Prevalence rate of cytomegalovirus infection in individuals with and without systemic lupus erythematosus

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Abstract

Background: The role of cytomegalovirus (CMV) infection in triggering or exacerbating systemic lupus erythematosus (SLE) remains a subject of debate. The aim of this study was to compare the prevalence rate of CMV infection between individuals with and without SLE.

Materials and Methods: This cross-sectional comparative study recruited 52 consecutive patients with SLE (based on the criteria determined by the Systemic Lupus Collaborating Clinics, 2012) and 52 healthy subjects. The exclusion criteria were immunodeficiency and other background diseases. CMV infection was assessed according to serology (enzyme-linked immunosorbent assay) and polymerase chain reaction (PCR).

Results: Immunoglobulin G (IgG) was positive in all participants. Immunoglobulin M (IgM) was positive in eight SLE patients (15.4%) and none of the controls (p = 0.003). The PCR was positive in four SLE patients (7.7%) and none of the controls (p = 0.041). IgM level was not related to age, gender, literacy, marital status, family history, SLE disease activity index (SLEDAI), or duration of the disease (p > 0.05).

Conclusion: According to this study, CMV infection was higher in SLE patients but was not related to the type of organ involvement, type of immunosuppressive drug, or SLEDAI.

Keywords: Cytomegalovirus, Systemic lupus erythematosus, Infection
Introduction
Systemic lupus erythematosus (SLE) is a rheumatologic disease leading to functional disability in 6.2% of cases (1). Like any other autoimmune disorder, the onset of SLE depends on both genetic and environmental factors. In recent decades, some researchers have suggested viral infections to be involved in the etiology of SLE. They also reported the potential of viruses to increase morbidity and mortality rates in patients with lupus (2-4). Recent evidence has highlighted the etiological role of retroviruses, such as human endogenous retroviruses (ERV), in the development of SLE (4,5). Some viruses, e.g. cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19, have also been found to trigger the exacerbation of SLE (3,6,7).

CMV infection has been linked with the risk of many autoimmune diseases such as multiple sclerosis (MS), SLE, systemic sclerosis, and rheumatoid arthritis (8). Several features of CMV, including its ability to manipulate adaptive and innate immune functions [9-12], large coding capacity [13], lytic replication in multiple tissues [14], and lifelong persistence during subsequent phases of latency and reactivation, along with its high prevalence in human populations, could explain its frequently identified association with not only some autoimmune disorders like SLE, but also further acquired disorders like arteriosclerosis [15], immune aging [16], and a few types of tumors [17]. Several reports have indicated the possible role of CMV infection in the onset or exacerbation of SLE, but have failed to clarify its exact role. Since the two diseases share similar manifestations, it is difficult to determine whether the symptoms are caused by CMV infection or the exacerbation of SLE. Despite the absence of definite evidence of the association between CMV and SLE, previous reports studies have suggested that CMV pp65 subfragment peptide is highly immunogenic and can elicit the production of antibodies that cross-react with nuclear proteins and could be pathogenic in genetically susceptible individuals (18, 19). Therefore, this study was performed to compare the prevalence of CMV infection in individuals with and without SLE.

Materials and Methods
This cross-sectional comparative study recruited 52 consecutive SLE patients (diagnosed based on the criteria determined by the Systemic Lupus Collaborating Clinics, 2012) who were referred to the rheumatology clinic of Hazrat-e-Rasoul Hospital and 52 healthy individuals. The exclusion criteria were immunodeficiency and other background diseases. Age, gender, literacy, marital status, SLE disease activity index (SLEDAI), major organ involvement, type of treatment, and SLE duration were recorded in a specific form (20). The diagnosis of CMV infection was made by two methods, i.e. detection of anti-CMV antibodies by enzyme-linked immunosorbent assay (ELISA) and detection of CMV antigen by polymerase chain reaction (PCR), (Cytomegalovirus PCR Detection Kit, CinnaGen company, Iran). SLEDAI, a list of 24 clinical and laboratory items, was used for the measurement of disease activity. Helsinki Declaration was respected across the study and authors paid the costs. Chi-square and t test were applied for data analysis. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and p-values less than 0.05 were considered significant.

Results
The participants’ mean age was 36.63 ± 10.58 years (range: 20-65 years) in the SLE group and 37.55 ± 12.42 years (range: 20-58 years) in the control group (p = 0.684). Females constituted 80.8% and 76.9% of the SLE and control groups, respectively (p = 0.631). Immunoglobulin G (IgG) was positive in all participants of both groups. Immunoglobulin M (IgM) was positive in eight SLE patients (15.4%) and none of the controls (p = 0.003). The PCR was positive in four SLE patients (7.7%) and none of the controls (p = 0.041). IgM level was not related to age, gender, literacy, marital status, family history, disease activity (SLEDAI), and duration of the disease (p > 0.05). The mean SLEDAI was 7.12 ± 5.86 and 5.45 ± 4.32 in those with positive and negative IgM, respectively (p > 0.05). The mean disease duration was 5.37 ± 3.02 and 6.28 ± 4.49 years in those with positive and negative IgM, respectively (p > 0.05). As
shown in Tables 1 and 2, neither the type of treatment nor the type of organ involvement was related to IgM level (p > 0.05).

### Table 1. The relationship between the type of treatment and immunoglobulin M (IgM) level

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IgM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Yes</td>
<td>0.158</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0.347</td>
</tr>
<tr>
<td>Corticosteroid Pulse Therapy</td>
<td>Yes</td>
<td>0.387</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0.361</td>
</tr>
</tbody>
</table>

### Table 2. The relationship between main organ involvement and immunoglobulin M (IgM) level

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>IgM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Yes</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0.997</td>
</tr>
<tr>
<td>Kidney</td>
<td>Yes</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0.848</td>
</tr>
<tr>
<td>Brain</td>
<td>Yes</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0.992</td>
</tr>
<tr>
<td>Lung</td>
<td>Yes</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0.979</td>
</tr>
</tbody>
</table>

Discussion

A higher prevalence of CMV antibodies should be expected in SLE patients if CMV plays any causative role in the pathogenesis of SLE. Studies in different countries have yielded contradictory results in this regard. Compared to research in some other countries, European studies found a greater association between SLE and CMV seroprevalence (21-25).

In our study, IgG was positive in all 104 participants but IgM was significantly higher in the SLE group. PCR detected CMV DNA in 7.7% of the patients with SLE and none of the controls. The same finding was reported by some other studies. Rasmussen et al. found a higher rate of CMV infection in lupus patients (26).

In 2007, Barazilia et al. observed elevated CMV IgG titers in the sera of SLE patients (27). Berkun et al. concluded that cytomegalovirus IgM and Epstein-Barr virus early antigen IgG (but not other Epstein-Barr virus antigens) were significantly more prevalent in SLE patients than in controls (28). In another report, percentage of patients with human CMV-DNA copy number > 2.0 x 10^2 copies/ml was higher than this copy number in controls which as statistically significant(29).

Su et al. examined the serum samples of 87 patients with SLE and 97 patients with cerebrovascular accidents (CVA) (30) and found the prevalence of anti-CMV IgM to be significantly higher in the SLE group than in the CVA group. In another study, PCR showed the presence of CMV and EBV DNA in respectively 30.3% and 51.5% of SLE patients (31).

Contrary to the findings of the recent study, Su et al. showed that the severity of clinical features and SLEDAI scores were significantly higher in SLE patients with positive anti-CMV IgM compared to those with negative anti-CMV IgM (30). Another study reported higher morbidity and mortality in SLE patients with positive CMV pp65 antigenemia assay (32).

There are some reports about the relationship between CMV infection and the type of organ involvement in lupus patients. One study highlighted a relation between positive CMV and Raynaud’s phenomenon in lupus nephritis (33). Many case reports have also confirmed the association between CMV infection and hemophagocytic syndrome in lupus patients (34-36). Ramos-Casals et al. also reported CMV to be related to poor prognosis in patients with SLE (37). However, there were not any significant associations between CMV infection and type of organ involvement in our study. On the other hand, because of the similarity between lupus manifestations and CMV infection, it is difficult to determine whether the symptoms are due to CMV infection or the exacerbation of SLE.

Some studies have reported acute CMV infections in SLE patients. In 2008, Ramos-Casals et al. evaluated the impact of viral infections on the management on SLE patients and found 36 SLE patients who presented with organ-specific viral infections (mainly pneumonitis, colitis, retinitis, and hepatitis) (37).

In 2011, Kelkar et al. described a case of CMV retinitis in a patient with SLE on immunosuppression. Immunosuppressive therapy seems to be the leading cause of CMV reactivation in lupus patients (38).

Despite dissimilarities between the results of various studies, previous research generally confirms the link between lupus and CMV infection. Therefore, screening for CMV is suggested in all SLE patients. The screening may decrease the recurrence
rate and side effects of immunosuppressive drugs. Nevertheless, further studies with larger sample size and multi-center sampling are required to obtain more conclusive evidence.

Conflict of interest
Authors declare no conflict of interest.
References:


33. P. Stratta, C. Canavese, G. Ciccone et al., “Correlation between cytomegalovirus infection and Raynaud’s phenomenon in lupus...