Deficit Schizophrenia: Association With Serum Antibodies to Cytomegalovirus

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Background: Patients with deficit schizophrenia differ from nondeficit patients with schizophrenia relative to several neurobiological correlates and relative to the risk factors of family history and season of birth. Exposure to human herpesviruses is a possible risk factor for schizophrenia. We hypothesized that there would be deficit/nondeficit difference in the prevalence of serum antibodies to human herpesviruses. *Methods*: In deficit ($N = 88$) and nondeficit ($N = 235$) schizophrenia patients, we measured IgG class antibodies to the 6 known human herpesviruses: herpes simplex virus type 1, herpes simplex virus type 2, cytomegalovirus, Epstein-Barr virus, human herpes virus 6, and varicella-zoster virus. *Results*: Deficit categorization was associated with the presence of serum antibodies to cytomegalovirus (odds ratio = 2.01, $p = .006$). This association remained significant after covarying for positive psychotic symptoms and demographic features known to be associated with cytomegalovirus seropositivity and after correcting for multiple comparisons. An association between herpes simplex virus type 1 and deficit status was not significant after covarying for potentially confounding variables. No other human herpesvirus was significantly associated with deficit versus nondeficit categorization. *Conclusions*: The association between deficit schizophrenia and cytomegalovirus antibody seropositivity provides further evidence for differences in etiopathophysiology between deficit and nondeficit schizophrenia.

Key words: schizophrenia/negative symptoms/deficit/infection/epidemiology

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Introduction

Deficit schizophrenia is a putative schizophrenia subtype made up of individuals with schizophrenia who have primary and enduring negative symptoms such as restricted affect and diminished social drive.[1] This group comprises approximately 20–25% of patients with chronic schizophrenia.[2–3] The deficit/nondeficit categorization is stable longitudinally,[4–5] and its construct validity is supported by between-group differences in several clinical characteristics in addition to the severity of negative symptoms. For instance, as a group, patients with deficit schizophrenia have less severe depression and anxiety but poorer social functioning than do those with nondeficit schizophrenia. This difference in function cannot be attributed to more severe psychotic symptoms (hallucinations, delusions, and disorganization) in the deficit group, as in most studies, these symptoms are equal or less severe in the deficit group.[6] Patients with deficit and nondeficit schizophrenia also differ with regard to several neurobiological features, such as brain structure and regional brain activation, eye-tracking dysfunction, postmortem correlates, and neurocognitive impairment.[7–16]

Patients with deficit and nondeficit schizophrenia also differ with regard to risk factors. Although schizophrenia is associated with an increased risk of winter birth,[17] deficit schizophrenia has an association with summer birth, compared to both nondeficit schizophrenia and to the general population.[18–20] Deficit and nondeficit schizophrenia also differ with regard to family history, in terms both of morbid risk of schizophrenia in relatives and of sibling concordance for the deficit/nondeficit categorization.[21–23]

Exposure to human herpesviruses is a possible biological risk factor for schizophrenia. Human herpesviruses include herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), human herpes virus 6 (HHV-6), and varicella-zoster virus (VZV). All of these viruses are capable of infecting the central nervous system and establishing latent infection. Exposure to CMV has been associated with recent onset schizophrenia,[24] and maternal antibodies to HSV-2 are associated with an increased risk of schizophrenia in the offspring.[25] Treatment with the antiviral medication valacyclovir has been shown to decrease symptoms in individuals with schizophrenia who have

serological evidence of infection with CMV.[26] Serological evidence of infection with HSV-1 has also been associated with cognitive impairment in individuals with schizophrenia.[27] In view of the other deficit/nondeficit differences in risk factors that have been reported, we hypothesized that there would also be differences in the prevalence of serum antibodies to human herpesviruses in deficit and nondeficit schizophrenia.

Methods and Materials

The sample consisted of 323 individuals with schizophrenia who were recruited from outpatient treatment sites in central Maryland. All participants met DSM-IV criteria for schizophrenia or schizoaffective disorder. Patients were initially screened for eligibility on the basis of chart diagnoses; the final diagnosis of each participant was made by 1 of 2 board-certified psychiatrists. Other inclusion criteria were age between 18 and 65 inclusive and receipt of a stable regimen of psychotropic medications that conformed to Patient Outcome Research Team treatment recommendations[28] for at least 3 weeks prior to the study visit. Exclusion criteria were current substance abuse during the past 1 month; any history of intravenous substance abuse; mental retardation; any clinically significant medical disorder that would affect cognitive performance such as epilepsy, history of encephalitis, or head trauma or any other reported neurological disorder of the central nervous system that had resulted in past or current treatment; clinically apparent herpesvirus infection; or recent treatment with antiviral medications.

The study was approved by the Institutional Review Boards of the Sheppard Pratt Health System and the University of Maryland School of Medicine, and all participants provided written informed consent after the study procedures were explained. Patients were interviewed and rated on the Positive and Negative Syndrome Scale (PANSS).[29] Patients were also administered a brief cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A).[30] The RBANS is made up of 12 subtests that are used to calculate 5 index scores and a total score. Test indexes are Immediate Memory (comprising list-learning and story memory tasks), Visuospatial/Constructional (comprising figure-copy and line orientation tasks), Language (comprising picture naming and semantic fluency tasks), Attention (comprising digit span and coding tasks), and Delayed Memory (comprising 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 a standard deviation of approximately 15 based on a normative study group of 540 healthy subjects, ranging in age from 20 to 89, matched to the U.S. Census on gender, ethnicity, and years of education. The index scores are combined to

Table 1. Demographic and Clinical Characteristics of the Deficit and Nondeficit Groups

Variable	Deficit (N = 88)	Nondeficit (N = 235)	P Value
Age	43.3 (9.9)	41.5 (9.9)	.14
% Caucasian	67	77	.08
% Male	60	60	.92
Age of onset	23.0 (7.6)	20.6 (7.0)	.01
Conceptual disorganization	2.8 (1.4)	2.8 (1.4)	.85
Hallucinations	2.5 (1.6)	3.0 (1.7)	.03
Delusions	3.0 (1.5)	3.6 (1.3)	<.001
Emotional withdrawal	3.2 (1.1)	2.8 (1.2)	.01
Poor rapport	2.7 (0.9)	2.3 (1.1)	.003
Social withdrawal	3.1 (1.1)	2.7 (1.2)	.006
Poverty of speech	2.5 (1.3)	1.8 (1.2)	<.001

yield an RBANS total score, which is a measure of overall cognitive functioning.

As diagnoses of deficit versus nondeficit schizophrenia based on the Schedule for the Deficit Syndrome (SDS)[1] were not available, the Proxy for the Deficit Syndrome (PDS) was used. This method has been previously described in detail[3] and is based on the distinctive combination of high negative symptom scores and an absence of dysphoria that characterizes deficit patients.[1, 3, 31–32] Consistent with previous applications of the PDS, a score was assigned to each patient, based on the sum of PANSS item scores: PDS = blunted affect – (guilt + anxiety + depression + hostility). Based on prevalence assumptions, cutoff points were then used to define putative deficit and nondeficit groups: subjects with scores of −17 to −5 were categorized as nondeficit (N = 235), and subjects with scores of −4 to 1 were categorized as deficit (N = 88). Although in some applications of the proxy, an ambiguous group has been omitted, the validity testing of this categorization showed that the groups had the desired characteristics (see below).

Although the PDS method has been validated by comparison with categorizations based on the SDS,[3] the validity of the categorizations in this sample was further assessed by comparing the characteristics of the deficit and nondeficit groups to those in the literature.[3, 6, 31] This comparison largely confirmed the validity of the current categorizations (see table 1). By definition, the deficit group had significantly more severe blunted affect but was less dysphoric. The 2 groups did not differ significantly relative to age, race, gender, or PANSS scores on conceptual disorganization. In addition, the deficit group had (1) significantly more emotional withdrawal, poor rapport, social withdrawal, and poverty of speech; (2) less severe delusions, hallucinations, suspiciousness, and somatic concern; and (3) a slightly later age of onset. In short, most of the greater negative symptoms in the deficit group could be attributed to a greater severity of primary negative symptoms, as the deficit group did not have more severe psychotic symptoms or dysphoria.

Each patient provided a blood sample at the time of the symptom and cognitive assessment. We employed solid-phase immunoassay techniques to measure IgG class antibodies to human herpesviruses in the serums of all participants. Details of the methods have been previously described.[27] Assays were performed for the measurement of antibodies to the following members of the herpesvirus family: HSV-1, HSV-2, CMV, EBV, HHV-6, and VZV.

Univariate associations between deficit status and seropositivity for the herpesviruses were calculated using chi-square analyses. In the case of a significant association (see below), multivariate logistic regression was then performed to predict deficit status including other potentially confounding variables that were associated with deficit status in our sample: age of illness onset and the severity of hallucinations and delusions.

Results

The sample of 323 individuals with schizophrenia comprised 193 men and 130 women with a mean age of 42.0 years (s.d. 9.9). A total of 216 individuals in the sample (73.2%) were Caucasian. The mean years of education in the sample was 12.7 years (s.d. 2.4). Age of illness onset averaged 21.2 (s.d. 7.3), and the duration of illness, 20.8 years (s.d. 10.0). In terms of their current medication use, all participants were receiving antipsychotic medications; 267 out of 323 (82.7%) of the participants were receiving atypical antipsychotic medications, of whom 107 (33.17%) participants were receiving olanzapine, and 88 (27.3%) were taking clozapine. The proportion of patients receiving these medications did not differ by deficit status (all $p > .05$). The percentage of subjects categorized as deficit was not significantly different between those with schizoaffective disorder (25%) and those with schizophrenia (32%; chi-square = 2.07, p = .15).

The mean PANSS total score of the sample was 71.1 (s.d. 13.7), and the mean RBANS total score was 68.3 (s.d. 14.6). As expected,[10] patients with deficit status had a lower mean RBANS total score than nondeficit patients, 64.2 (s.d. 13.9) versus 69.8 (s.d. 14.5; $F = 9.98$, $p = .002$). There were also significant differences between the deficit and nondeficit groups on the RBANS indexes of Immediate Memory (61.4 [s.d. 16.3] versus 68.6 [s.d. 18.0]; $F = 10.58$, $p = .001$), Delayed Memory (65.3 [s.d. 19.1] versus 71.6 [s.d. 18.5]; $F = 7.29$, $p = .007$), and Visual/Constructional (72.4 [s.d. 17.7] versus 78.2 [s.d. 18.7]; $F = 6.43$, $p = .012$) but not Language (82.1 [s.d. 14.6] versus 85.4 [s.d. 14.9]; $F = 3.11$, $p = .079$) or Attention (72.6 [s.d. 17.0] versus 74.5 [s.d. 16.9]; $F = 0.87$, $p = .352$).

Deficit status was significantly associated with the presence of antibodies to cytomegalovirus (chi-square = 7.67, $p = .006$). Using the most conservative approach to multiple comparisons, this would yield a corrected p value of $6 \times .006 = .036$. A total of 46 of the 88 (52.3%) deficit patients were CMV seropositive, while 83 of the 235

(35.3%) nondeficit patients were CMV seropositive. In a maximum-likelihood multinomial logistic regression model, the association between CMV antibody status and deficit status remained significant when including the covariates of age, gender, and age of onset (odds ratio = 2.00; 95% CI 1.18, 3.38; $p > .01$). Adding the PANSS scores for hallucinations + delusions did not change the pattern or significance of the results.

There was a univariate association between herpes simplex virus type 1 and deficit status (chi-square = 5.05, $p = .025$). However, this association became nonsignificant in the multinomial logistic regression when including age, gender, age of onset, and hallucinations + delusions (odds ratio = 1.67; 95% CI 0.99, 2.80; $p = .053$). There was not a significant association between deficit status and antibodies to other herpesviruses tested, including HSV-2, HHV-6, VZV, EBV.

Discussion

In this study we found an association between deficit status and antibodies to cytomegalovirus among outpatients with schizophrenia. The association was specific to CMV, as no significant association was found between deficit status and the serologic status of other of the herpesviruses when controlling for potentially confounding variables. However, the association between deficit status and herpes virus type 1 is suggestive and deserves further testing given the conservative nature of our analysis. The association between deficit status and CMV remained significant after correcting for multiple comparisons. Inclusion of both schizoaffective and schizophrenia subjects had little impact on the pattern of results, as the prevalence of deficit subjects was similar across the 2 disorders. Of note, the prevalence of CMV in our sample is similar to that which has been found in young adults living in North America when measured by specific antibody assays.[33]

The validity of the proxy method for categorizing deficit and nondeficit subjects is crucial for our interpretation that the deficit group is associated with CMV antibodies. The criteria for deficit schizophrenia requires enduring negative symptoms, and the proxy formula we used does not directly address some of the clinical features used to define deficit schizophrenia. However, the proxy method has replicated the association of the deficit group with summer birth that has also been found using the SDS.[20] In addition, in a direct comparison of SDS and proxy categorizations, the agreement was good.[3] In the current study, the proxy also yielded clinical groups whose clinical features are largely those one would expect to find using the SDS. The association with CMV also remained significant after varying for other important, potentially confounding clinical and demographic variables; covarying should also decrease problems from miscategorization, as many of these variables are causes of secondary negative symptoms. Although the proxy has

miscategorizations compared to the SDS, any miscategorizations should bias studies toward finding a lack of an association, rather than create a false association.

This evidence for an association between deficit schizophrenia and CMV antibodies is consistent with the extensive evidence of neurobiological differences between deficit and nondeficit schizophrenia. Most family history studies have found that the deficit group appears to be more "familial" than nondeficit schizophrenia[21–23]; however, a strong genetic contribution to the etiology of deficit schizophrenia does not preclude an environmental risk factor. The risk factor of season of birth also differs between the 2 groups,[20–23] as does neurocognitive function.[7–8, 10–11, 14, 16, 34–35] There are also reports of gross and microscopic differences in brain structure.[9, 12–13, 36] There is a previous report of an association between borna virus and deficit schizophrenia,[37] but that finding has not yet been replicated.

It is not clear from our present findings whether CMV plays a role in the etiology of deficit schizophrenia. However, our findings are consistent with previous studies indicating an increased prevalence of antibodies to CMV in individuals with recent onset schizophrenia[24] and with a study showing that the antiherpes drug valacyclovir can improve symptoms in individuals with schizophrenia who have antibodies to CMV.[26] Additional studies should be performed to further define the role of CMV and related viruses in the etiopathogenesis of schizophrenia. Clarification of this relationship may lead to new methods for the diagnosis and treatment of this disorder.

Acknowledgments

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