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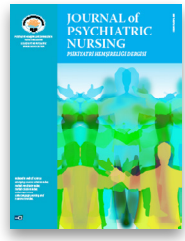

Original Article

Cytomegalovirus in the etiopathogenesis of schizophrenia and suicide risk: A case-control study

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Abstract

Objectives: The aim of this case-control study is to investigate the possible relationship between Cytomegalovirus (CMV) infection and schizophrenia or suicidal behavior.

Methods: A total of 274 individuals, including 134 patients with schizophrenia and 140 healthy controls were included in this case-control study. Sociodemographic characteristics, clinical data and suicidal risk scores of the participants were recorded during face to face interviews, and serum CMV IgG seroprevalence was determined.

Results: The demographic and clinical data of the participants included in the study were as follows: the mean age was 30.82±0.59 years; 50.7% were female and 49.3% male; 5.1% were illiterate, 26.3% were primary school graduates, 42.3% were secondary middle school graduates, 26.3% were undergraduates; the mean Suicide Behaviors Questionnaire-Revised (SBQ-R) score was 6.27±3.12. Seropositivity rate of CMV IgG was found to be 64.6% (177/274). It was determined that CMV IgG seropositivity rates were 48.6% (68/140) in the healthy control group and 81.3% (109/134) in the schizophrenia group, and the relationship between schizophrenia and CMV IgG seropositivity was statistically significant ($p<0.001$). CMV IgG seropositivity rates were 61.5% in the non-suicide risk and 70.7% in the suicide risk group, and the relationship between CMV IgG seropositivity and suicide risk was not statistically significant ($p=0.137$).

Conclusion: The potential effects of latent CMV infection on dopamine and other neurotransmitter levels may play a role in the etiopathogenesis of schizophrenia. Nevertheless, further studies on CMV and schizophrenia are needed and may lead to improved treatments for schizophrenia.

Keywords: CMV; schizophrenia; suicidal risk.

Schizophrenia is a chronic psychiatric disorder that is usually characterized by hallucinations and/or delusions, which differs with cognitive, emotional and other functional impairments of behavior and often progresses with relapses. It is thought that more than 21 million people worldwide are affected by schizophrenia.[1] Although the pathogenesis of schizophrenia has not been fully explained, it is suggested that this disease is caused by the interaction between genetic and environmental factors. Neurotropic pathogens, those microorganisms that can infect the central nervous system (CNS) have been shown to be one of the most important agents in environmental factors for years.[2,3] This hypothesis is supported by the involvement of schizophrenia-related genes in the immunological functions responsible for host-pathogen interactions.[4,5] In addition, the fact that the incidence of schizophrenia increases after prenatal/pediatric infections and in individuals born in winter and urban areas has been found to support this hypothesis.[6–9]

Some viruses in the Herpesviridae family [Herpes Simplex Virus-1 (HSV-1), Herpes Simplex Virus-2 (HSV-2), Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV)], detected in a significant part of the general population, and *Toxoplasma gondii* (*T. Gondii*), a parasite transmitted primarily from cats, are shown as candidates for environmental risk factors for schizophre-

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What is known on this subject?

- Although the etiopathogenesis of schizophrenia is not fully known, it is thought that microorganisms may play important roles in the etiopathogenesis of the disease.

What is the contribution of this paper?

- When literature data were examined, the limitation in the number of studies examining the possible relationship between cytomegalovirus and schizophrenia was remarkable. The aim of this study is to examine this relationship in terms of biological psychiatry and contribute to national and international literature.

What is its contribution to the practice?

- Microbiological tests may be used in a wider scope together with the clarification of etiopathogenesis in people followed up with a schizophrenia diagnosis.

nia.[2] These pathogens are claimed to be environmental risk factors for schizophrenia and also have common characteristics such as a relatively slow proliferation and the ability to be virtually invisible from the immune system with special mechanisms to create latent infections.[10] For this reason, it is thought that the primary and/or latent infections of these pathogens can affect important CNS functions and neurodevelopmental processes.

CMV is a β-herpes virus only seen in humans and can only be transmitted via direct contact (saliva, blood, semen, vaginal secretion, breast milk). Infection rates increase with age and the CMV infection rate is, similar to schizophrenia, reported to be higher in low socioeconomic groups.[11] The primary infection of CMV is generally asymptomatic. In the latent infection following primary infection, the virus is hidden from the immune system and is generally kept under control by cytokines and continues its presence throughout life.[12] CMV, a neurotrophic virus, is known to have an affinity for the limbic system, one of the areas of the brain that is thought to be affected in patients with schizophrenia.[13] For this reason, it is thought that latent CMV infection plays an important role in the etiology of schizophrenia and an increase in CMV antibodies have been detected in schizophrenic patients.

Detailed investigation of the underlying mechanisms in schizophrenia gains more and more importance due to the worldwide increase in the prevalence of schizophrenia, risk factors of the disease and uncertainty etiology. In this study, CMV IgG antibody levels in patients diagnosed with schizophrenia and psychiatrically healthy individuals were examined comparatively to investigate the possible relationship between latent CMV infection and increased risk of schizophrenia.

Materials and Method

Sample

This case control study included 274 cases (134 schizophrenia patients and 140 healthy controls) between the ages of 18 and 61 years. The study was approved by the Istanbul Aydın University Clinical Research Ethics Committee with the decision number B.30.2.AYD.0.00.00-480.2/217.

Schizophrenia Group

A total of 134 patients diagnosed with schizophrenia according to DSM-5 that completed their acute treatment at Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Department of Mental Health and Diseases, and who were followed up with maintenance treatments and agreed to participate in the study orally and in writing, were included. Exclusion criteria were as follows: being under 18 or over 65 years of age, having an additional psychiatric diagnosis, using medications for any physical illness, dementia or the presence of a physical disease affecting the CNS, a history of head injury that caused loss of consciousness, mental retardation, language problems that would prevent speaking/understanding, a history of alcohol or substance abuse in the past year and not being able to give informed consent.

Health Control Group

Healthy controls were included in the study to compare CMV IgG seroprevalence with the schizophrenia group. Inclusion criteria for the healthy controls were as follows: being between 18 and 65 years of age, not having a psychiatric diagnosis themselves or a first-degree relative, not having used psychiatric medications, including antidepressants and not having received a neurological diagnosis. A total of 140 healthy volunteers fulfilling these criteria were included in the study with appropriate age and gender distribution. Patients and volunteers who agreed to participate in the study, were informed about the study and signed the volunteer consent form.

Sociodemographic and Clinical Data Form

The sociodemographic and/or clinical data form was completed for the included 274 participants. Sociodemographic data such as age, sex, marital status, educational status, profession, family type, place of residence and economical status of all participants were recorded. For the schizophrenia patients, the clinical data form was used to record data such as medication regimen, time since diagnosis and psychiatric diagnosis status in first degree relatives.

Suicide Behaviors Questionnaire (SBQ)

The risk of suicide of the patients was determined with the Suicide Behaviors Questionnaire (SBQ), containing four questions. The first question evaluates past suicide history based on determining suicide plans and attempts with six options, the second suicidal thoughts with five options, the third suicide threat with two options and the fourth repeatability of suicide with five options. A score of ≥7 was evaluated as suicidal risk for the healthy control group and a score of ≥8 was evaluated as suicidal risk for the schizophrenia group and/or participants, who were determined to have shown suicidal behavior.[14]

Table 1. Sociodemographic characteristics and SBQ scores of the groups

	Healthy controls (n=140)	Schizophrenia (n=134)	Total (n=274)
Sex, n (%)			
Female	69 (49.3)	70 (52.2)	139 (50.7)
Male	71 (50.7)	64 (47.8)	135 (49.3)
Age, mean±standard deviation (min.-max.)	28.54±0.73 (18–59)	33.21±0.9 (18–61)	30.82±0.59 (18–61)
Educational status, n (%)			
None	7 (5)	7 (5.2)	14 (5.1)
Primary school	19 (13.6)	53 (39.6)	72 (26.3)
Middle school	59 (42.1)	57 (42.5)	116 (42.3)
Undergraduate	55 (39.3)	17 (12.7)	72 (26.3)
SBQ total score, mean±standard deviation (min.-max.)	5.32±2.72 (3–15)	7.28±3.2 (3–16)	6.27±3.12 (3–16)

SBQ: Suicide Behaviors Questionnaire.

Measurement of CMV IgG Levels

Venous blood samples from all participants were collected into 5 mL vacutainer tubes using the standard blood collection apparatus with aseptic techniques. The blood samples collected were centrifuged at 2000 rpm for 10 minutes and the serum samples obtained were transferred to 2 mL Eppendorf tubes. Serum samples were stored at -20°C until analysis. CMV IgG levels were determined according to the manufacturer's recommendations with Chemiluminescence ELISA (Enzyme-Linked Immunosorbent Assay) method by using the Diagnostic Automation, Inc. Chemiluminescence CMV IgG (Calabasas, CA, USA) kit, which sensitivity and specificity ratios were reported as 97% and 98% respectively.

Statistical Analyses

Conformity of continuous variables to normal distribution was checked by Shapiro-Wilk test and homogeneity of group variances was checked by Levene test. The mean of two independent groups in terms of variables that meet the prerequisites of the parametric tests were compared with the Student's t-test. The group means of variables that do not meet the prerequisites of the parametric tests were compared with Mann Whitney-U test. Categorical variables were evaluated with Fisher's exact test. IBM SPSS Statistics for Windows, Version 19.0 (SPSS 19, Armonk, NY: IBM Corp.) program was used in data analysis. P>0.05 was considered statistically significant.

Results

A total of 274 participants, 139 women (50.7%) and 135 men (49.3%) were included in the study. The patients were aged between 18 and 61 years and the mean age was 30.82±0.59 years. Of the participants 14 were illiterate (5.1%), 72 (26.3%) were primary school graduates (26.3%), 116 were middle school graduates (42.3%) and 72 were undergraduates (26.3%). The total SBQ score for all participants was calculated as 6.27±3.12, as 5.32±2.72 for the healthy control group and as 7.28±3.2 for the schizophrenia group. Table 1 shows the descriptive statistical data regarding gender, age, educational level and SBQ score distributions of the participants.

Table 2. Relationship between CMV IgG seroprevalence and the relationship between group and suicide risk

	CMV IgG seroprevalence n (%)		p value
	Negative	Positive	
Group			
Healthy controls	72 (51.4)	68 (48.6)	<0.001
Schizophrenia	25 (18.7)	109 (81.3)	
Suicide risk			
No	70 (38.5)	112 (61.5)	0.137
Yes	27 (29.3)	65 (70.7)	

CMV: Cytomegalovirus.

CMV IgG levels in serum samples obtained from participants were determined by Chemiluminescence ELISA method in accordance with the manufacturer's recommendations and Samples were evaluated as seronegative and seropositive for CMV IgG according to the number of antibodies (IU/mL). The general CMV IgG seropositivity in the study samples was 64.6% (177/274). It was determined that CMV IgG seropositivity rates were distributed as 48.6% (68/140) in the healthy control group and 81.3% (109/134) in the schizophrenia group and that the relationship between the diagnosis of schizophrenia and CMV IgG seropositivity, when compared with the healthy control group, is highly statistically significant (p<0.001). CMV IgG seroprevalence of the participants was compared with suicide risk and CMV IgG was seropositive in 61.5% (112/182) of the participants without suicide risk and in 70.7% (65/92) of the participants who were determined to have suicide risk. The relationship between CMV IgG seropositivity and suicide

risk was not found statistically significant (p=0.137). Table 2 presents data showing the relationship between the participants' CMV IgG seroprevalence and suicide risk.

Discussion

In this study, CMV IgG positivity was found to be 48.6% in the psychiatrically healthy control group and 81.3% in the patient group diagnosed with schizophrenia. The relationship between CMV IgG positivity and schizophrenia diagnosis was found to be highly statistically significant (p<0.001). The relationship between CMV IgG positivity and SBQ scores of the participants was found to be 61.5%. However, since 70.7% of the participants were evaluated as having suicide risk, the relationship was not found to be statistically significant (p=0.137).

In a review of 14 studies conducted on a similar basis, it was reported that there was no difference in terms of CMV IgG levels between the schizophrenia patient and control groups. However, in this review examining older studies (1973–1992), the authors stated that in the studies, CMV IgG was investigated using methods with low sensitivity, the schizophrenia group was not sufficiently structured according to current information and that this may be the reason why no relationship was found between schizophrenia and CMV IgG.[15] In studies carried out as of 2015 it was reported that CMV infection is related to schizophrenia, affective disorder, a decrease in cognitive functions and suicide risk.[16–18] In addition, a case-control study with 81,912 cases carried out in Denmark in 2019 reported that CMV was statistically related to the state of having any psychiatric illness.[19] In a study reporting a new single nucleotide polymorphism (SNP) detected in schizophrenia, it was stated that this SNP reported for schizophrenia is related to CMV infection - especially maternal - and environmental genetic studies with specification on CMV infection are needed in elucidating the etiology of schizophrenia.[20]

Studies reporting that antipsychotics, used in the maintenance of schizophrenia also reduce CMV replication, and antiviral agents used in the treatment of CMV also regress symptoms related to schizophrenia strengthened the possible relationship between CMV and schizophrenia. A study evaluated 65 schizophrenia patients with clinical follow-up, who received valacyclovir for 16 weeks. Of the 65 patients, 21 were CMV IgG seropositive and as a result of the 16-week valacyclovir treatment, it was reported that there was a statistically significant (p<0.05) improvement in the overall scores of the positive and negative syndrome scale (PANSS).[21] A double-blind and prospective study was designed based on CMV infection increasing cyclooxygenase-2 (COX-2) and the correlation between infection and schizophrenia. This study included a total of 50 schizophrenic patients with acute exacerbation and while half of the patients received risperidone and celecoxib (Selective COX-2 inhibitor), the other half received risperidone and placebo. The authors reported that a decrease in the PANSS scores of all groups was achieved after treatment. However, compared to the group receiving risperidone and placebo, the decrease in the total PANSS score was higher in the group receiving risperidone and celecoxib and this difference was found to be statistically significant.[22]

Some studies reported that there might be a relationship between inflammatory processes, such as infectious agents, and suicide. In a study carried out in Turkey with a healthy group of students with no psychiatric diagnosis, it was reported that impulsive behaviors such as suicide risk and bodily harm are particularly associated with *Toxoplasma gondii* parasite (p<0.001).[23] In this case-control study no statistically significant relationship was found between CMV IgG positivity and suicide risk (p=0.137). However, in a cohort study of 2018 with 1,292 patients with different psychiatric diagnoses (733 schizophrenia, 483 bipolar disorder and 76 major depression), a possible correlation between CMV, HSV-1, EBV, HHV-6 and *Toxoplasma gondii* IgG antibodies and suicide was investigated and only the relationship between increased CMV IgG antibody levels and death due to suicide was found to be highly statistically significant (p=0.002).[24] In a cross-sectional study carried out in America with a total of 162 psychiatrically diagnosed cases (65 schizophrenia, 59 bipolar disorder and 38 major depression), of which 72 had a suicide history and 90 did not, a statistically significant relationship was reported between CMV IgM levels and suicide risk (p=0.011). However, the relationship between CMV IgG levels and suicide risk was not found to be statistically significant (p>0.05).[16] The reason for the relationship observed between CMV and suicide risk can be explained by direct mechanisms such as neurotropic microorganisms having the ability to increase dopamine and other neurotransmitter levels or indirect mechanisms such as increasing immune system toll-like receptor activities in response to CMV infection.[25]

Conclusion

Despite controversial data on the subject, there is a potential correlation between CMV, known to be a neurotropic virus, and schizophrenia as well as many other psychiatric diseases. An unsuccessful suicide attempt, which is the biggest risk factor for suicidal behavior is an important cause of death worldwide and is common in those with psychiatric illness. Although the risk of suicide can be estimated by scales such as SBQ, reliable biomarkers indicating this risk are not yet available. Therefore, it is thought that long prospective based research using molecular methods and involving more cases are needed to predict a multifactorial psychiatric disease such as schizophrenia and difficult to predict behaviors such as suicide attempt.

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terpretation – Ö.A.; Literature search – Ö.A., Ö.F.D.; Writing – Ö.A., Ö.F.D.; Critical review – Ö.A., Ö.F.D.

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