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Association Between Cytomegalovirus Infection and Obsessive-Compulsive Disorder: A Serological, Molecular and Cytokine-Based Study

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Abstract

Background. Cytomegalovirus (CMV), a member of the Herpesviridae family (subfamily Betaherpesvirinae), is highly prevalent worldwide (seroprevalence 45-100%) and can cause severe disease in immunocompromised hosts. Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder affecting at least 2% of the population, in which immune dysregulation has been implicated.

Objective. To investigate the association between CMV infection and OCD using serological, cytokine, and molecular markers.

Methods. Ninety Iraqi participants were enrolled: 60 OCD patients (40 females, 20 males) and 30 healthy controls, aged 20-60 years. CMV-specific IgG, IgM, PP65 antigen, IL-6, and TNF-α were measured by ELISA, and CMV DNA was detected by real-time PCR of the UL83 (PP65) gene.

Results. OCD patients showed significantly higher positivity than controls for CMV IgG (96.67% vs 56.67%), IgM (75.00% vs 20.00%), and PP65 antigen (90.00% vs 16.67%) (P = 0.000). IL-6 (191.28 ± 74.03 vs 14.33 ± 8.22) and TNF-α (581.26 ± 90.01 vs 45.10 ± 16.10) were markedly elevated, and CMV DNA was detected in 45% of patients versus none of the controls (P = 0.000). No significant associations were found with gender or occupation.

Conclusions. CMV infection and the accompanying immune activation are significantly associated with OCD, consistent with Khanna et al. (1997), suggesting that CMV-induced immune dysregulation may contribute to OCD pathogenesis.

1. Introduction

Human cytomegalovirus (CMV) is a member of the *Herpesviridae* family and is considered one of the most widespread viral infections affecting humans. Although infection is often asymptomatic in healthy individuals, CMV may cause serious complications in people with weakened immune systems, such as transplant recipients, patients receiving immunosuppressive therapy, and infants infected during pregnancy [1]. CMV infection is widely distributed across the world, and studies have reported that the proportion of individuals with CMV antibodies varies considerably between populations, ranging from about 45% to almost 100% [2]. After the primary infection, CMV persists in a latent form within the host and can reactivate later, particularly when immune defenses become weakened. Transmission occurs through contact with CMV-infected body fluids during both initial infection and periods of reactivation. CMV infections are usually asymptomatic in immunocompetent hosts but may cause life-threatening complications in immunocompromised individuals [3].

Congenital CMV infection is a major cause of nerve damage in children, leading to growth retardation, hearing loss, permanent disability, and microcephaly. In immunocompromised patients, CMV can cause severe infections such as fever, hepatitis, pneumonitis, encephalitis, and retinitis [4]. In addition, people with higher CMV antibody titers have been reported to exhibit higher levels of depression and anxiety [5].

Obsessive-compulsive disorder (OCD) is a chronic and disabling psychiatric condition that affects nearly 2% of the global population and contributes significantly to the burden of mental-health disorders. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), OCD is characterized by the presence of persistent intrusive thoughts, urges, or images (obsessions) accompanied by repetitive behaviors or mental acts (compulsions) performed to relieve anxiety or distress [6]. Neurobiological investigations have indicated that abnormalities in specific brain regions play an important role in the pathophysiology of OCD. Functional neuroimaging studies have consistently demonstrated altered activity within the orbitofrontal cortex, anterior cingulate cortex, and basal ganglia, which are key structures involved in emotional regulation and behavioral control [7].

In addition to neurobiological mechanisms, genetic and immunological factors have also been suggested to influence the development of OCD. Several genetic studies have reported associations with genes involved in neurotransmitter systems such as dopamine, serotonin, and glutamate. Furthermore, alterations in immune-related pathways, including transforming growth factor-β (TGF-β) and components of the complement system, have been implicated in the disorder [8]. Immunological abnormalities have also been reported in patients with OCD, including an increased frequency of certain human leukocyte antigen (HLA) alleles such as HLA-DR4, suggesting that immune dysregulation may contribute to disease susceptibility [9]. Previous studies have explored the potential association between viral infections and psychiatric disorders; for example, elevated IgG antibody levels against several viruses, including herpes simplex virus-1, CMV, varicella-zoster virus, measles, and mumps, have been reported in patients with OCD compared with healthy individuals [10]. These findings support the hypothesis that infectious agents may play a role in the pathogenesis of OCD. Therefore, the present study aimed to investigate the possible relationship between CMV infection and obsessive-compulsive disorder.

2. Materials and Methods

2.1 Collection of Samples

This study was conducted on patients diagnosed with obsessive-compulsive disorder (OCD). Samples were collected from the Educational Laboratories at Medical City Hospital, Baghdad, Iraq, between April and July 2020. A total of 90 individuals were enrolled, including 60 OCD patients and 30 healthy controls. Ethical approval was obtained from the hospital, and informed consent was obtained from all participants. All patients were diagnosed clinically by a consultant psychiatrist based on clinical evaluation and biochemical examination. Demographic and clinical information was obtained through direct interview. Plasma samples were separated by centrifugation and stored at -20 °C until analysis.

2.2 Serological and Biochemical Assays

2.2.1 Detection of CMV IgG and IgM

Anti-cytomegalovirus IgG and IgM antibodies were measured using a commercial ELISA kit (Cusabio, USA). All reagents and samples were brought to room temperature before use, and samples were centrifuged again after thawing. The number of wells was determined and a blank well was included. The assay was performed according to the manufacturer's instructions.

2.2.2 Detection of CMV PP65 Antigen

The CMV PP65 antigen was detected using a qualitative ELISA kit (Cusabio, USA). All reagents and samples were allowed to reach room temperature (18-25 °C) for 30 min prior to analysis. The microplate and reagents were checked to ensure correct labeling and integrity. The assay was performed according to the manufacturer's protocol.

2.2.3 Measurement of IL-6 and TNF-α

Serum interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured using commercial ELISA kits (Cusabio, USA). All reagents and samples were prepared and processed according to the manufacturer's instructions.

2.3 Molecular Detection of CMV

2.3.1 Viral DNA Extraction

Viral DNA was extracted from plasma samples using the gSYNC DNA Extraction Kit (Geneaid, USA) according to the manufacturer's protocol.

2.3.2 DNA Quantification

The concentration and purity of the extracted DNA were assessed using a NanoDrop spectrophotometer (Thermo Scientific, USA) by measuring absorbance at 260/280 nm.

2.3.3 Real-Time PCR Amplification

Real-time PCR was performed to detect human cytomegalovirus DNA based on amplification of the UL83 (PP65) gene using the method described by Gault et al. (2001). The primers used are listed in Table 1.

Table 1. Primers used for amplification of the CMV UL83 (PP65) gene

Primer	Sequence (5'-3')	Tm	Product size
UL83 gene (F)	TACAAGCGATACGCGAGACC	65 °C	137 bp
UL83 gene (R)	GATGCGATACTGGCTGGTGA		

Reference sequence: Human herpesvirus-5 strain TR tegument protein pp65 (UL83) gene, complete cds — GenBank: KJ743149.1.

2.3.4 qPCR Reaction Mixture

The qPCR master mix was prepared using Real MOD Green SF 2× qPCR Mix according to the manufacturer's instructions, as shown in Table 2.

Table 2. Components of the qPCR reaction mixture

PCR master mix	Volume
DNA template	5 µL
Forward primer (10 pmol)	1 µL
Reverse primer (10 pmol)	1 µL
qPCR master mix	10 µL
qPCR water	3 µL
Total volume	**20 µL**

2.3.5 Thermal Cycling Conditions

Table 3. Real-time PCR thermocycler conditions

Step	Condition	Cycles
Pre-denaturation	95 °C, 5 min	1
Denaturation	95 °C, 20 s	40
Annealing/Extension	60 °C, 30 s	
Detection (scan)	—	
Melt cycle	65-90 °C	

2.3.6 Data Analysis

Real-time PCR data were analyzed by calculating the threshold cycle (CT) value, which represents the cycle number at which a positive amplification signal was detected. Statistical analyses of serological and cytokine data were performed using the chi-square test for categorical variables and the t-test (with LSD for multiple groups) for continuous variables; a P-value ≤ 0.05 was considered significant.

3. Results

3.1 Serological Detection of CMV (IgG, IgM, and PP65)

The serological markers of cytomegalovirus infection (IgG, IgM, and PP65 antigen) were evaluated in 60 OCD patients and 30 healthy controls. A significantly higher seropositivity rate was observed in OCD patients for all CMV markers compared with healthy individuals. CMV-IgG was detected in 96.67% of patients versus 56.67% of controls; CMV-IgM in 75.00% versus 20.00%; and CMV-PP65 antigen in 90.00% versus 16.67%. These differences were statistically significant (P = 0.000) (Table 4).

Table 4. Seropositivity of CMV IgG, IgM, and PP65 in OCD patients and healthy controls

Marker	Group	Positive	Negative	χ^2	P-value
IgG	Patients (n=60)	58 (96.67%)	2 (3.33%)	23.04	0.000*
	Healthy (n=30)	17 (56.67%)	13 (43.33%)		
IgM	Patients (n=60)	45 (75.00%)	15 (25.00%)	24.63	0.000*
	Healthy (n=30)	6 (20.00%)	24 (80.00%)		
PP65	Patients (n=60)	54 (90.00%)	6 (10.00%)	47.63	0.000*
	Healthy (n=30)	5 (16.67%)	25 (83.33%)		

** P-value ≤ 0.05 considered significant.*

3.2 Effect of Gender on CMV Serological Markers

The distribution of CMV IgG, IgM, and PP65 according to gender is presented in Table 5. No statistically significant differences were observed between male and female OCD patients for any CMV marker.

Table 5. CMV IgG, IgM, and PP65 according to gender in OCD patients

Marker	Male (n=20) Positive	Female (n=40) Positive	Negative (M / F)	P-value
IgG	20 (100%)	38 (95.00%)	0 / 2 (5.00%)	0.309
IgM	15 (75.00%)	30 (75.00%)	5 (25%) / 10 (25%)	1.00
PP65	18 (90.00%)	36 (90.00%)	2 (10%) / 4 (10%)	0.741

** P-value ≤ 0.05 considered significant.*

3.3 Effect of Occupation on CMV Serological Markers

The relationship between CMV serological markers and occupation (students, employees, and others) was evaluated (Table 6). Although slight variations were observed, no significant differences were found among occupational groups.

Table 6. CMV IgG, IgM, and PP65 positivity according to occupation in OCD patients

Marker	Students (n=20)	Employees (n=28)	Others (n=12)	P-value
IgG	20 (100%)	26 (92.86%)	12 (100%)	0.307
IgM	13 (65.00%)	24 (85.71%)	8 (66.67%)	0.199
PP65	19 (95.00%)	25 (89.28%)	10 (83.33%)	0.559

*Values are positive cases, n (%). * P-value ≤ 0.05 considered significant.*

3.4 Serum IL-6 and TNF-α Levels in Patients and Controls

Serum IL-6 and TNF-α concentrations were significantly higher in OCD patients compared with healthy controls. IL-6 levels were markedly elevated in patients (P = 0.000), as were TNF-α levels (P = 0.000) (Table 7).

Table 7. Serum IL-6 and TNF-α levels in OCD patients and healthy controls

Parameter	Patients (n=60), M ± SD	Healthy (n=30), M ± SD	t-value	P-value
IL-6	191.28 ± 74.03	14.33 ± 8.22	13.01	0.000*
TNF-α	581.26 ± 90.01	45.10 ± 16.10	20.44	0.000*

** P-value ≤ 0.05 considered significant.*

3.5 Effect of Gender on IL-6 and TNF-α

No statistically significant differences were found between male and female OCD patients with regard to IL-6 and TNF-α levels (Table 8).

Table 8. IL-6 and TNF-α levels according to gender in OCD patients

Parameter	Male (n=20), M ± SD	Female (n=40), M ± SD	t-value	P-value
IL-6	188.55 ± 55.33	192.65 ± 73.77	0.20	0.660
TNF-α	620.15 ± 90.01	561.82 ± 88.20	-1.49	0.593

*df = 58. * P-value ≤ 0.05 considered significant.*

3.6 Effect of Occupation on IL-6 and TNF-α

IL-6 and TNF-α levels did not differ significantly among students, employees, and other occupational groups (Table 9).

Table 9. IL-6 and TNF-α levels according to occupation in OCD patients

Parameter	Students, M ± SD	Employees, M ± SD	Others, M ± SD
IL-6	193.95a ± 72.99	196.18a ± 71.89	176.91a ± 73.98
TNF-α	575.42b ± 89.70	566.92b ± 88.00	623.91a ± 90.01
LSD	IL-6 = 55.58	TNF-α = 35.94	

Different superscript letters within a row indicate a statistically significant difference; the same letter indicates no significant difference.

3.7 Molecular Detection of CMV by Real-Time PCR

Real-time PCR analysis targeting the CMV UL83 (PP65) gene demonstrated amplification in OCD patient samples, whereas no amplification was observed in healthy controls (Fig. 1). CMV DNA was detected in 45% of OCD patients, while all healthy controls were negative; the difference between patients and controls was statistically significant (P = 0.000) (Table 10).

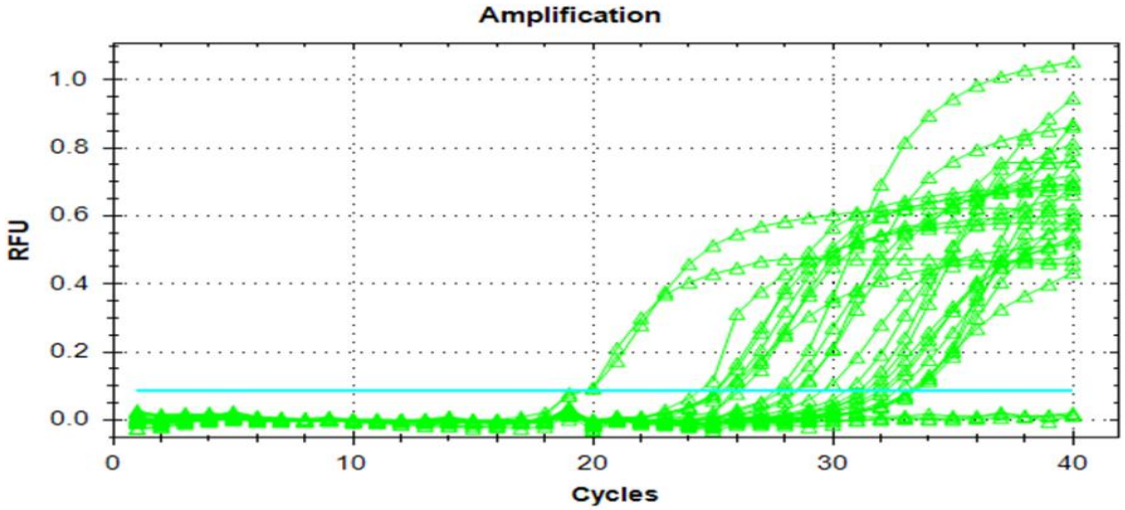

Fig. 1. Real-time PCR amplification curve of the CMV UL83 gene.

Table 10. CMV DNA detection by real-time PCR in OCD patients and healthy controls

Group	N	Positive	Negative	P-value
Patients	60	27 (45.00%)	33 (55.00%)	0.000*
Healthy	30	0 (0%)	30 (100%)	
χ^2 = 19.28				

** P-value ≤ 0.05 considered significant.*

4. Discussion

Khanna et al. (1997) examined IgG antibodies against measles, mumps, varicella-zoster virus, cytomegalovirus (CMV), and herpes simplex virus-1 in 76 individuals with obsessive-compulsive disorder (OCD) and compared them with healthy controls, noting that the titers of various viral antibodies were noticeably higher and implying that viral infections might play a part in the pathophysiology of OCD. The current study therefore sought to examine the connection between OCD and CMV infection.

The study included 60 OCD patients and 30 healthy controls. Serological and molecular methods were used to assess CMV-specific IgG, IgM, PP65 antigen, IL-6, TNF-α, and CMV DNA levels. OCD patients had considerably greater levels of IgG, IgM, and PP65 than controls, indicating increased exposure to or reactivation of CMV in OCD. Lachmann et al. (2018) reported that CMV seroprevalence is higher in women than in men; however, in the present study no significant difference was observed between sexes, which may be due to differences in sample size and population characteristics.

Phillips et al. (2008) demonstrated that higher CMV-specific IgG titers are associated with increased symptoms of depression and anxiety. In agreement with these findings, the present study showed significantly elevated CMV antibody titers in OCD patients, suggesting a possible role of CMV in psychiatric symptoms. Human CMV is known to target cell-cycle regulation, transcription, and immune modulation, thereby optimizing the cellular environment for viral replication (Baillie et al., 2003). CMV infection has also been shown to impair TNF-receptor signaling and to activate TNF-α expression, leading to immune dysregulation and inflammatory responses.

Li et al. (2014) conducted a 12-year longitudinal study assessing anti-CMV IgG, CMV DNA, and IL-6 levels in older women, and discovered that those with detectable CMV DNA had noticeably greater IL-6 levels. In the present study, patients with detectable CMV DNA likewise had greater IL-6 levels, although this difference was not statistically significant, most likely because of variations in the patient group and study design. Notably, CMV-DNA-negative patients had considerably higher CMV-IgG levels, suggesting recent or reactivated infection.

Konuk et al. (2007) found that TNF-α and IL-6 levels in OCD patients were noticeably higher than those of healthy controls. Likewise, the current study showed that OCD patients had significantly higher levels of both cytokines. These results lend credence to the idea that inflammatory processes and immunological dysregulation are key components of OCD pathogenesis.

Real-time PCR was used in this study to detect CMV DNA. This technique allows sensitive detection of low viral loads and is useful for monitoring disease and therapeutic response (Caliendo et al., 2001). Although CMV is a cell-associated virus, viral DNA can be detected in plasma and serum (Tedder et al., 2002). The molecular results of the present study showed a significant association between CMV DNA and OCD. Differences between the PCR and serological results can be explained by viral latency, during which CMV DNA may be difficult to detect while IgG antibodies remain elevated and reflect previous infection (El Sanousi et al., 2016). Overall, the present findings provide evidence that CMV infection and immune activation may contribute to the development or progression of OCD.

5. Conclusion

Cytomegalovirus is a common viral infection that persists for life after initial exposure. While CMV is normally asymptomatic in healthy people, it can cause considerable immunological activation, especially in immunocompromised hosts. Obsessive-compulsive disorder is a persistent mental condition with multiple causes, including genetic, neurobiological, and immunological aspects.
In this study, both serological and molecular methods were used to investigate the association between CMV and OCD. Significant increases in CMV-specific IgG, IgM, and PP65 antigen, elevated IL-6 and TNF-α levels, and the presence of CMV DNA were observed in OCD patients compared with healthy controls; no significant associations were found with gender or occupation. These findings indicate a significant association between CMV infection and OCD, suggesting that CMV-induced immune dysregulation may play a role in OCD pathogenesis. Further studies with larger populations and longitudinal designs are recommended to clarify the causal relationship.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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