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Exposure to herpes simplex virus, type 1 and reduced cognitive function

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ABSTRACT

Herpes simplex virus, type 1 (HSV-1) causes cold sores, keratitis and rarely, fatal encephalitis. The infection is lifelong, with sensory ganglia serving as reservoirs of latent infection. Recently, exposure to HSV-1 has also been repeatedly associated with reduced cognitive function among healthy individuals without prior encephalitis. Though HSV-1 does not elevate risk for schizophrenia (SZ) *per se*, exposure is likewise associated with impaired cognitive functions among SZ patients. The range of cognitive changes observed in HSV-1 exposed persons has not been investigated systematically, nor is it known whether interaction between HSV-1 exposure and SZ related factors contributes to the impairment among SZ patients. Persons with or without schizophrenia/schizophreniform disorder ($N = 298$ total, DSM IV criteria) were assessed for HSV-1 exposure using serum HSV-1 antibody titers. The Penn Computerized Neurocognitive battery was used to assess eight cognitive domains with respect to accuracy and speed. There were no significant case–control differences in HSV-1 exposure. The SZ/schizophreniform disorder cases were significantly impaired in all cognitive domains compared with the controls. HSV-1 exposure was also associated with reduced cognitive function in the entire sample, but the magnitude of the effects and their patterns differed from the SZ related changes. Further, statistically significant interactions between HSV-1 exposure and SZ case status were not detected. HSV-1 exposure does not elevate risk for SZ, but it is associated with reduced function in specific cognitive domains regardless of SZ diagnostic status. An 'epidiagnostic' model for the association is proposed to explain the results.

1. Introduction

Herpes simplex virus, type 1 (HSV-1), a human specific double stranded DNA virus infects mucosal membranes, corneal tissues and the central nervous system (CNS). Beginning in the intra-uterine period, HSV-1 exposure increases cumulatively with age, with exposure rates exceeding 70% in older adults (Smith and Robinson, 2002). Following primary infection through mucosal membranes, HSV-1 virions migrate to the trigeminal ganglion located within the blood brain barrier, culminating in lifelong cycles of latent infection and reactivation in the CNS (Cleator and Klapper, 2004). While latent infection is asymptomatic and has been considered to be harmless, viral particles replicate during the reactivation phase and migrate along sensory nerves to cause recurrent mucosal and skin lesions such as 'cold sores' and rarely, encephalitis (Steiner et al., 2007). The trigeminal ganglia (located inside the blood brain barrier) are favored sites for latent HSV-1 infection, but viral DNA has also been found in the fronto-temporal gray matter in 34% of individuals dying from causes other than HSV-1 encephalitis,

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suggesting that cortical brain regions may be targeted for persistent infection (Baringer and Pisani, 1994).

Because it can cause lifelong infection in the CNS, HSV-1 infection is a plausible risk factor for cognitive impairment (Nelson and Demmler, 1997). While severe cognitive impairment and other neurological deficits are prominent sequelae among survivors of HSV-1 induced encephalitis, Becker has suggested that such dysfunction can occur even in the absence of acute HSV-1 encephalitis, because repeated reactivation can lead to neuronal cell death (Becker, 1995). Consistent with Becker's predictions, two studies of apparently healthy individuals and one community based study indicate that reduced cognitive function does occur in HSV-1 exposed individuals (Dickerson et al., 2008) (Strandberg et al., 2003) (Watson et al., 2012); one other community based study did not detect a significant association (Aiello et al., 2006). Though HSV-1 has not convincingly been demonstrated as a risk factor for schizophrenia (SZ), five other studies have reported alterations in working memory as well as executive functions among SZ patients exposed to HSV-1; we are not aware of any studies that reported non-significant associations (Dickerson et al., 2003; Shirts et al., 2008; Yolken et al., 2011; Gur et al., 2007b; Watson et al., 2012; Schretlen et al., 2010) (reviewed by Prasad et al., 2012b). Among HSV-1 exposed first-episode antipsychotic-naïve schizophrenia patients, a temporal decline in executive function has also been reported (Prasad et al., 2011). In a previous study of 413 individuals with schizophrenia, it was found that individuals who had levels of CRP $\geq$ 5.0 μg/ml had significantly lower cognitive scores than individuals with schizophrenia who did not have elevated CRP levels (Dickerson et al., 2007).

Three MRI studies indicate reduced gray matter volume in fronto-temporal regions among persons with early course schizophrenia exposed to HSV-1 infection (SZ) (Prasad et al., 2007; Schretlen et al., 2010; Pandurangi et al., 1994). Recently, a double-blind placebo-controlled trial among HSV-1 exposed SZ patients indicated improvement in cognitive performance after antipsychotic medications were supplemented with valacylovir (a specific anti-herpes medication) or placebo (Prasad et al., 2012a, b). Another study also reported impaired cognitive function among patients with bipolar I disorder exposed to HSV-1 compared with unexposed patients (Dickerson et al., 2004). A substantial body of evidence thus supports the notion that persistent HSV-1 infection is associated with impaired cognitive function among persons with or without psychiatric illnesses (Prasad et al., 2012b). However, the range of cognitive changes has not been evaluated comprehensively because several studies have used composite measures of cognitive function (reviewed by Prasad et al., 2012b). Therefore, in the present study a range of cognitive domains were evaluated using a computerized neurocognitive battery (Gur et al., 2001b). It is also unclear whether individuals with SZ are particularly prone to the cognitive effects observed in relation to HSV-1 infection, reflecting interactions between HSV-1 exposure and other illness related factors that impair cognitive function. The present study was thus conducted in order to evaluate 'epidiagnostic' interaction between SZ/schizophreniform disorder and HSV-1 exposure, in other words, whether the cognitive impairment well known in SZ/schizophreniform disorder patients reflect an interaction between HSV-1 exposure and other illness related variables. We investigated HSV-1 exposure and cognitive function in a group of patients with SZ/schizophreniform disorder, as well as controls screened for the absence of SZ/schizophreniform disorder.

2. Methods

2.1. Design

The study included individuals with schizophrenia and non-psychotic control participants. A series of univariate analyses were initially used to evaluate associations between individual cognitive variables and diagnostic status (SZ/control), as well as HSV-1 exposure (present/absent), including demographic variables as covariates. For cognitive variables that were significantly associated with diagnostic status as well as HSV-1 exposure, interactions between diagnostic status and HSV-1 exposure were tested further.

2.2. Site

The study was conducted at the Department of Psychiatry, Postgraduate Institute of Medical Education and Research (PGIMER) – Dr. Ram Manohar Lohia Hospital (RMLH), Delhi, a publicly funded facility that caters to all strata of Delhi.

2.3. Recruitment strategy

Individuals diagnosed with SZ/schizophreniform disorder were referred by treating clinicians for screening and inclusion in the study. For inclusion in the control group, healthy individuals without a history of SZ/schizophreniform disorder or substance abuse were sought from communities in Delhi and evaluated in the same manner as the cases (Thomas et al., 2007). The control sample was recruited from all socio-economic groups by approaching community leaders, non-governmental community organizations and physicians working in the area. Individuals with a history of substance abuse, medical or neurological disorders (head injury, encephalitis, and epilepsy) and those unable to complete cognitive tests were excluded from the SZ/schizophreniform disorder case and the control groups. So the SZ cases referred henceforth include schizophreniform disorder cases also in our sample.

2.4. Clinical assessment

The primary diagnostic interview schedule was the Hindi version of the Diagnostic Interview for Genetic Studies (DIGS) (Deshpande et al., 1998), a semi-structured interview schedule. The DIGS was administered to all the cases and diagnosis was established on the basis of DSM IV criteria by a team of psychiatrists and psychologists after discussing the detailed information. Schizophreniform disorder was diagnosed when the symptom criteria for schizophrenia were met, but the duration was less than 6 months, and social and occupational decline was uncertain. The DIGS was administered to all controls in the same manner as the cases.

2.5. Cognitive assessment

The University of Pennsylvania Neurocognitive Computerized Battery (Penn CNB) has been validated to yield quantitative measures of cognitive domains in healthy subjects (Gur et al., 2001a, 2010, 2012). It has also been used to show deficits in persons with SZ (Gur et al., 2001a) and in probands and family members (Gur et al., 2007a,b; Calkins et al., 2010, 2013).

2.5.1. Cognitive domains assessed

Abstraction and mental flexibility (ABF): The Penn Conditional Exclusion Test measures concept formation and flexibility. Subjects decide which of four objects does not belong with the other three. The 3 sorting principles change, and feedback is used to develop new strategies.

Attention (ATT): The Penn Continuous Performance Test (Penn CPT) uses a CPT paradigm where participants respond to seven-segment displays whenever one forms a digit or letter.

Working memory (WM): The Letter N Back Test consists of 0-back, 1-back and 2-back conditions.