

SEROPOSITIVITY OF NEUROTROPIC INFECTIOUS AGENTS IN FIRST-EPIISODE SCHIZOPHRENIA PATIENTS AND THE RELATIONSHIP WITH POSITIVE AND NEGATIVE SYMPTOMS

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SUMMARY

Background: According to the neurodevelopmental model, schizophrenia is a disorder that occurs as a result of different etiologic factors during brain development, including viral infections. However, it is unclear whether these infections are related to the disease or whether they affect the symptom pattern. We investigated the presence of four herpes viruses (EBV, CMV, HSV-1 and HSV-2) in first-episode schizophrenia patients and compared seropositive with seronegative patients and healthy volunteers to reveal the etiological role of viral agents on schizophrenia symptoms.

Subjects and methods: Ninety-two first-episode patients who met the DSM-IV diagnostic criteria for schizophreniform disorder were included the study, along with 88 healthy volunteers. The presence of the four herpes viruses was investigated with serological methods (ELISA) in both groups. Positive and negative symptoms were evaluated with Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS).

Results: There was no difference between the patient and control groups in terms of seropositivity of the four viruses. We found that SANS scores of HSV-1 and CMV seropositive schizophrenia patients were significantly higher than the scores of patients with seronegative schizophrenia. No difference was found in SAPS scores.

Conclusions: The results suggest a role of HSV and CMV infections in negative symptoms. This supports the hypothesis that viruses do not directly give rise to schizophrenia, but patients who were previously been infected with these viral agents may be prone to schizophrenia, and some of the symptom patterns may be related to different agents.

Key words: first-episode – infectious – schizophrenia – seropositivity - symptoms

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INTRODUCTION

According to the neurodevelopmental model, schizophrenia is a developmental disorder that begins to occur during brain development (Owen et al. 2011). Studies have shown that genetic predisposition, viral infections, pregnancy, and childbirth complications may have effects on developmental disorders in the brain (Buchanan & Carpenter 2005). The relationship between viral infections and schizophrenia has previously been discussed in terms of etiology (Brown et al. 2004, Dalman et al. 2008). Some authors have revealed the relation of exposure to HSV-1 and brain morphometric changes in patients with schizophrenia and bipolar disorder (Schretlen et al. 2010). Based on this idea, a new hypothesis has been proposed that environmental factors like viral agents such as cytomegalovirus (CMV) or herpes simplex virus (HSV) do not directly cause schizophrenia or bipolar disorder, but patients with these diseases may be more susceptible to the impact of exposure to viral agents. Such susceptibility may be more apparent on some of the symptom patterns (cognitive impairment, negative symptoms, etc.) (Shirts et al. 2008, Yolken et al. 2011, Watson et al. 2013, Houenou et al. 2014).

A relationship between antibody levels of some viral infections, especially herpes group infections and cognitive impairment in schizophrenia has been proposed (Shirts et al. 2008, Yolken et al. 2011, Watson et al. 2013). The relationship of cognitive impairment in schizophrenia patients with HSV-1 and CMV has been examined in many studies (Dickerson et al. 2003, Shirts et al. 2008, Houenou et al. 2014). Herpes viruses are a large family that includes important human pathogens that can cause persistent lifelong infections. Cytolytic viruses are a rapidly growing member of this family. The most important feature of these viruses is that they go through recurrent cycles of latency and reactivation (Jerome et al. 2007). They generally exhibit tropism to the temporal region in herpes encephalitis, particularly to the hippocampus and thereby thought to cause hippocampal dysfunction.

Hippocampal volume reduction is one of the common brain structural changes in HSV encephalitis, along with memory impairment (Geuze et al. 2005). In animal studies, HSV-1 has been found in the hippocampus, amygdala, midbrain, and brainstem (Barnett et al. 1993). HSV infection leads to encephalitis presenting with latent clinical pictures or reactivation in less than 0.5% of individuals (Jerome et al. 2007). In the iPSC

model, activated HSV-1 led to lysis of neurons but not during latency. Gene expression profile differed with greater number of genes showing altered expression compared to quiescent infection. However, glutamatergic genes showed altered expression in both latent and reactivated phases. Reactivation of HSV-1 infections causes severe cognitive decline and post-infectious sequelae due to encephalitis (Steiner et al. 2007).

Prefrontal cortical gray matter volume reduction (Prasad et al. 2007, Prasad et al. 2011) and progressive cognitive impairment (Prasad et al. 2011) have been reported in patients with schizophrenia who have been exposed to HSV-1 virus. Cognitive impairment was improved after antiviral therapy (Prasad et al. 2013). Lower cognitive performance was found in HSV-1 seropositive patients with schizophrenia. A decline of gray matter was associated with a decrease of cognitive performance (Prasad et al. 2010, Prasad et al. 2013, Houenou et al. 2014). Even in HSV-1 infections without encephalitis, deterioration in working memory has been identified, and a relationship between this deterioration and findings of fMRI studies has been shown (D'Aiuto et al. 2014).

Cytomegaloviruses (CMVs) are slow growing and remains latent in secretory glands and kidneys (causing excessive growth of infected cells) (Mocarski et al. 2007). CMV is a disease agent that can be seen all over the world at all levels of socio-economic status. 60-70% of adults have been exposed to this virus. Seroprevalence in developing countries is close to 100%. CMV is also one of the highest-risk viruses for infection to the fetus during pregnancy, and congenital CMV infection can cause deafness, learning disabilities, and mental retardation in infants (Hodinka et al. 2007).

On the cell surface, the virus prevents the presentation of antigens to CD8 cytotoxic T lymphocytes and CD4 T cells by inhibition of MHC I expression and cytokine-induced MHC II expression in antigen-presenting cells (Mocarski et al. 2007). In schizophrenia, studies have shown that peripheral lymphocytes are affected, particularly in the form of an increase in B lymphocytes, reduction of T lymphocytes, and increase in T lymphocytes in the cerebrospinal fluid (Yolken & Torrey 1995). In addition to the effects at the cellular level, there are studies indicating that this virus shows particular affinity to gray matter, making pathological changes in limbic areas correlated with clinical symptoms (Shinmura et al. 1997, Arai et al. 2003, Yolken et al. 2008, Houenou et al. 2014). Despite findings of a relationship between CMV seropositivity with measurable cognitive measures in schizophrenia patients (Watson et al. 2013), there are studies claiming otherwise. In two large-scale studies, no relationship between CMV seropositivity and general cognitive function was determined (Yolken et al. 2011, Houenou et al. 2014). This was interpreted by some as a lack of low-sensitivity tests used in these studies (Houenou et al. 2014).

Most of the previous studies have evaluated a single microbiological agent. So, different study populations arise for different agents, and these results are difficult to compare. In a recent study, we thought that simultaneous examination of multiple agents in the same population may shed light on agent interactions or possible etiopathogenic pathways (Li et al. 2013).

Despite increasing evidence about cognitive findings, there have been no further studies on positive and negative symptoms. Most of the studies have examined chronic patients, large samples, and symptoms in acute patients. Because of the chronic nature of the disease, symptoms can change over time. With treatment, patients may have an increased risk of infections as a result of hospitalizations or lifestyle factors. So, we thought that it would be important to evaluate seropositivity and its relation to positive and negative symptoms in the first episode of the disease. We aimed to investigate the relationship of the positive and negative symptoms of schizophrenia with certain viral agents reported to be associated with cognitive impairment. For this purpose, the relationship between the serological findings of the herpes virus family with positive and negative symptoms in schizophrenic patients was examined.

SUBJECTS AND METHODS

Subjects

This study was conducted at the Department of Psychiatry, Gulhane Military Medical Faculty (GMMF), Ankara, Turkey, between February 2009 and January 2014. The study included 92 patients with schizophrenia and 88 healthy volunteers. Patients meeting criteria for first acute psychotic episode and schizophreniform disorder according to the DSM-IV (APA 2000) diagnostic criteria were included in the study. According to duration criteria of DSM-IV, all patients were meeting the criteria for schizophrenia after 6 months, so the diagnoses were termed as schizophrenia after that period. Patients who had organic diseases, any other psychiatric illness, or a previous psychotic episode were not included in the patient group. The control group was recruited from hospital staff willing to participate in the study and had no organic or psychiatric diseases. Written informed consent was obtained from all individuals from the control group and from patients or their relatives in case of psychotic disorders.

Methods and instruments

Ten ml of venous blood was taken from the participants, and the serum was separated and maintained at -80° C for subsequent evaluation. The presence of EBV, CMV, HSV-1, and HSV-2 was investigated by a serology (ELISA) method for patients and the control group.

Negative and positive symptoms of the disease were evaluated by the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). SANS was developed by Andreasen (1990) to measure the level, distribution, and intensity of negative symptoms. It contains 25 items with the following subscales: affective flattening, avolition, anhedonia, and attention. SAPS was also developed by Andreasen (1990) to measure the level, distribution, and intensity of positive symptoms. It has 35 items with the following sub-scales: hallucinations, delusions, bizarre behavior, and formal thought disorder. The Turkish versions of SANS and SAPS were reported to be reliable by Erkok et al. (1991).

Gülhane Military Medical Academy, School of Medicine Ethics Committee approved the study protocol.

Statistical analyses

The obtained data were analyzed with SPSS 15.0. Continuous variables were presented as the mean \pm standard deviation, and categorical variables were expressed as numbers and percentages. The Student *t* test was used for continuous variables, and the chi-square test was used for discrete variables when comparing the cases. Statistical significance was taken as $p < 0.05$.

RESULTS

Sociodemographic characteristics

Patients had similar characteristics to the controls in terms of sociodemographic variables such as age, gender, and education level. The mean age of the patients was 21.77 ± 2.30 , while that of the control group was 22.32 ± 3.21 . 7.6% of the patients and 7.5% of the control group were women.

Comparison of serological findings of patients with the control group

EBV IgG was positive in 56.5% of patients ($n=52$) and 53% ($n=47$) of the control group. There was no difference between the patient group and control group in terms of EBV IgG ($p > 0.05$). CMV IgG was positive in 45.6% of patients ($n=42$) and 40% ($n=36$) of the control

group. There was no difference between the patient group and control group in terms of CMV IgG ($p > 0.05$). HSV-1 IgG (52% in the patient group, 48% in the control group) and HSV-2 IgG (12% in the patient group, 20% in the control group) showed no significant difference between the patients and the control groups ($p > 0.05$), (Table 1).

The relationship of psychometric measures with serological findings of patients (Table 2)

Herpes Simplex Virus 1 (HSV-1): the mean SANS score of HSV-1 IgG (+) patients was found to be 46.6 ± 15.8 , and that of the HSV-1 IgG (-) patients was 39.9 ± 15.9 . There was a statistically significant difference between the two groups ($t=2.028$, $p=0.046$). There was no difference between groups in terms of SAPS scores.

Herpes Simplex Virus 2 (HSV-2): mean SANS and SAPS scores did not differ between HSV-2 IgG (+) and HSV-2 IgG (-) patients.

Citomegalovirus (CMV): the mean SANS score of CMV IgG (+) patients was 47.5 ± 13.5 , and that of the CMV IgG (-) patients was 40.0 ± 17.4 . There was a statistically significant difference between the two groups ($t=2.336$, $p=0.022$). There was no difference between groups in terms of SAPS scores.

Epstein-Barr virus (EBV): there was no difference in SANS and SAPS scores between EBV IgG (+) patients and EBV IgG (-) patients.

DISCUSSION

The SANS scores of HSV-1 or CMV IgG seropositive patients with schizophrenia were significantly higher than those of HSV-1 or CMV IgG seronegative schizophrenia patients. There is little research on the association of positive and negative symptoms and serological findings. An association between EBV infection (not other Herpes viruses) and subclinical positive psychotic symptoms was found in one study, but it did not examine a clinical schizophrenia population (Wang et al. 2011). In our schizophrenia population, we found an association of HSV-1 and CMV with negative symptoms, but no association was found for EBV. Also, no association was found with respect to positive symptoms.

Table 1. Serological Findings of Schizophrenia and Control Groups

Serological Variables	Groups				Statistical Analysis
	Schizophrenia (n=92)		Control (n=88)		
	Positive n (%)	Negative n (%)	Positive n (%)	Negative n (%)	
EBV IgG	52 (56.5)	40 (43.5)	47 (53)	41 (47)	$\chi^2=0.176$, $p=0.675$
CMV IgG	42 (45.6)	50 (54.4)	36 (40)	52 (60)	$\chi^2=0.412$, $p=0.521$
HSV-1 IgG	47 (52)	45 (48)	43 (48)	45 (52)	$\chi^2=0.021$, $p=0.884$
HSV-2 IgG	11 (12)	81 (88)	18 (20)	70 (80)	$\chi^2=2.403$, $p=0.121$

Table 2. Comparison of SANS and SAPS Scores in Seropositive and Seronegative Groups in Schizophrenia Patients

Virus		Seropositive Group	Seronegative Group	Statistical Analysis
EBV	N	52	40	Total: 92
	SANS Score	40.7±15.3	46.5±17.5	t=1.657, p=0.102
	SAPS Score	59.5±16.5	66.5±18.3	t=1.324, p=0.193
CMV	N	42	50	Total: 92
	SANS Score	47.5±13.5	40.0±17.4	t=2.336, p=0.022
	SAPS Score	65.4±14.8	60.3±19.9	t=0.969, p=0.338
HSV-1	N	47	45	Total: 92
	SANS Score	46.6±15.8	39.9±15.9	t=2.028, p=0.046
	SAPS Score	59.6±17.2	65.6±17.7	t=1.137, p=0.262
HSV-2	N	11	81	Total: 92
	SANS Score	45.8±16.1	42.8±16.6	t=0.559, p=0.578
	SAPS Score	58.8±16.0	63.4±17.8	t=0.548, p=0.586

Previous studies on viral infectious agents in schizophrenia focused more on etiological factors. According to some authors, there is no relationship between schizophrenia and viral agents (Ozcankaya et al. 2000, Minzenberg et al. 2009). Recently, clinical studies have investigated how the neurotropic agents contribute to the clinical picture of schizophrenia rather than the etiology. The findings obtained in our study have been considered while keeping in mind the studies explaining the effect of viral agents in patients with schizophrenia (particularly cognitive effects).

There is a possible effect of viral infections on early neurodevelopment, and these viral agents can show neurotropism to regions associated with negative symptoms. There are links between the brain regions thought to be associated with positive, negative, and cognitive symptoms in patients with schizophrenia. Microbiological agents which appear with various deficits in schizophrenia, such as HSV-1 and CMV, are thought to cause cognitive impairment by affecting these brain areas (Prasad et al. 2012, Houenou et al. 2014).

MRI studies of patients with schizophrenia found that HSV-1-seropositive schizophrenia patients have a more atrophic left frontal cortex compared to seronegative schizophrenia patients (Pandurangi et al. 1994). First-episode seropositive schizophrenia patients in particular have decreased volumes of bilateral prefrontal cortex and anterior cingulate cortex compared to seronegative schizophrenia patients (Prasad et al. 2007). Studies that examined the relationship between cortical performance and volumetric findings found a close relationship between cognitive function parameters and volumetric changes in the prefrontal cortex, parahippocampus, anterior cingulate gyrus, and fusiform gyrus in HSV-1 seropositive schizophrenic patients (Minzenberg et al. 2009, Schretlen et al. 2010, Prasad et al. 2012, Prasad et al. 2013).

CMV is thought to show tropism to gray matter in its latent period (Shinmura et al. 1997, Tsutsui et al. 2005, Tsutsui et al. 2009, Perron et al. 2009). In human studies, CMV showed particular affinity to the temporal

region (Hoffmann et al. 2010) and limbic structures (Yolken et al. 2008), whereas the affinity was to the hippocampus in animal models (Shinmura et al. 1997, Arai et al. 2003). MRI findings of CMV infection in patients with schizophrenia showed decreased hippocampal volume in the patient group. Thus, attention was drawn to the negative correlation between right hippocampal volume and the density of virus antibodies.

A negative correlation was found between performance on the California Verbal Learning Test in patients with schizophrenia and antibody density (Houenou et al. 2014). These studies support the animal model studies showing hippocampal CMV tropism, particularly during latent infection (Shinmura et al. 1997, Arai et al. 2003, Wang et al. 2011). Studies with human and animal models suggest CMV has many effects that may affect the healthy development of neural structuring during early periods. Infected fetuses in particular were found to have smaller temporal lobe volumes (Mucci et al. 2007, Cascella et al. 2008). Some cognitive test performance has been associated with CMV in schizophrenia (Shirts et al. 2008). A relationship was also demonstrated between CMV seropositivity and deficit schizophrenia characterized by negative symptoms (Beers et al. 1995). Patients with deficit schizophrenia have poor cognitive function (Millhouse & Wigdahl 2000) and hippocampal dysfunction (Shi et al. 2009).

In line with the studies outlined above, it can be understood that HSV-1 affects structures related to the frontal cortex, prefrontal cortex, and cingulate gyrus, while CMV affects the temporal lobe and limbic structures. Some anatomical areas are associated with negative symptoms. The overlap of anatomical areas may clarify the question of why HSV-1 and CMV are associated with negative symptoms. The mechanism of the relationship between HSV-1, CMV, and volumetric reduction is not known clearly. Animal studies also support that reactivation of latent viral infection causes neuronal death (Stefansson et al. 2009, Mansur et al. 2012). Viral reactivation may underlie the volumetric reduction in brain tissue, and this neural loss may cause

cognitive deterioration in patients with schizophrenia (Prasad et al. 2011). Even postmortem studies support that viral reactivation causes a reduction in the synapses, axons, and dendrites of neurons (Millhouse & Wigdahl 2000). A similar situation can also be associated with negative symptoms. Neural loss may lay the groundwork for the emergence of negative symptoms in patients. There are circuits and regions of the brain thought to be associated with negative symptoms in patients with schizophrenia. CMV and HSV-1 (in latency and the reactivation period) are thought to affect the brain regions associated with these symptoms. Like in a previous study (Houenou et al. 2014), it is not known in our study when the patients encountered HSV-1 or CMV. This undermines our view on the effect of these viruses in the early neurodevelopmental period.

Another possible cause of the pathology of latent viral infections in schizophrenia is the chronic inflammatory reactions that these agents cause and the anti-inflammatory process that occurs in response. Relationships between immune response and schizophrenia have been proposed in different studies. Strong relationships between the genetic structures related to the disease and the HLA polymorphism have been demonstrated in schizophrenia (Shi et al. 2009, Stefansson et al. 2009). A relationship of schizophrenia with high amounts of proinflammatory cytokines and anti-inflammatory mediators has also been reported (Mansur et al. 2012).

The relationship between latent CMV infection and decreased cognitive performance was suggested to occur due to a chronic inflammatory response, and its cause was believed to be associated with decreased hippocampal volume (Jarskog et al. 2006). Studies with animal models also suggest that CMV disrupts neural development by affecting inflammatory processes (Koontz et al. 2008). PET studies also support the views on hippocampal inflammation in chronic schizophrenia (Almanzar et al. 2005). A relation was established between decreased hippocampal volume and poor cognitive performance in patients with schizophrenia (Marsland et al. 2006, Marsland et al. 2008, Mondelli et al. 2010).

Some studies showed mice expression of hippocampal GRIN1 failed after CMV infection (Kosugi et al. 2005). This failure may explain the association between CMV and impaired hippocampal function. It can even explain the negative symptoms developing after both CMV and HSV-1 infection.

Another explanation may be that negative symptoms become apparent because of the effect on cognitive functions. There is a close relationship between negative symptoms of schizophrenia and cognitive function (Harvey et al. 2006). This type of relationship is particularly prominent in deficit schizophrenia. The effect on the negative symptoms may be indirectly affected by cognitive dysfunction.

The most important limitation of our study is that the patients did not know when they were infected. Another limitation is the absence of simultaneous neuroimaging. The quantitative level of antibodies of patients and their relationship with SANS and SAPS scores should also have been studied. Follow-up studies including larger populations and neuroimaging findings will provide guidance about this issue.

CONCLUSIONS

The results suggest an effect of HSV and CMV infections on negative symptoms. This supports the hypothesis that viruses do not directly give rise to schizophrenia, but patients with these diseases are sensitive to viral agents, and some of the symptom patterns may be related to different agents.

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