The Risk for Schizophrenia From Childhood and Adult Infections

The theory that infection plays a causal role in schizophrenia has its origins during the dawn of the scientific approach to biological psychiatry. Inspired by the bacteriological revolution in medicine and subsequent observations by psychiatrists and neurologists, Kraepelin proposed that focal infection is a potential cause of "dementia praecox" (1). Following the 1918 influenza pandemic, Menninger reported on a "schizophrenic syndrome" among individuals afflicted by acute infection; while this syndrome differed from other forms of schizophrenia in that most cases exhibited complete recovery, it appeared to be distinct from classical delirium (2). Although attempts were made to validate these assertions, the means to subject them to rigorous hypothesis testing were lacking, and this theory gradually faded from serious consideration, lying dormant for many subsequent years.

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Recently, a growing number of investigators have recognized that an infectious hypothesis for schizophrenia is both biologically plausible and testable. Authorities from several diverse disciplines, including infectious disease, neonatology, pediatrics, neurology, and obstetrics and gynecology have long known that infections during prenatal and postnatal life have many neuropsychiatric sequelae, including behavioral problems, mental retardation, learning disabilities, and mood alterations (3). A further clue was the well-replicated excess of births of preschizophrenic patients during the winter and early spring, a period marked by a peak in the occurrence of infections such as influenza (4). These observations led to a resurgence of interest in this hypothesis, particularly with regard to prenatal and perinatal infection.

Initial epidemiologic studies on this question focused on "ecologic" designs, in which population-level data on epidemics were used to define the infectious exposures (5). A series of these studies suggested associations between various types of infections and schizophrenia risk among individuals who would have been in utero during these epidemics, though there were several failures to replicate these findings. Investigators have since capitalized on several unique resources that have come into existence within the past several years, making it possible to validate infection in individual pregnancies by use of maternal biomarkers in well-characterized birth cohorts. Although the findings are far from definitive, these studies have demonstrated that prenatal exposure to various infectious agents, including influenza, *Toxoplasma gondii* (*T. gondii*), genital/reproductive pathogens, and immunologic disturbances such as elevated interleukin-8, is associated with an increased risk of schizophrenia (6). While these investigations are few in number and the sample sizes are modest, the relative risks of these and other infections are generally greater in magnitude than for most individual putative susceptibility genes for schizophrenia. Moreover, several studies of prenatal infection and antiviral-like inflammatory responses in animal models have revealed neurophysiologic, neurocognitive, and behavioral abnormalities that are consistent with those observed in schizophrenia (7).

Concurrent with these studies is the emergence of a literature suggesting that infections during childhood and adulthood may also increase risk for schizophrenia. Child-

hood infection is generally not well documented in large data sets, and systematic follow-up of infection-exposed children into the age of risk for schizophrenia is rarely achieved. In an enlightening article in this issue, Dalman and colleagues report that they overcame some of these limitations by capitalizing on national Swedish registries containing data on childhood hospitalizations for infection and on psychiatric hospitalizations of these individuals in adulthood. The study is based on a national cohort of 1.2 million children who were born in the early 1970s to the middle 1980s and on hospitalizations among members of this cohort for treatment of CNS infections from birth to age 12. Data on subsequent psychotic illnesses were extracted until 2002. The infections ascertained were comprehensive and included both viral and bacterial pathogens; the primary outcome in this study was nonaffective psychosis. The authors report a 50% increased risk of nonaffective psychosis among individuals who were exposed in childhood to viral CNS infections; this association was attenuated only modestly after adjustment for potential confounders. The finding was similar when the outcome was restricted to schizophrenia. In contrast, there was no increased risk of nonaffective psychosis following exposure to bacterial CNS infections. Post hoc analysis of specific infections revealed that CNS infection with mumps virus was related to a nearly threefold increased risk of nonaffective psychosis and that infection with cytomegalovirus increased the risk of this outcome by a factor of greater than 16 (though the latter analysis was based on a small number of exposed individuals).

As discussed by the authors of this study, prior to vaccination efforts, mumps was the most common cause of aseptic meningitis or mild encephalitis, and it is highly neurovirulent. Although the mechanism by which childhood mumps might increase risk of schizophrenia is unclear at present, this virus has been noted to result in persistent CNS infection and to adversely affect neurodevelopment; the resulting problems include memory and learning difficulties, motor and sensory abnormalities, and disruptions in hearing and vision.

Strengths of the study design include the extensive, national coverage of both childhood infection and nonaffective psychosis outcome and the prospectively acquired data. One limitation of this study is the use of registry data on psychiatric diagnosis, though as noted by the authors, registry diagnoses of schizophrenia in Sweden have been validated with chart review diagnosis by DSM-IV criteria. A second limitation is that infection was defined as hospitalization for CNS infection, so that milder infections would not have been detected. Another potential cause of underascertainment, not noted by the authors, is that CNS infections may have such dramatic consequences on neuropsychiatric function that psychotic illnesses may not have been considered as primary diagnoses.

Several recent studies have shown elevated serum levels of antibody to *T. gondii* in patients with schizophrenia, and preclinical studies suggest neurobehavioral disturbances during acute infection with this parasite (8). Since these findings have focused almost exclusively on patients who have already developed the syndrome, it is possible that lifestyle factors that are secondary to schizophrenia may have accounted for these observations. In an attempt to address this question, Niebuhr et al. conducted an interesting study that investigated associations between antibody to *T. gondii* and schizophrenia among individuals discharged from the U.S. military. The study capitalized on archived serum samples that were collected from military personnel for mandatory testing of HIV. Unlike most previous studies, this investigation featured sera banked prior to the diagnosis of schizophrenia in many cases.

Personnel who were discharged from military service for a diagnosis of DSM-IV schizophrenia, based on extensive psychiatric examinations, and who had banked serum available were ascertained from physical disability agency databases maintained by the U.S. military. Comparison subjects with banked serum were selected from the

same population of military personnel, had never been given diagnoses of mental health disorders, and were well matched to the index subjects.

The authors found higher serum antibody levels (quantified as optical density values) for *T. gondii* in their schizophrenia sample than in the matched comparison subjects; this difference was statistically significant. In a further analysis, the authors found a somewhat higher *T. gondii* antibody level 2–3 years prior to diagnosis and a significantly higher level within 0.5 year of diagnosis. There was also, however, a significantly elevated *T. gondii* antibody level following the diagnosis of schizophrenia. Hence, the question of whether lifestyle factors associated with schizophrenia may have contributed to the findings remains unresolved. Moreover, the findings were not entirely consistent, in that no increased risk of schizophrenia was observed for other intervals of time prior to diagnosis. In addition, it was not completely clear whether *T. gondii* optical density values among subjects who were seronegative for this infection were included in the analysis; such values are not interpretable.

Taken together, these two articles provide further evidence that certain infections during childhood and adulthood might be risk factors for schizophrenia. If infectious etiologies for schizophrenia can be definitively demonstrated, this may have significant implications for efforts aimed at preventing this disorder. The rationale for this work is rooted in a long and distinguished history representing some of our greatest successes in preventive medicine, including the elimination of polio and congenital rubella (9). The identification of these and other infectious risk factors, and appropriate preventive interventions, required rigorous and painstaking epidemiologic studies. The reduction of morbidity and mortality from these interventions rivals those of other established medical treatments.

With regard to schizophrenia, several infections that have been associated with this disorder can be effectively treated with antibiotics and prevented by vaccination and by minimizing the occurrence of risk factors for these infections. In order to realize the ultimate goal of preventing schizophrenia through these interventions, it will be essential not only to maximize methodologic rigor and to replicate associations between infections and schizophrenia in distinct populations, but also to markedly improve statistical power to detect these associations. Furthermore, it is unlikely that these infections operate in isolation to increase vulnerability to schizophrenia. Hence, it will be critical in future work to identify susceptibility genes and other developmental precursors that act to modify and mediate the effects of infection on schizophrenia risk. Toward this end, efforts to enroll substantially larger, population-based samples for these investigations should be encouraged.

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