Neurotropic Infectious Agents and Cognitive Impairment in Schizophrenia

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The links between infectious agents and risk for schizophrenia have been widely debated, but few investigations have focused on “epidiagnostic” effects, eg, whether exposures to infectious agents alter key clinical aspects of the disorder, such as cognitive impairment. The present theme issue evaluates epidiagnostic cognitive effects of two common infectious agents, namely Herpes Simplex Virus, type 1 and Toxoplasma gondii.

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The first article of the theme issue indicates that exposure to Herpes Simplex Virus, type 1 (HSV-1) may not be entirely benign for patients with SZ, even though it has not been implicated as a risk factor for schizophrenia (SZ) per se. The word herpes, derived from the Greek “herpein” (“to creep”), describes an unusual characteristic of HSV-1, ie, its proclivity to “creep” along sensory nerves following primary infection in mucosal membranes or in the skin.1 The retrograde transport takes it to sensory nerve ganglia as well as cortical regions, where it establishes lifelong infection. HSV-1 evades and even hijacks the body’s cellular processes to lie in a relatively dormant state in the nuclei of host neurons. Sporadic reactivation culminates in anterograde transport to sensory nerve endings in mucosal and skin membranes, where typical lytic eruptions reappear. Thus, HSV-1 establishes persistent, ineradicable, lifelong cycles of latency and lytic reactivation. The infection has wide ranging clinical effects, including asymptomatic states, mucosal lesions or devastating encephalitis in immune-compromised individuals and rarely, in otherwise immune competent persons. Whether the repeated latency/reactivation cycles impair neuronal survival, particularly in the brain is not known. In the first article of the theme issues, Prasad et al suggest ominous effects of persistent infection that are particularly notable in SZ patients exposed to HSV-1: (1) structural damage in the cortical gray matter; (2) cognitive impairment; (3) cognitive deterioration over time. The review suggests small to medium effect sizes for the associations between exposure and cognitive impairment, but the population attributable fraction is likely to be 15% or higher, based on a recent association study2 and exposure rates over 70% even in middle-aged US adults (http://www.cdc.gov/nchs/nhanes.htm).

Genome-wide association studies (GWAS) indicate that HLA variants are associated with SZ risk predominantly in Caucasian ancestry samples, but the basis for the associations is uncertain.3 In the second article of this issue, Bamne et al report nominal associations with the Caucasian-GWAS SNPS in an African American case-control sample. As HLA molecules play a critical role in host immune responses to infection, Bamne and colleagues also investigated the SZ associated SNPs in relation to HSV-1 exposure. No significant associations were found, apart from a curious nominal association with rs3130297. One allele of this SNP elevates risk for SZ, while the other allele is associated with HSV-1 exposure. Analysis of additional replicative samples could clarify whether the epidiagnostic effects reviewed by Prasad et al are related to such host genetic variation.

Toxoplasma gondii (TOX), the focus of the third theme issue article is a protozoan with unusual clinical features. It infects diverse warm-blooded animals (including rodents), with cats serving as the definitive host for sexual reproduction of the parasite. Presumably to facilitate transfer from rodents to feline species, TOX reduces feline fear in infected rodents.4,5 TOX infections also occur in 10%–20% of US adults, with exposure rates that approach 50% in other countries. Humans are considered accidental hosts for TOX as further transmission of
the parasite to feline species ceases, except for unlikely but plausible cases of infected humans becoming preys of tigers and lions. Reminiscent of its effects on rodent behavior, TOX exposure has also been associated with elevated risk for accidents in humans in addition to its well-known devastating prenatal effects. More important for SZ research, meta-analysis of over 30 case-control studies indicates elevated SZ risk in association with TOX infection. The basis for the association is not known. Kannan and Pletnikov (this issue) show that TOX infection impairs measures of spatial learning and memory in rodents. Because analogous variables are also impaired in SZ patients, it would be important to see whether TOX exposure explains some of the cognitive impairments in SZ patients.

The associations discussed in the theme issue do not conclusively prove causal links between HSV-1 or TOX exposure and cognitive impairment. Cohort-based studies and treatment studies are needed. Recently, a double-blind placebo-controlled study of HSV-1 exposed SZ patients revealed significant improvement in verbal memory, working memory, and visual object learning following treatment with valacyclovir, a drug used to treat reactivated HSV-1 infection. Such studies may indicate novel remedies for cognitive impairment in SZ. They will also establish paradigms that may help us sift through the trove of data that are being generated by the NIH-funded Human Microbiome Project, which aims to characterize trillions of microorganisms harbored in the human body (http://commonfund.nih.gov/hmp/index.aspx).

References