus, Infection.

Introduction

Despite tremendous effort over several decades, the etiology and pathogenesis of schizophrenia, a major psychiatric disorder with a lifetime morbid risk of approximately 1% worldwide, has not been clearly defined.

The heritability of schizophrenia is estimated to be approximately 60–80% from twin studies, after accounting for the effects of shared environment. However, the mode of inheritance remains uncertain. The evidence currently available suggests the involvement of multiple genetic risk factors, with possible epistatic interactions. Since the concordance rates among monozygotic twins are estimated to be 40–70%, non-genetic environmental factors are likely to contribute to the development of schizophrenia. Indeed, epidemiological studies have suggested the involvement of several environmental factors, including infectious agents and perinatal head trauma. Thus, schizophrenia may be due to genetic variation, environmental risk factors, and their interactions. Several studies have suggested that prenatal and perinatal infections, as well as other environmental insults, may affect the immune reaction, including cytokines or neuronal development, and lead to the development of schizophrenia in genetically susceptible individuals. Thus, another source of the discrepancy in the previous genetic studies may have been the failure to account for environmental risk factors.

The objective of this study was to elucidate the role and pathogenesis of viral infection as an etiological factor and pathogenesis of schizophrenia.

Infection and Neurodevelopment

The neurodevelopmental hypothesis of schizophrenia has been supported by se-
veral studies. \cite{17-20} Cytoarchitectural studies have suggested that the disruption of neuronal circuits during development might be an important pathophysiologic mechanism of schizophrenia. \cite{18-21} The incidence of minor physical malformations is increased in patients with schizophrenia, \cite{22} and disturbed neuronal formation and migration were found in the postmortem brains of patients with schizophrenia. \cite{23}

Viruses are ubiquitous human pathogens with established teratogenic effects on the central nervous system. \cite{24} One of the strengths of the viral hypothesis for schizophrenia is the fact that viruses have been shown to possess the ability to target specific types of neurons in the central nervous system. \cite{25}

The concordance rates for schizophrenia in monozygotic twins are higher than those for the general population. \cite{1} Concordant monozygotic twins are more likely to have been monochorionic and to have shared a single placenta, whereas discordant monozygotic twins appear more likely to have been dichorionic with separate placentas. This suggests that prenatal development may also be important in the etiology of schizophrenia. \cite{26} Monochorionic twins usually share fetal blood circulation and are therefore likely to share infections. Teratogenic viruses may affect one or both members of a twin pair. \cite{27} These results are consistent with the hypothesis that fetal infections may be a significant etiological factor in schizophrenia \cite{26} and give the viral hypothesis of schizophrenia an advantage over environmental mechanisms. \cite{28} Perinatal or obstetric complications have been reported to be associated with schizophrenia, \cite{29} which may suggest that viral infections are etiological factors involved in the development of schizophrenia because obstetric complications can increase perinatal exposure to viruses. \cite{30}

Central nervous system infections during childhood are associated with an increased risk of adult-onset schizophrenia. \cite{31} In addition, prenatal infections in the pregnant mother, which were mediated by the immune response through various cytokines, might affect the neurodevelopment of the fetus and may be associated with schizophrenia. \cite{32-35} Fathers can also transmit infectious agents to the fetus by infected sperm, \cite{14} which may explain the finding of an increased risk of schizophrenia in children with older fathers. \cite{36}

**Infection and Autoimmunity**

Exposure to a virus having molecular homology with the host protein could elicit an autoimmune reaction throughout several possible mechanisms. \cite{37} Viral infections are capable of triggering or promoting autoimmune diseases of the nervous system after a latency period. \cite{38}

There is evidence of impaired immune responses in patients with schizophrenia. \cite{8,39} A subgroup of patients with schizophrenia may show the features of an autoimmune process. \cite{40} Several studies have reported autoantibodies against the brain constituents of patients with schizophrenia. \cite{8,39,41} Several groups have reported the increased occurrence of autoantibodies against specific areas of the brain in patients with schizophrenia. \cite{42-44}

The observed discordance rates for twins could also be explained by the presence of a virus-triggered autoimmune reaction. The expression of disease from viral infection could be affected by different immune responses in monozygotic twins. \cite{45}

**Putative Viral Infectious Agents as Etiological Factors of Schizophrenia**

Several viral infectious agents, namely influenza virus, Borna disease virus, herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), toxoplasma gondii (TOX) and cytomegalovirus (CMV) were found to be putative significant etiological factors for schizophrenia. They are plausible candidates for schizophrenia because they could induce latent infection and invade the central nervous system. \cite{46} The delay would thus account for the lag time between perinatal infection from the parents and the onset of the disorder in adolescence. Raised titers for antibodies to HSV 1&2, TOX, CMV were detected among first break cases of schizophrenia. \cite{8}

CMV is a prevalent viral pathogen spread through close personal contact, and the majority of persons with acute CMV will experience an inapparent infection. \cite{47} Familial correlation for CMV antibodies has been reported. \cite{48} It is uncertain whether the increased risk of schizophrenia is due to CMV infection in the patients, their parents, or both: however, recent evidence of symptom reduction among patients treated with anti-viral medication \cite{49} favors a direct effect of CMV infection on the symptoms of schizophrenia in some patients. The associations among patients with elevated paternal antibodies are intriguing. The CMV antigen was found in the temporal cortex of the postmortem brains of schizophrenic patients. \cite{50} Antibodies to CMV were also detected in the cerebrospinal fluid (CSF) of patients with schizophrenia. \cite{51,52}

TOX is an intracellular protozoan that infects cats and can cause chronic nervous system infection or psychosis. \cite{53} Antibodies to Toxoplasma were detected in the first case of schizophrenia. \cite{54}

Herpes virus antigens were detected in postmortem brain \cite{55} and CSF. \cite{56} The offspring of the mothers with elevated levels of total IgG and IgM immunoglobulins and antibodies to herpes simplex virus type 2 are at an increased risk for the development of schizophrenia and other psy-
chotic illnesses in adulthood.\textsuperscript{37} Herpes virus and cytomegalovirus could induce latent infection and apoptosis in the brain of the proband following perinatal infection.\textsuperscript{38}

Several reports have shown a lack of association between those pathogens and schizophrenia.\textsuperscript{46,59} There were no differences in the cellular and humoral activities to HSV-1 and HSV-2 and no difference between serum antibody levels of the schizophrenic patients and control individuals with CMV.\textsuperscript{59} HSV-1, HSV-2 and TOX could not have been found in the orbital frontal cortex of psychiatric patients.\textsuperscript{46} Studies aimed at the detection of antibodies to herpes viruses showed controversial results.\textsuperscript{49,57,60}

Seropositivities to Borna disease virus (BDV) were higher in patients with schizophrenia than in the general population.\textsuperscript{46,62} The ability of Borna virus to infect limbic structures has increased the interest in this agent as a possible cause of schizophrenia.\textsuperscript{63} However, it is difficult to identify at-risk patients because no single psychiatric disorder has been associated with BDV infection.\textsuperscript{64}

The influenza virus has also been a suspected etiologic factor involved in the development of schizophrenia since the discovery of an increased risk of schizophrenia among individuals who were in the second trimester of gestation during the influenza epidemic.\textsuperscript{65} Numerous studies investigating the relationship between the influenza virus and schizophrenia have shown inconsistent results.\textsuperscript{66} A recent report showed serologic evidence for the involvement of prenatal influenza in the etiology of schizophrenia by demonstrating the increased risk of schizophrenia in those exposed to influenza during the first trimester.\textsuperscript{67}

**Infection and Subtypes of Schizophrenia**

Schizophrenia is a heterogeneous disease associated with different etiological factors. The clinical subtypes of the disease may reflect the variable pathophysiological mechanisms of schizophrenia.\textsuperscript{68,69}

Subtypes of schizophrenia could be the result of insults occurring at different stages of neurodevelopment, and thus affecting different neural circuits.\textsuperscript{28} Accordingly, viral infections during development may engender only a portion of the multiple disease subtypes that are subsumed under the rubric of schizophrenia.\textsuperscript{28} Conversely, a viral infection could give rise to multiple disease subtypes depending on the timing of the infection and the characteristics of the host, such as immunogenetics, prior pathogen exposure, and neurocircuitry reserve.\textsuperscript{28}

A previous study reported an association between serum antibodies to herpes simplex virus 1 and cognitive deficits in individuals with schizophrenia.\textsuperscript{69} Gestational maternal infections predicted the diagnosis of systematic catatonia and suggested distinct schizophrenia phenotypes based on different etiological mechanisms.\textsuperscript{70} The subgroups of patients with schizophrenia had different seropositivity to Borna disease virus.\textsuperscript{71,72} However, the association between infection and the various subtypes of schizophrenia has not yet been well established.

**Constraints on the Investigation of Infectious Agents**

The viral hypothesis of schizophrenia has not yet been defined, despite numerous studies showing an association between congenital or perinatal viral infections and schizophrenia. Most of the problematic issues of the viral hypothesis of schizophrenia are related to the variability between the methods of study used and the failure to identify a specific virus as being consistently associated with schizophrenia.\textsuperscript{8,39,73} Furthermore, it is hard to establish a causal relationship between viral infections and the immune abnormalities to viral infections in schizophrenia due to the latency period between the putative infection and psychiatric diagnosis. In cases of schizophrenia, the markers of a viral infection, such as inclusion bodies or viral antigens, may be undetectable at autopsy because the infection could insidiously disrupt development and then be cleared from the brain prior to the manifestation of symptoms decades later.\textsuperscript{8}

Infections from several pathogens have been implicated following case-control analyses in schizophrenia.\textsuperscript{8} They include the direct investigation of the putative etiological agent, as well as the estimation of appropriate antibodies. Both types of analyses are imperfect, since the critical infection needs to be posited during the prenatal or post-natal period.\textsuperscript{15} Exposure to infectious agents continues throughout life, and older people tend to have a much higher prevalence of antibodies than younger individuals. The number of antibodies against infectious agents were higher for parents than for probands, which is consistent with their age differential.\textsuperscript{74} It remains unclear whether maternal or paternal infection of those who had elevated antibody titers to pathogens might have affected their proband during the perinatal period. Nevertheless, the estimation of antibody titers can be used as a convenient proxy measure. Until now, studies that examined putative infectious etiological agents, including various viruses, did not show consistent associations with schizophrenia, and the results of other promising studies have not been replicated.\textsuperscript{8,57,75}

**Conclusion**

Schizophrenia is a neurodevelopmental disorder with
a high familial concordance. Viral infection during the fetal or neonatal period is assumed to be one of the etiologic factors of schizophrenia. Several viruses that could affect the host immune response and neurodevelopment have been reported to be associated with schizophrenia. However, the pathogenesis of schizophrenia and the relative contribution of viral infections to schizophrenia have not yet been defined because of methodological problems.

Assuming that schizophrenia is a disorder with different subtypes and associated with a variety of etiological, genetic, immune and environmental factors, it is possible that viral infections could influence the pathological mechanism of schizophrenia depending on the case. Therefore, the influence of viral infection should be a primary focus of future studies concerning schizophrenia.

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