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Neuroanatomic and cognitive abnormalities related to herpes simplex virus type 1 in schizophrenia

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ABSTRACT

Herpes simplex virus 1 (HSV-1) tends to replicate in the temporal cortex and can damage the limbic system. The presence of serum antibodies to HSV-1 is associated with cognitive impairment in adults with schizophrenia, suggesting that cerebral gray matter abnormalities might distinguish patient subgroups defined by HSV-1 exposure. We assessed 43 adult outpatients with schizophrenia. The assessment included clinical interviews, neurocognitive testing, anatomic brain magnetic resonance imaging and measures of serum IgG antibodies specific to herpes simplex viruses 1 and 2. We then compared 25 patients who tested positive for antibodies to HSV-1 with 15 who were seronegative for both HSV-1 and HSV-2. The seropositive patients performed significantly worse than the seronegative patients on four neuropsychological measures of psychomotor speed, executive functioning, and explicit verbal memory. Voxel-based morphometric analyses revealed that the same patients showed reduced gray matter volume in the anterior cingulate and areas of the cerebellum. Finally, performance on the test of psychomotor speed and executive functioning that showed the largest between-group effect size correlated with reduced gray matter volume in some of the same brain regions (cingulate and cerebellum) that distinguished the two HSV-1 subgroups. In these outpatients with schizophrenia, HSV-1 seropositivity and performance on a cognitive test that is highly sensitive to it co-localize to closely overlapping brain regions.

1. Introduction

Schizophrenia (SZ) might result from a genetic susceptibility whose expression is potentiated by environmental risk factors (Bayer et al., 1999). Some investigators have focused on psychosocial risk factors, while others have emphasized biological factors (Cannon and Clarke, 2005). Prenatal or early childhood infections have been considered because individuals born in months when transmissible infections are likely to occur have 5–8% greater risk of developing SZ than those born at other times (Torrey et al., 1997). However, other explanations of this association have been offered (Tochigi et al., 2004).

One possible contributory infectious agent is the herpes simplex virus 1, or HSV-1 (Yolken, 2004). While there is no direct evidence that exposure to HSV-1 is more common among individuals with SZ, indirect evidence justifies research. Individuals with SZ and serum immunoglobulin G (IgG) antibodies to HSV-1 in the absence of acute infection perform worse on cognitive testing than SZ patients without

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antibodies to HSV-1 (Dickerson et al., 2003a; Shirts et al., 2008). An association between asymptomatic HSV-1 seropositivity and selective cognitive deficits also appears in persons with bipolar disorder (Dickerson et al., 2004). In these studies, patients who tested positive for HSV-1 had particular difficulty on tests of memory, , psychomotor speed, and executive functioning, although milder deficits were observed on tests of visuospatial ability and attention as well.

Persisting memory and other cognitive deficits are often seen following recovery from acute HSV-1 encephalitis (Utley et al., 1997; Hokkanen and Launes, 2000). Structural neuroimaging studies have found persisting neuroanatomic abnormalities among individuals with amnesia following herpes encephalitis. Colchester et al. (2001) found that patients with amnesia due to herpes encephalitis showed significantly reduced volume of the hippocampus, parahippocampal, medial temporal, anterolateral temporal, and frontal cortices. Using voxel-based morphometry (VBM; Ashburner and Friston, 2000) to assess gray matter (GM) abnormalities, Gitelman et al. (2001) found that five adults with a history of herpes simplex encephalopathy showed reduced GM concentration in the medial temporal lobes, anterior and lateral temporal cortex, gyrus rectus, and insula. Thus, brain changes might extend beyond the limbic structures in which viral antigens and HSV-related tissue damage ordinarily occur to include the lateral temporal cortex.

In the only known study of brain morphological changes associated with HSV-1 in adults with SZ, Prasad et al. (2007) compared 15 HSV-1 seropositive patients with first-episode SZ to 15 HSV-1 seronegative patients with first-episode SZ and 44 healthy controls. Compared to their seronegative counterparts, SZ patients with antibodies to HSV-1 showed reduced GM volume in Brodmann area (BA) 9 of the prefrontal cortex and in the anterior cingulate (BA 32) bilaterally on VBM. Similar findings emerged when seropositive SZ patients were compared with seropositive healthy controls. However, aside from a single area in motor cortex, HSV-1-related GM abnormalities were not observed in healthy adults. Prasad et al. interpreted their findings as suggesting that persons vulnerable to SZ could mount a different type of host response to HSV-1 than persons without SZ. Alternatively, they suggested that HSV-1 might be a risk factor for SZ. While these findings are intriguing, Prasad et al. (2007) observed no HSV-1-related and morphological abnormalities in mesial or lateral temporal cortex where the virus tends to replicate. Nor did their 30 first-episode SZ patients show GM abnormalities relative to healthy controls on VBM, which is unusual (Meisenzahl et al., 2008). These investigators did not report cognitive testing, so it is unknown whether their SZ patients would have shown HSV-1-related cognitive deficits.

In sum, HSV-1 tends to replicate in and damage mesial and lateral temporal lobe tissue. Acute herpes simplex encephalopathy often leads to severe persisting amnesia, and latent HSV-1 infection has been associated with mild but widespread cognitive deficits in patients with SZ. Acute HSV-1 encephalopathy also is associated with the onset of psychosis in some individuals (Schlitt et al., 1985). The only known VBM study of HSV-1 in patients with SZ found GM abnormalities in prefrontal cortex and the anterior cingulate, but did not test cognitive functioning. In the present study we examined brain morphometry and cognitive function in SZ patients with versus without antibodies to HSV-1. We hypothesized that SZ patients with antibodies to HSV-1 would evince both cognitive deficits and GM abnormalities referable to either the temporal lobe or to the prefrontal cortex and anterior cingulate.

2. Method

2.1. Participants

Fifty adults with SZ were recruited primarily from outpatient clinics of the Johns Hopkins and Sheppard Enoch Pratt hospitals in Baltimore, Maryland, although 3 were recruited as inpatients and assessed immediately prior to discharge. All participants were 19 to 56 years old, met *DSM-IV* (American Psychiatric Association, 1994) diagnostic criteria for schizophrenia, denied current substance abuse or dependence, were not intellectually disabled, and had no neurological disorder or condition (such as epilepsy or history of traumatic brain injury with >1 hour loss of consciousness) associated with significant cognitive impairment. One patient refused blood testing and could not be assayed for viral exposure, and six refused brain MRI scanning or produced unusable imaging data. Thus, 43 patients completed assessment. Of these, 25 tested positive for antibodies to HSV-1, and 18 tested negative for HSV-1. However, 3 patients who were negative for HSV-1tested positive for antibodies to HSV-2. Because HSV-2 can also replicate in the brain, we excluded these 3 participants to create a HSV-1 negative sample with the fewest possible confounds. Therefore, our final sample included 40 participants: 25 who tested positive for HSV-1 and 15 who tested negative for HSV-1 and HSV-2. Their demographic and clinical characteristics are shown in Table 1. This study was approved by the Johns Hopkins Medicine and Sheppard Enoch Pratt IRB committees. All subjects gave written informed consent to participate.

The diagnosis of schizophrenia was made by a board-certified psychiatrist (N.G.C.) who specializes in schizophrenia based on a modified Structured Clinical Interview for DSM-IV Axis I Disorders-Clinical Version (SCID-CV; First et al., 1997) together with a review of available records and collateral information from a knowledgeable informant. The psychiatrist also rated each patient's symptom severity using the Schedules for Positive and Negative Symptoms (SAPS/SANS; Andreasen and Olsen, 1982). We recorded each participant's reported age at illness onset, total number of hospitalizations for psychiatric treatment, and current medications, although the latter data were used for analyses only when they were judged to be reliable.

2.2. Immunological assays

A venous blood sample was obtained from each participant. Solid phase immunoassay techniques were used to measure IgG antibodies to HSV-1 and HSV-2 as previously described (Dickerson et al., 2003a). Reactions of serum aliquots to specific antigens immobilized on a solid phase surface served to quantify IgG antibodies via sequential reactions of bound antibodies with enzyme-labeled antihuman IgG and enzyme substrates. Antibodies to HSV-1 and HSV-2 were assayed using purified viral envelope glycoproteins gG1 and gG2, respectively, as the solid phase antigens. These glycoproteins allow for the