Further Evidence of Infectious Insults in the Pathogenesis and Pathophysiology of Schizophrenia

Accumulating evidence in recent years indicates that infection may play an important role in the etiology and pathophysiology of schizophrenia. Although much attention has been given to infectious diseases during the prenatal period, recent studies suggest that infections during childhood and adulthood may also influence risk of the disorder and alter associated neuromorphologic and neuropsychological outcomes.

Toxoplasma gondii (*T. gondii*), an intracellular parasite that has long been known to disrupt fetal brain development, has been associated with schizophrenia in many studies that have assessed seropositivity to this microbe in adults with schizophrenia (1). The direction of causality has been unclear, however, given that alterations in behavior may increase the risk of exposure to *T. gondii*. Hence, studies that prospectively evaluate the relationship between this infection before diagnosis of schizophrenia and the risk of developing schizophrenia may help clarify the nature of this relationship.

In the present issue of the *Journal,* Pedersen et al. (2) report using a population-based study of a cohort of pregnant women in Denmark, whose newborns were screened for toxoplasma IgG levels, to evaluate the relationship between elevated antibody levels and later diagnosis of psychiatric disorders in these women. Blood spots that were taken from offspring 5–10 days after birth were assayed for this antibody, and the neonatal titers were linked to diagnoses of schizophrenia spectrum disorder and other psychiatric diagnoses by using national population registries. The authors found that mothers whose neonates had the highest IgG levels exhibited a 1.7-fold, statistically significant increase in risk of later developing schizophrenia spectrum disorders, after adjustment for several potential confounders.

The study featured several notable strengths, including analysis of prospectively acquired data, the population-based sample, and the large number of pregnancies, though it was not without limitations. First, the sample was ascertained from five counties, which excluded about two-thirds of Denmark, and the women were required to agree to have blood drawn during the first trimester in order to participate. However, as noted by the authors, over 90% of the mothers approached agreed to have blood drawn. Second, because maternal antibody titers were present for only one-fourth of the women in the sample, maternal exposure was inferred on the basis of infant antibody levels, which were available for the offspring of all mothers who participated. Although maternal and infant antibody levels were highly correlated, 43% of the variance in maternal antibody titers was not accounted for by the infant titers. Notwithstanding the fact that the fetus does not mount an immune response to *T. gondii,* meaning that all *T. gondii* antibody was of maternal origin, the unexplained variance may have been secondary to other factors, including placental transport of antibody to the fetus.

These findings are consistent with those of a previous study by Niebuhr et al. (3), which suggested that higher *T. gondii* IgG antibody titer levels in young adults were related to later diagnosis of schizophrenia. The findings of the two studies are similar but not completely concordant, as the Niebuhr study was based on a group of U.S. military personnel.

In another study reported in this issue, Prasad et al. (4) assessed the relationship between herpes simplex virus type 1 (HSV1) seropositivity, longitudinal changes in gray

matter volume quantified by magnetic resonance imaging and deformation fields analysis, and cognitive performance in first-episode, antipsychotic-naive patients with schizophrenia and healthy comparison subjects at baseline and over a 1-year period. The authors found significant loss of gray matter volume in the posterior cingulate gyrus of HSV1-exposed schizophrenia patients over 1 year of follow-up. HSV1 exposure was also associated with a decline in performance on the Wisconsin Card Sorting Test over this time period in the patients with schizophrenia. Moreover, there was a significant correlation between the change in posterior cingulate volume and change in perseverative errors over the 1-year follow-up, which was most prominent among the HSV1-seropositive schizophrenia patients.

The findings of this study are of considerable interest given previous associations between HSV1 and neuromorphologic (5) and neurocognitive abnormalities in schizophrenia. Recent observations that are consistent with these findings also suggest that maternal exposure to infection is related to deficits in executive functioning, including performance on the Wisconsin Card Sorting Test (6). The present publication represents a significant advance over this work by demonstrating relationships between HSV1 and deleterious changes in these outcomes over time. If replicated, it is possible that HSV1 and perhaps other infectious microbes could explain at least some of the cognitive decline during the early stages of schizophrenia and perhaps some of the progressive morphologic changes. In spite of these promising findings, the study has limitations that need to be acknowledged. First, there was significant attrition in the study group over time, though as noted by the authors, the prevalences of HSV1 exposure and clinical and demographic factors were similar in the subjects who were followed up and those who were lost to follow-up. Second, no decline in prefrontal cortex volume, which is more tightly associated with executive functioning than the posterior cingulate, was observed, possibly because of the relatively small number of participants.

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As noted by the authors of these articles, further work is necessary to elucidate pathogenic mechanisms that may explain the observed associations. In both studies, active CNS infection is unlikely to have been responsible for the pathogenic outcomes given that the serologic evidence was based solely on IgG antibody, which most likely reflects infections at some point in the past, though particularly high titers could reflect a recent or reactivated infection. Hence, alterations of brain functioning are most likely related to latent infections. As noted by Pedersen et al. (2), one possibility is that *T. gondii* may cross-react with epitopes present in the brain; antibodies (mainly IgG) to several infectious agents, including HSV1, have been demonstrated to bind to human neural tissue (7). It is interesting that previous studies have implicated beta-hemolytic streptococcal infections in a subgroup of subjects with childhood-onset obsessive-compulsive and tic disorders, and this association was supported by evidence of antineuronal antibodies and symptomatic improvement with immunomodulatory therapies (8). Prasad et al. (4) speculate that the neuromorphologic and neuropsychological alterations associated with HSV1 seropositivity may have been secondary to apoptosis, oxidative damage, and chronically elevated cytokines, although these processes were not directly investigated.

In conclusion, these publications add to a body of literature suggesting that environmental exposures may play a more important role in the etiopathogenesis of schizophrenia than has been previously assumed. In addition to infection, environmental insults that have been implicated include nutritional deficiencies, fetal hypoxia, maternal stress, cannabis use, and childhood trauma (9). The promise of this work is underscored by the fact that many infectious exposures and other environmental insults are treat-

able and preventable. For example, several proven hygienic measures exist to prevent exposure to *T. gondii,* such as avoidance of undercooked meat, access to safe drinking water, and reducing contamination of cat litter boxes with oocysts. With regard to HSV1, however, there are no known preventive strategies and while antiviral medications such as acyclovir can reduce healing time, it does not prevent the immune response to this microbe (10), nor, as discussed by Prasad et al. (4), does it slow cingulate cortex neuronal loss in animal studies. Further prospective epidemiologic and clinical neuroscience studies are necessary to substantiate these findings, complemented by animal models on candidate pathogenic mechanisms.

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