ORIGINAL ARTICLE

Association of Serum Antibodies to Herpes Simplex Virus 1 With Cognitive Deficits in Individuals With Schizophrenia

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Background: Cognitive deficits are a characteristic feature of schizophrenia and contribute to the profound disabilities associated with this illness. Some of the cognitive deficits that occur in individuals with schizophrenia are similar to those found in individuals who have recovered from central nervous system infections with human herpesviruses.

Methods: We measured cognitive functioning and serologic evidence of infection with human herpesviruses in 229 outpatients with schizophrenia. We evaluated cognitive functioning with the Repeatable Battery for the Assessment of Neuropsychological Status. For each patient, serum IgG class antibodies with specificities for the following potentially neurotropic human herpesviruses were measured by means of a solid-phase immunoassay: herpes simplex viruses 1 and 2, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, and varicella-zoster virus. We determined the association between serologic evidence of herpesviruses infection and cognitive functioning by univariate and multivariate analyses, including demographic and clinical factors associated with cognitive functioning.

Results: We found that serologic evidence of infection with herpes simplex virus 1 is an independent predictor of cognitive dysfunction in individuals with schizophrenia. Discriminant function analysis indicated that much of the difference in cognitive functioning could be attributed to immediate memory. We found no significant association between cognitive dysfunction and serologic evidence of infection with other human herpesviruses.

Conclusion: Serologic evidence of herpes simplex virus 1 infection is associated with cognitive impairment in schizophrenia.

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SCHIZOPHRENIA IS a pervasive neuropsychiatric disorder of unknown etiology affecting 1.1% of adults in the United States in a 1-year period.[1] Cognitive deficits are a major feature of schizophrenia. As a group, individuals with schizophrenia perform more poorly on a broad range of cognitive tasks than do age-matched control subjects from the general population.[2] The degree of cognitive dysfunction varies among affected individuals and is generally persistent during the course of the schizophrenia illness.[3] Cognitive deficits can occur before the onset of the other symptoms of schizophrenia or the initiation of antipsychotic therapy.[4-6] The extent of the cognitive deficits has little correlation with the severity of characteristic schizophrenia symptoms such as hallucinations and delusions.[7]

Against the background of generalized cognitive impairment in schizophrenia, evidence suggests that some aspects of cognitive function are specifically impaired. Difficulties with memory, especially the learning of new verbal and visual material, are especially pronounced in many individuals.[8] Executive functioning, including tasks of reasoning, abstraction, and fluency, has also been found to be particularly impaired in patients with schizophrenia.[9,10]

Cognitive dysfunction in schizophrenia is a major contributing factor to the profound social disabilities that accompany the illness.[11] Cognitive deficits have been associated with patients' impairments in performing day-to-day tasks,[12] responding to rehabilitation interventions,[13] and attaining employment.[14] Patients' cognitive deficits also hinder their social relationships and add to the burden of their family members. Cognitive deficits do not remit between illness episodes and are generally not responsive to currently available pharmacological treatments.[15]

Herpesviruses are enveloped, double-stranded DNA viruses that are capable of infecting humans and many other animal species. Herpesviruses can establish latent infections after cellular replication and

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covalent integration of viral DNA into the host genome.[16,17] Integrated herpesvirus DNA can become reactivated after a number of stimuli, with the resulting production of virus particles and the subsequent infection of additional cells.[18] This process can lead to the establishment of a lifelong cycle of recurrent infections.[19,20] These infections are generally associated with the development of persistent IgG class antibodies to defined viral proteins. These protein levels can be measured in the blood of infected individuals and used for studies of viral exposure and epidemiology.[21-24]

Many herpesviruses are capable of infecting cells within the human central nervous system. Human herpesviruses with neurotropic potential include herpes simplex viruses 1 (HSV-1) and 2 (HSV-2), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and human herpesvirus 6 (HHV-6).[25] For some of these viruses, such as CMV,[26] VZV,[27] and EBV,[28] infection of the central nervous system is rare and occurs primarily in individuals whose immune system is compromised due to congenital or acquired immunodeficiency states. Herpes simplex virus 2 can cause infections of the central nervous system in neonates and is an occasional cause of central nervous system infection in adults.[29] Herpes simplex virus 1[25] and HHV-6[30] can cause infection of the central nervous system in otherwise healthy individuals who do not have any apparent immune defect. Herpesvirus infections of the central nervous system can result in varying degrees of encephalitis, which can be associated with a high degree of morbidity and mortality in the absence of antiviral therapy.[31] Herpesviruses can also cause self-limited infections of the central nervous system that can be difficult to detect during the acute phase of infection.[32]

Herpesvirus infections of the central nervous system can be associated with a number of neurological sequelae. These sequelae include deficits in memory and executive functioning that are similar to those found in some individuals with schizophrenia.[33,34] Some individuals with acute herpesvirus infections of the central nervous system also display psychiatric symptoms such as psychosis and mania.[35-37] In addition, evidence of herpesvirus DNA have been found in postmortem brain samples obtained from a small number of individuals with schizophrenia.[38,39] Results of serologic studies have indicated that some populations of individuals with schizophrenia have increased evidence of exposure to human herpesviruses,[40-43] although this has not been found in all study populations.[44-46] The clinical and epidemiological parameters associated with exposure to herpesviruses in individuals with schizophrenia have not been clearly delineated.[47]

We hypothesized that herpesvirus infections may contribute to the cognitive deficits that are present in some individuals with schizophrenia. We tested this hypothesis by measuring antibodies to herpesviruses with neurotropic potential in individuals with schizophrenia and determining the association between the serologic evidence of infection and cognitive functioning.

METHODS

The study cohort consisted of 229 outpatients with schizophrenia drawn from several treatment and rehabilitation programs in central Maryland. Most of the participants (n=139) were recruited for a study to determine the presence of antibodies to infectious agents in schizophrenia. Additional subjects in the study (n=90) were participants in a placebo-controlled study of eicosapentaenoic acid as an adjunctive medication treatment for the symptoms of schizophrenia.[48] All participants met the following inclusionary criteria: (1) aged 18 to 65 years; (2) maintained on a regimen of psychotropic medications that conformed with Patient Outcomes Research Team treatment recommendations[49]; (3) diagnosis of schizophrenia or schizoaffective disorder according to the criteria of the *DSM-IV* by 1 of 2 board-certified psychiatrists (including J.J.B.); (4) the absence of mental retardation, substance abuse or dependence within the past 3 months, or other serious medical disorders; and (5) the absence of clinically apparent herpesvirus infection or recent treatment with antiviral medications, as assessed by self-report.

The studies were approved by the Institutional Review Board of the Sheppard Pratt Health System, Baltimore, Md, and Chestnut Lodge Hospital, Rockville, Md, following established guidelines. All patients provided written informed consent. At the screening visit, a blood sample was obtained and patients were interviewed and rated on the Positive and Negative Syndrome Scale (PANSS).[50] Patients were also administered form A of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[51] The RBANS was selected for the measurement of cognitive functioning because it is sensitive to the level and type of cognitive impairments that are often found in individuals with schizophrenia.[52] Test indexes included immediate memory (list learning and story memory tasks), visuospatial/constructional (figure copy and line orientation tasks), language (picture naming and fluency tasks), attention (digit span and coding tasks), and delayed memory (list recall, story recall, figure recall, and list recognition tasks). Each index score is expressed as an age-adjusted standard score with a mean of approximately 100 and an SD of approximately 15 based on a group of 540 healthy subjects who ranged in age from 20 to 89 years and were matched to US census data by sex, ethnicity, and level of education. The index scores were combined to yield a total RBANS score that is a measure of overall cognitive functioning.

The study cohort of 229 patients consisted of 139 men (61%) and 90 women (39%). The mean age was 42.1 years (SD, 9.5 years; range, 18-64 years). A total of 185 patients (81%) were white. In terms of their educational level, 40 (17%) had less than a high school education, 75 (33%) were high school graduates only, 67 (29%) had graduated from high school and completed up to 2 years of college, and 47 (21%) had completed college. The mean age of illness onset among the sample was 21.5 years (SD, 7.1 years); the mean age at first hospitalization was 23.3 years (SD, 7.1 years). The mean duration of illness was 20.7 years (SD, 10.1 years). The mean period since the last hospitalization was 48.5 months (SD, 59.8 months). Diagnoses were divided among paranoid type (n=50 [22%]), residual type (n=3 [1%]), undifferentiated type (n=77 [34%]), disorganized type (n=8 [3%]), and catatonic type (n=1 [0.4%]) and schizophrenia and schizoaffective disorder (n=90 [39%]). In terms of medication, 68 patients (30%) were receiving clozapine, and an additional 112 (49%) were receiving other atypical antipsychotic medications at the time of the study. Sixty-four patients (28%) were receiving medications with anticholinergic activity at the time of the study. The study was performed from February 1, 1999, through April 30, 2001.

Serum antibodies of the IgG class were measured by modifications of previously described solid-enzyme immunoassay systems.[53] Assays were performed for the measurement of levels of antibodies to the following members of the herpesvirus family: HSV-1, HSV-2, CMV, EBV, HHV-6, and VZV. The as-

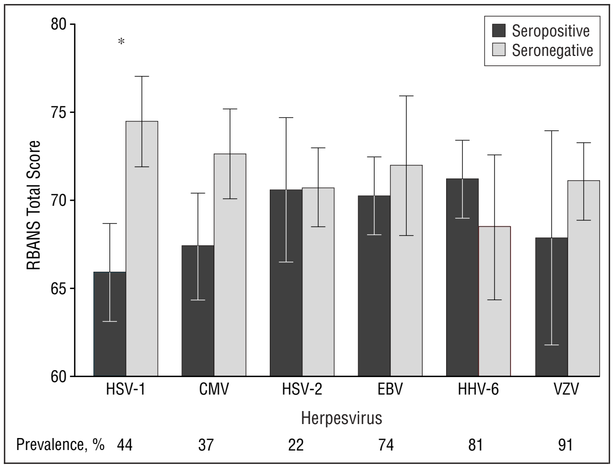

Figure 1. Cognitive functioning in individuals with schizophrenia related to serologic evidence of infection with specific herpesviruses. Levels of IgG class antibodies to herpesviruses were measured by means of an enzyme immunoassay, and cognitive functioning was measured by the total score of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in individuals with schizophrenia (N=229). Bars indicate the mean scores (±95% confidence intervals [CIs]) of individuals who were seropositive or seronegative for the indicated herpesvirus. The percentage of individuals in the total study population who were seropositive for the indicated herpesvirus is shown in the lower line. The asterisk indicates $P<.001$ between the RBANS total score for herpes simplex virus 1 (HSV-1) seropositive and seronegative individuals as calculated by 1-way analysis of variance; the differences between the RBANS total scores in terms of seroreactivity to the other viruses were not statistically significant (at the level of $\alpha=.008$). CMV indicates cytomegalovirus; EBV, Epstein-Barr virus; HSV-2, herpes simplex virus 2; HHV-6, human herpesvirus 6; and VZV, varicella-zoster virus.

says were performed by the reaction of diluted aliquots of patient and standard control serum samples to antigens immobilized onto a solid-phase surface, with the subsequent quantitation of IgG antibodies by reaction of bound antibodies with enzyme-labeled anti–human IgG and enzyme substrate. The optical density of the ensuing enzyme-substrate reaction was quantified by means of spectrophotometric instrumentation. Assays of antibodies with specificity for HSV-1 and HSV-2 were performed using purified viral envelope glycoproteins gG1 and gG2, respectively, as the solid-phase antigens. The use of these glycoproteins allows the distinguishing of antibodies to these serologically related viruses.[54] Reagents for these assays were obtained from Focus Laboratories, Inc (Cypress, Calif). The assays for antibodies to CMV, EBV, HHV-6, and VZV used antigens derived from virion proteins as previously described.[40] Reagents for these assays were obtained from IBL-Hamburg GmbH (Hamburg, Germany).

The immunoassays were performed by means of the reaction of test serum to the solid-phase antigen. After the removal of unreacted serum samples by washing, the amount of antibody binding to the solid-phase antigen was quantitated by means of subsequent reaction with enzyme labeled anti–human IgG and enzyme substrate and the measurement of the optical density of the ensuing visibly colored substrate product in a microplate colorimeter. Each assay was performed with patient and standard serum samples that contained low but detectable levels of antibodies to the target antigen. The amount of antibody in each sample was expressed in terms of the ratio of optical density of the test sample to that of the standard sample. For initial determination of positivity, a patient's sample was considered to be reactive if it yielded a ratio of at least 1.1. This cutoff value is based on clinical trials of the assays for antibodies to HSV-1 and HSV-2.[55,56] Additional analyses were also performed using ratios of 0.9, 1.3, 1.5, and 2.0 to define reactivity. Quantitative analyses were also performed using the ratios as continuous variables without predefined cutoff values. The prevalence of infection for each herpesvirus was calculated by dividing the number of individuals who were reactive by the number of individuals in the total population. The prevalence of infection was also determined by means of quintile performance in the RBANS by dividing the number of individuals in each quintile who were reactive by the total number of individuals in each quintile.

For each infectious agent, we used univariate analyses of variance to determine the relationship between infection status and the RBANS total score. We also used univariate analyses of variance and Pearson correlations to determine the relationship between the RBANS total score and demographic and clinical variables that might be expected to affect cognitive functioning. We defined statistical significance in the univariate analysis as $\alpha=.008$ in light of the multiple comparisons inherent in the analysis of antibodies to 6 different viruses. Factors that displayed statistical significance in univariate analysis were entered into an analysis of covariance to define independent associations with the RBANS total score. Herpes simplex virus 1 infection status, which displayed an independent association with the RBANS total score, was further analyzed to define the relationship between HSV-1 infection and the RBANS index scores. This analysis was performed by univariate analyses of variance using a critical value of $\alpha=.008$ in light of the comparison of the total score and 5 indexes. We used a multivariate discriminant function analysis[57] to define the components of the RBANS that provided the most significant contribution to the association with the total score. We also determined the Pearson correlation coefficient between the quantitative level of antibodies, expressed as the ratio calculated as described above, and the RBANS total score using a critical value of $\alpha=.008$. Additional analyses were performed using data obtained from the subset of 142 individuals from the study cohort who had completed high school or up to 2 years of college. Analyses of this subset were undertaken to determine the association between antibodies and RBANS scores in a subset of individuals who had a relatively narrow range of educational achievement. All of the analyses other than the discriminant functions were performed using the Stata Statistical Package, version 7.0 (Stata Corp, College Station, Tex). Discriminant function analyses were performed with the NCSS-2000 Statistical Software Package (NCSS Statistical Software, Kaysville, Utah).

RESULTS

Initial analyses consisted of univariate comparisons to determine the association between cognitive functioning and serologic evidence of infection with human herpesviruses. As displayed in **Figure 1**, we found that serologic evidence of infection with HSV-1 ($F=19.40$; $P<.001$) was associated with decreased cognitive functioning as measured by the RBANS total score. We did not find a statistically significant association between cognitive functioning and evidence of infection with HSV-2, CMV, EBV, HHV-6, or VZV. Univariate analyses were also performed to examine the association between cognitive functioning and demographic or clinical variables that might be associated with decreased cognitive performance. We found that the RBANS total score was associated with educational level, race, and PANSS negative symptoms, but not with PANSS positive or general symptoms, sex, duration of illness, age at illness onset, age at first hospitalization, or interval since the last hospitalization. We also found no statistically significant association between RBANS total score and the proportion of subjects who were taking clozapine or other atypical antipsychotic or anticholinergic medications.

We then performed a multivariate analysis of covariance to determine the independent predictors of RBANS total score. As depicted in **Table 1**, this analysis indicated that serologic evidence of infection with HSV-1, educational level, and the PANSS negative symptom score were independent predictors of the RBANS total score. A model using these factors has an R^2 value of 0.31, indicating that approximately 30% of the variance of cognitive functioning can be explained by these variables.

The overall prevalence of HSV-1 infection in the study population was 101 (44%) of 229 (Figure 1). Individuals who were seropositive for HSV-1 did not differ from those who were seronegative in terms of age, race, sex, marital status, duration of illness, age at first hospitalization, PANSS scores, or use of atypical antipsychotic or anticholinergic medications. However, as depicted in **Figure 2**, the prevalence of infection within the study population varied widely depending on cognitive functioning, as assessed by quintiles within the population. The prevalence of HSV-1 infection was 67% in the individuals who scored in the lowest 20th percentile of cognitive functioning and 27% in the individuals who scored in the highest 20th percentile (χ^2=21.6; P<.001). The relative risk ratio for HSV-1 seropositivity associated with being in the lowest 20th percentile of RBANS total score compared with being in the highest 20th percentile was 5.33 (95% confidence interval [CI], 2.67-11.37). We also examined this relationship in a subset of 142 individuals from the study cohort who had an educational attainment of high school completion or up to 2 years of college. In this group, the prevalence of HSV-1 infection was 66% for individuals who scored in the lowest 20th percentile of cognitive functioning and 27% for individuals who scored in the highest 20th percentile of cognitive functioning (χ^2=20.1; P<.001). For these individuals, the relative risk for HSV-1 seropositivity associated with being in the lowest 20th percentile of RBANS total score was 5.16 (95% CI, 2.28-12.41).

We further explored the specific parameters of cognitive dysfunction associated with serologic evidence of HSV-1 infection by analyzing the relationship between infection status and the RBANS index scores. As depicted in **Table 2**, we found that serologic evidence of HSV-1 infection was associated with deficits on the immediate memory (F=23.52; P<.001), visuospatial/constructional (F=9.35; P=.002), and attention (F=12.83; P<.001) indexes. A forward stepwise discriminant function analysis of the RBANS index scores listed in Table 2 indicated that the most significant difference in cognitive functioning between individuals who were seropositive and seronegative for HSV-1 could be attributed to the immediate memory index (F=23.5; P<.001).

The antibody levels that we measured were expressed as a ratio of signal generated by reaction of the test serum to the viral antigen divided by the signal generated by the binding of standard serum samples with defined reactivity. These analyses were performed using a ratio of at least 1.1 to define reactivity. We examined the effect of using other cutoff values on the relationship between HSV-1 reactivity and the RBANS total score. As depicted in **Table 3**, the use of cutoff levels of at least 0.9, 1.1, 1.3, 1.5, and 2.0 resulted in a significant association between HSV-1 reactivity and the RBANS total score for the entire study cohort. A statistically significant association between HSV-1 reactivity and RBANS total scores was also found at all of these cutoff values in the subset of 142 individuals from our population who had completed high school or up to 2 years of college (Table 3). We found that the RBANS total score was inversely correlated with the level of antibody to HSV-1 in the entire study population (r=–0.28; P<.001) and in the subset of 142 individuals who had completed high school or up to 2 years of college (r=–0.29; P<.001).

Table 1. Multivariate Analysis of RBANS Total Score With Clinical Variables and Infection Status*

Associated Variable	F Value	*P* Value
HSV-1	10.25	<.002
Education	35.43	<.001
PANSS negative score	21.64	<.001
Race	3.77	.054

Abbreviations: HSV-1, herpes simplex virus 1; PANSS, Positive and Negative Syndrome Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

*Variables significant in the univariate 1-way analysis of variance (P<.008) were included in a multivariate analysis of covariance resulting in the indicated F and P values. R^2 for the overall analysis of covariance was 0.31. Analysis was performed on data from all 229 study participants.

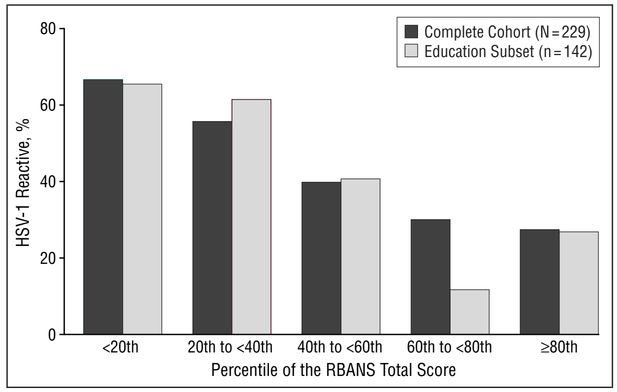

Figure 2. Prevalence of herpes simplex virus 1 (HSV-1) infection by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score. The prevalence of HSV-1 infection was calculated for quintile subgroups of RBANS total score for the entire cohort of 229 individuals with schizophrenia and the subset of 142 individuals who completed high school or up to 2 years of college (education subset). Reactivity to HSV-1 was defined as having an immunoassay ratio of at least 1.1. The differences among RBANS subgroups were statistically significant for the entire cohort (χ^2=21.6; P<.001) and the education subset (χ^2=20.1; P<.001).

COMMENT

Our study identified a statistically significant association between serologic evidence of infection with HSV-1 and decreased cognitive functioning in individuals with schizophrenia. Discriminant function analysis indicated that most of the differences in cognitive functioning could be attributed to immediate memory. Serologic

Table 2. Scores on the RBANS by HSV-1 Infection Status

Measure	HSV-1 Group, Mean (SD) Seropositive (n = 101)	HSV-1 Group, Mean (SD) Seronegative (n = 128)	F Value*	*P* Value*
RBANS immediate memory index	63.4 (17.2)	74.7 (17.8)	23.52	<.001
RBANS visuospatial/constructional index	75.6 (19.0)	83.4 (19.1)	9.35	.0025
RBANS language index	83.2 (14.5)	86.9 (15.3)	3.41	.07
RBANS attention index	71.2 (17.1)	79.2 (16.5)	12.83	<.001
RBANS delayed memory index	68.1 (18.8)	74.6 (18.6)	6.96	.009
RBANS total score	65.9 (14.3)	74.5 (14.8)	19.40	<.001

Abbreviations: HSV-1, herpes simplex virus 1; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.
*Determined by 1-way analysis of variance as described in the "Methods" section.

Table 3. RBANS Total Scores for HSV-1 Seropositive and Seronegative Individuals as Determined by Different Cutoff Values

Cutoff Ratio*	No. (%) Reactive	RBANNS Total Score, Mean (95% CI)† HSV-1 Seropositive Individuals	RBANNS Total Score, Mean (95% CI)† HSV-1 Seronegative Individuals	F Value‡	*P* Value‡
		Complete Cohort (N = 229)			
0.9	104 (45)	66.4 (63.6-69.2)	74.3 (71.7-76.9)	16.3	<.001
1.1	101 (44)	65.9 (63.1-68.8)	74.5 (71.9-77.1)	19.4	<.001
1.3	100 (44)	65.9 (63.0-68.7)	74.5 (71.9-77.0)	19.6	<.001
1.5	97 (42)	65.6 (62.7-68.6)	74.4 (71.9-77.0)	20.4	<.001
2.0	94 (41)	65.0 (62.9-68.9)	74.1 (71.6-76.6)	17.3	<.001
		Education Subset (n = 142)§			
0.9	59 (42)	65.2 (61.7-68.9)	74.6 (70.4-76.9)	12.2	<.001
1.1	57 (40)	64.7 (61.2-68.2)	73.7 (70.5-77.0)	13.9	<.001
1.3	57 (40)	64.7 (61.2-68.2)	73.7 (70.5-77.0)	13.9	<.001
1.5	57 (40)	64.7 (61.2-68.2)	73.7 (70.5-77.0)	13.9	<.001
2.0	54 (38)	65.1 (61.4-67.7)	73.2 (70.0-76.4)	10.8	<.001

Abbreviations: CI, confidence interval; HSV-1, herpes simplex virus 1; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.
*Antibody levels to HSV-1 were measured by solid-phase immunoassay. The amount of color generated by the binding of enzyme-labeled IgG was measured by a microplate colorimeter and converted to a ratio on the basis of control reactions.
†Calculated using the indicated cutoff values to define HSV-1 reactivity for the indicated population.
‡Compared at each cutoff value by analysis of variance.
§Consisted of individuals who completed high school or up to 2 years of college.

evidence of HSV-1 infection was not associated with differences in the severity of psychotic symptoms.

The IgG antibody levels used in our analyses were determined by means of solid-phase enzyme immunoassays. These assay systems involve the reaction of patient sample to purified viral antigens and the subsequent quantitation of binding by reaction to enzyme-labeled anti–human IgG. Solid-phase enzyme immunoassays have the advantage of allowing for the measurement of antibodies directed at a number of different antigens using small volumes of serum samples and a unified assay format. However, since these assays make use of enzyme-substrate reactions, they require the performance of control reactions using serum samples of defined reactivity to provide accurate measurements. The reactivity of a patient sample is expressed as a ratio of the amount of color generated by the sample compared with that of the defined controls. For many types of statistical calculations, including the discriminant function and covariate analyses that we used, it is necessary to define a cutoff to define sample reactivity. For the initial analyses, we used a cutoff ratio of at least 1.1, which corresponds to an amount of enzyme substrate that is 10% greater than the reaction of a control with weakly positive results. The selection of this cutoff was based on clinical trials indicating that the use of this cutoff results in a high correlation with gold standard assays such as Western blot and the ability to isolate infectious virus in cell culture.[55,56] Using this cutoff, we found that there is a statistically significant association between HSV-1 reactivity and the RBANS total score as well as the immediate memory index of the RBANS. The use of other cutoffs did not alter the statistical relationship between HSV-1 reactivity and the RBANS total score or the immediate memory score (Table 3). We also found that the levels of antibodies to HSV-1, measured as the continuous variable of antibody ratio, were inversely correlated with the RBANS total score ($r = -0.28$; $P < .001$).

Some of the relative deficits noted in individuals with schizophrenia who were seropositive for HSV-1 are similar to the deficits that have been reported in previously healthy individuals who have recovered from episodes of HSV-1 encephalitis. The cognitive deficits in individuals with HSV encephalitis appear at the acute stage of the illness and then generally persist over many years.[34] Kapur et al[33] reported focal disturbances in verbal learning and memory retention attributed to neuronal damage after viral replication within the temporal lobes. Several investigators[58-60] have also reported that patients who have recovered from HSV-1 or HSV-2 encephalitis have deficits in word fluency and other aspects of executive functioning. Such deficits are associated with viral replication and tissue damage within orbitofrontal brain regions.[34] Neuronal damage to the limbic system, lingual gyrus, and inferior parietal lobe has also been documented in patients with cognitive impairment who underwent evaluation more than 1 year after the resolution of HSV-1 encephalitis.[61] These regions have been associated with abnormalities in some individuals with schizophrenia.[62]

We found that immediate memory was the primary factor that distinguished the overall cognitive performance of our patients with serologic evidence of HSV-1 infection from that of the patients who did not have serologic evidence of infection. This finding is consistent with findings of studies in patients recovering from encephalitis that indicate that memory is particularly vulnerable to the effects of HSV-1 replication within the central nervous system.[34,63]

Our study relied on the measurement of serum antibodies to purified herpesvirus proteins. The presence of these antibodies indicates that an individual has been exposed to the target virus at some point in life and that viral DNA has integrated into the host genome. However, the presence of antibody is not necessarily an indicator of active infection. We did not perform lumbar punctures in our study population. We thus could not directly measure herpesvirus antibodies or viral nucleic acids within the cerebrospinal fluid to evaluate for evidence of central nervous system infection. Because of the cross-sectional nature of our study, we also could not determine the timing of the patient's primary HSV-1 infection or the age at which cognitive dysfunction developed. None of our patients had undergone a documented episode of clinically apparent encephalitis. However, the patients in this cross-sectional study could not undergo assessment for the prior occurrence of self-limited HSV-1 infections of the central nervous system.[32] Future studies should prospectively investigate the timing of HSV-1 infection and the extent of viral replication within the central nervous system in individuals at risk for schizophrenia. These studies may more precisely define the relationship between HSV-1 infection and the development of cognitive dysfunction in individuals with schizophrenia.

Although we found a statistically significant association between cognitive functioning and the prevalence of antibodies to HSV-1 in individuals with schizophrenia, we did not find a significant association between cognitive functioning and the prevalence of antibodies to other human herpesviruses with neurotropic potential, including HSV-2, CMV, EBV, HHV-6, and VZV. These findings are consistent with those of studies indicating that HSV-1 is the principal member of the human herpesvirus family capable of infecting the central nervous system of immunocompetent individuals after the immediate neonatal period.[25] The specificity of the association also renders unlikely the possibility that our finding is related to increased incidental exposure to herpesviruses in individuals with schizophrenia. If this were the case, one would expect to find an association between cognitive dysfunction and increased level of antibodies to several members of the herpesvirus family in addition to HSV-1. We did not measure levels of antibodies to other viruses, such as enteroviruses or flaviviruses, which can infect the central nervous system and might be associated with cognitive impairment. We also did not measure the interaction between viruses and other genetic or environmental factors that might be associated with cognitive impairment in individuals with schizophrenia.[64] Furthermore, we did not perform virological or RBANS testing on individuals without schizophrenia, so our findings cannot be generalized to other populations. The full extent of the relationship between viral infection and cognitive impairment should be the subject of additional investigations.

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