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Proinflammatory Cytokine Profile in Cytomegalovirus Infection: Interplay Between IL-17 and TNF-α as Indicators of Immune Activation in a Case–Control Study

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Abstract
Background: Human cytomegalovirus (CMV) is a chronic viral infection that causes chronic immune activation and dysregulated cytokine signaling. In viral infections, proinflammatory cytokine plays a pivotal role in enhancing inflammatory cascades, and orchestrates host immune responses. may reflect the extent of immune activation and could also lead to the progression of diseases.
Objective: The aim of the present study was to critically assess the proinflammatory cytokine profile in CMV-infected females by measuring serum levels of IL-17, TNF-alpha, and C-reactive protein (CRP) and to determine their combined utility as biomarkers of systemic immune activation.
Methods: A case-control study was done on a sample of 60 female patients with a confirmed CMV infection (diagnosed by serological and/or molecular means) attending the Al-Sadr Teaching Medical City in Najaf, Iraq, and 30 healthy female controls. The study participants included 20-55 years of age. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum levels of IL-17, TNF-α, and CRP. All assays were performed in duplicate to provide analytical reliability. Statistical analysis was done with SPSS (version 25) and independent t-tests were used to compare groups and Pearson correlation was used to measure association between cytokines. A P-value < 0.05 was considered statistically significant.
Results: There was a significant increase in serum levels of IL-17, TNF-a and CRP in CMV infected patients relative to healthy individuals (P less than 0.0001). The significant rise in IL-17 levels reflects the activation of Th17-mediated immune pathways, which lead to the increased inflammatory signaling and recruitment of immune cells. Simultaneous up-regulation of TNF-a further enhances the inflammatory response, and supports the existence of a synergistic IL-17/TNF-a axis. Also, the CRP increase is an indicator of systemic inflammation and an engagement in the acute-phase response. It was found that there is a positive correlation between IL-17 and TNF-α levels indicating that proinflammatory signaling is coordinately regulated.
Conclusion: A strong and orchestrated proinflammatory immune response marked by high upregulation of IL-17, TNF-α and CRP is associated with CMV infection in females. The IL-17/TNF-α interaction is a critical (axis) that drives immune activation and can be a powerful biomarker of inflammatory status in CMV infection. These results have significant implications on CMV immunopathogenesis and the identification of possible targets that can be therapeutically modulated. To quantify their prognostic value and association with the severity of the disease, further longitudinal studies are justified.

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Keywords: CMV infection, IL-17, TNF- α, C-reactive protein, Immune activation biomarkers

Introduction

Human cytomegalovirus (CMV) is a ubiquitous 2 -herpesvirus that sets up life-long latency after primary infection and remains under constant immune surveillance. The world seroprevalence of CMV is between about 40 and over 90 depending on geographic, socioeconomic and demographic factors [1]. Despite the fact that immunocompetent individuals, growing evidence suggests that it has far-reaching and long-term implications on the host immune system and is associated with the persistence of immune activation and the onset of chronic low-grade inflammatory states [2].

The immunopathogenesis of CMV infection is complex and tightly regulated and is a dynamic interaction of both the innate and adaptive immune responses. The antiviral response is orchestrated by key components of the cellular system such as the natural killer (NK) cells, antigen-presenting cells and T lymphocytes [3]. However, CMV has evolved sophisticated immune evasion mechanisms, such as modulation of antigen presentation and interference with cytokine signaling pathways, which enable viral persistence and promote chronic immune stimulation [4]. Persistent immune activation may lead to dysregulated production of cytokines and can contribute to immunological imbalance.

Key contributors to the host response to CMV infection are proinflammatory cytokines. One of the most important regulators of inflammatory signaling is (TNF-α). It increases antiviral immunity by activating nuclear factor kappa B (NF-KB) pathways, enhances the recruitment of leukocytes, and promotes the clearance of infected cells. However, prolonged or excessive production of TNF-α has been associated with tissue damage, immune dysregulation and the exacerbation of chronic inflammatory diseases [5].

Another important critical proinflammatory cytokine that is involved in the host defense and immune modulation is IL-17 which is mainly secreted by Th17 cells. IL-17 stimulates neutrophils recruitment, and induces the expression of proinflammatory mediators, such as chemokines and cytokines. High levels of IL-17 have consistently been found in inflammatory diseases where they are correlated to disease severity and immune activation [6, 7]. The presence of amplified IL-17 expression has been linked with persistent immune activation and amplification of inflammatory signaling pathways in the context of viral infections like CMV [8].

Notably, IL-17 and TNF-α are closely coordinated and synergistic with each other. Their interaction promotes the transcription of proinflammatory genes, stabilizes inflammatory mRNA and amplifies downstream mediators, including interleukin-6 (IL-6), granulocyte-macrophage colony-stimulating factor (GM-CSF) and matrix metalloproteinases. This synergistic signaling constitutes a self-sustaining inflammatory loop, which can lead to prolonged immune activation and tissue damage in case of chronic viral infections [9, 10]. Thus, the study of the IL-17/TNF-α axis can be taken as the important consideration of the molecular mechanisms of the immunodulatory effect of CMV.

Along with the cytokines, CRP is a well-established acute-phase reactant synthesized by the liver in response to inflammatory stimuli, specifically IL-6. CRP is a sensitive biomarker of systemic inflammation and is an indicator of the strength of the host inflammatory response. High levels of CRP have been commonly observed in infectious and inflammatory diseases and can indicate continued immune activation during CMV infection [11].

Notably, sex-specific differences in immune responses have been increasingly recognized as important determinants of disease pathogenesis. Females usually have stronger immune responses, in part due to hormonal effects of estrogen which regulates the production of cytokines and Th17 differentiation [12, 13]. This increased immune responsiveness could affect the strength of cytokine responses in CMV infection and is the subject of particular study.

Although there is increasing interest in CMV-associated immune deregulation, the inter-relationship among IL-17, TNFα, and systemic inflammatory responses such as CRP especially within coordinated cytokine networks-remains inadequately characterised [14, 15]. A holistic assessment of these biomarkers can further give a more precise depiction of immune activation and inflammatory load in CMV infection. Thus, to evaluate and compare the profile of proinflammatory cytokines between CMV-infected females and non-infected individuals by measuring serum levels of IL-17, TNF-α, and CRP, as well as to examine the interactions between IL-17 and TNF-α as the possible indicators of the host immune activation.

Study Design and Setting

The case control study was a hospital-based study conducted in the Al-Sadr Teaching Medical City which is a major tertiary healthcare facility in Najaf, Iraq during the study period. The study population was limited to the female subjects that visited the hospital to undergo clinical assessment.

Study Population

This study enrolled a total of 90 female subjects, aged between 20-55 years and split into two cohorts. The number of patients in the sample was 60 females with proven infection of cytomegalovirus (CMV), and 30 apparently healthy females without any history of infectious or chronic illnesses. The members of the two groups were as closely matched in terms of age as possible in order to reduce the chances of confounding factors.

Inclusion and exclusion criteria.

Qualified participants were female patients of 20-55 years with proven cytomegalovirus (CMV) infection as evidenced by serological tests of CMV-specific IgM antibodies. Informed consent was obtained written informed consent before enrollment.

Participants were not eligible to participate when they had evidence of co-infections (viral, bacterial or parasitic), a history of chronic inflammatory or autoimmune diseases, or they were taking immunosuppressive or anti-inflammatory medications. Also, pregnant women and those with known endocrine or systemic disorders that could affect immune responses were not included in the study.

Sample Collection and Processing

Each participant was sampled under aseptic conditions and about 5 mL of the venous blood was collected. The samples were left to clot at room temperature then centrifuged at 3000 rpm and 10 minutes to separate serum. To maintain the stability of biomarkers, the obtained serum was aliquoted and stored at -20 o C until further analysis.

Immunological Measures.

In all participants, serum levels of IL-17, TNF -α, and CRP were measured. All the analytes were measured in compliance with the instructions of the manufacturer using commercially available enzyme-linked immunosorbent assay (ELISA) kits. The optical density was read with a microplate reader calibrated, and the concentrations of the biomarkers were calculated using standard calibration curves. Each sample was analyzed in two copies and proper internal quality control measures were taken to ensure the accuracy and reproducibility of the results.

Statistical Analysis

The statistical analysis was done using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). Continuous data were reported in terms of mean, SD after evaluating the data normality through Shapiro-Wilk test. To test the difference in means of differences between CMV-infected patients and control group, the independent samples t-test was used. Pearson correlation was used to test the correlation between the levels of the IL-17 and TNF-alpha. The P-value which was deemed statistically significant was below 0.05 in a two-tailed test. In some cases, the calculation of effect size (Cohen d) was done as the measures of the differences in groups.

Ethical Approval and Consent.

The Institutional Ethics Committee of the University of Kufa approved the study protocol. All the processes were held following the principles of the Declaration of Helsinki. All participants signed informed consent written, before enrollment and sample collection.

Results

The age distribution of CMV-infected patients and healthy controls is presented in Table [1]. The participants were mostly aged 20-30 years (45.0% of patients, 46.7% of controls). This was followed by the 31–40 years group (31.7% vs. 30.0%) and the 41–55 years group (23.3% in both groups).

Table 1: Age distribution of CMV-infected patients and healthy controls

Age group (years)	CMV patients (n = 60)	Controls (n = 30)	Total (n = 90)
20–30	27 (45.0%)	14 (46.7%)	41 (45.6%)
31–40	19 (31.7%)	9 (30.0%)	28 (31.1%)
41–55	14 (23.3%)	7 (23.3%)	21 (23.3%)
Total	60 (100%)	30 (100%)	90 (100%)

Serum IL-17 Levels in CMV Infection and healthy controls

The level of serum IL-17 was significantly higher in CMV-infected patients than in healthy controls. The mean ± SD values were 68.72 ± [1]3.94 pg/mL in patients and [1]3.67 ± 4.91 pg/mL in controls. This disparity was highly statistically significant (P < 0.0001), and suggested a strong proinflammatory immune response to CMV infection.

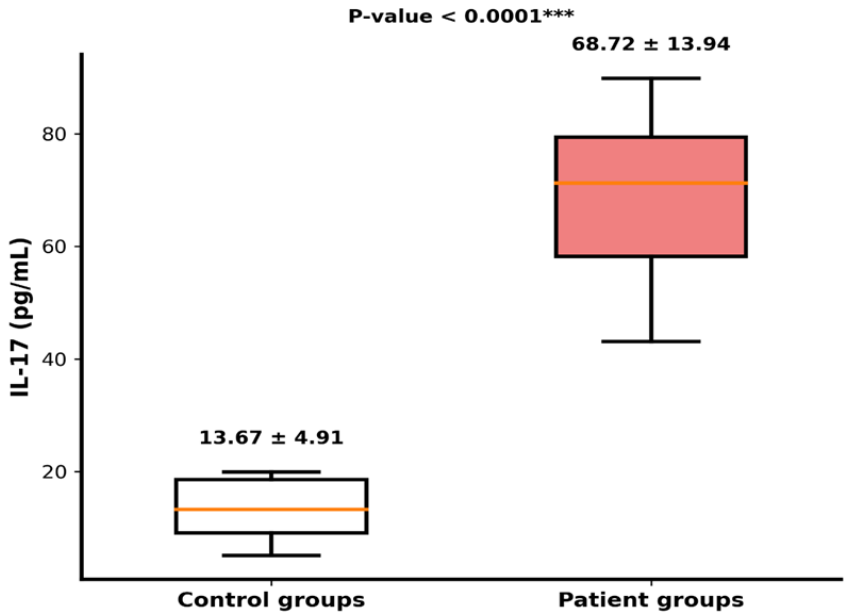

Fig 1: Comparison of IL-17 serum levels between control and CMV-infected groups.

TNF-α levels in CMV-infected patients and healthy control groups

The level of serum TNF-α was significantly high in CMV-infected patients as opposed to that of healthy controls. The mean ± SD values were 28.36 ± [1]4.72 pg/mL in patients and 7.18 ± 2.16 pg/mL in controls. This difference was significantly statistically (P < 0.0001) which indicated increased proinflammatory cytokine activity linked with CMV infection.

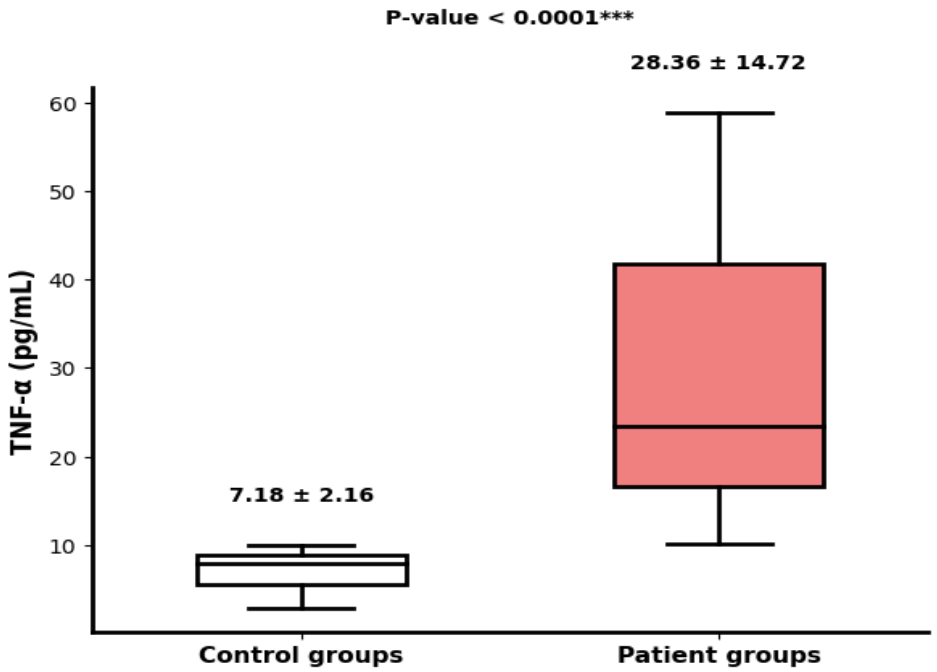

Fig 2: Elevated TNF-α levels in CMV-infected patients compared to healthy controls

Comparison of Serum C-Reactive Protein (CRP) Levels Between CMV-Infected Patients and Healthy Controls

The levels of serum C-reactive protein (CRP) were significantly high in CMV-infected patients than in their healthy counterparts. The mean ± SD values were [1]3.75 ± 5.81 mg/Lin patients and 2.87 ± 0.97 mg/Lin controls. This statistical difference was significantly ($P < 0.0001$) statistically significant, showing that there is systemic inflammation that is associated with CMV infection.

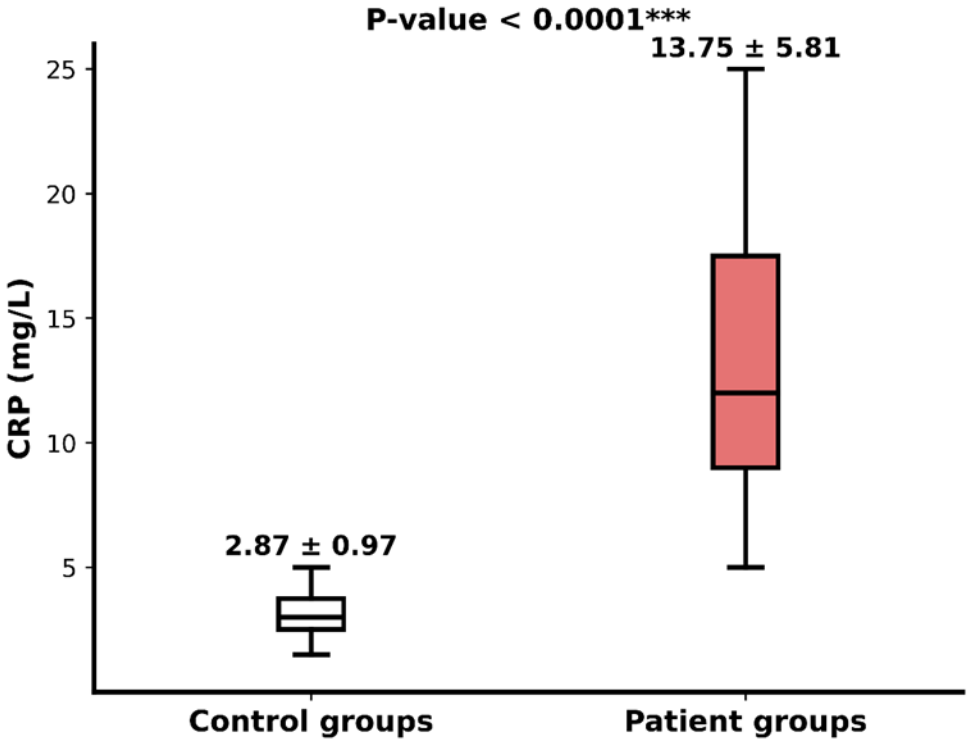

Fig 3: CRP levels in CMV-infected patients and healthy control groups

Discussion

The current study presents strong evidence that the presence of cytomegalovirus (CMV) infection in females is correlated with a robust of proinflammatory cytokines, in which there is a significant increase in IL-17, TNF-α and CRP. These results support the idea that CMV, even in immunocompetent individuals, is not only a latent pathogen but it is also an active driver of persistent immune activation and inflammatory remodelling.[16]

One of the most significant findings in this study is the significant rise in the level of IL-17, which means that the Th17 axis was activated. Th17 cells are an important

subgroup of CD4+ T lymphocytes that mediate a transition between innate and adaptive immunity, especially in the context of mucosal and antiviral defense. The activation of Th17 responses during CMV infection could be caused by the prolonged antigenic stimulation, and cytokine milieu polarization, in particular, through IL-6 and IL-23 dependent pathways [17, 18]. The IL-17 functions functionally to enhance the inflammatory response by stimulating the release of chemokines, including CXCL1 and CXCL8 thus facilitating the recruitment of neutrophils, and the maintenance of local immune activation. Although such a response can initially help to contain the virus, its persistence can predispose to immunopathology and chronic inflammatory conditions.

Simultaneously, TNF-α was also highly increased, which highlights its key role as a master regulator of antiviral immunity and inflammation. TNF-α plays multiple roles in immunity such as endothelial activation, increased leukocyte trafficking, and induction of apoptosis in infected cells [19]. Nevertheless, CMV has developed the ability to use the TNF-α signaling to ensure its persistence; experimental evidence has shown that TNF-α can be used to initiate viral reactivation of latent CMV [20]. It is this dual role, which brings to light, the kind of complex host-virus interaction that may involve immune responses inadvertently contributing to viral persistence.

The same results have been described in inflammation conditions where IL-17 was found to have a positive correlation with other proinflammatory cytokines such as IL-23, which suggests that IL-17 is part of a synergistic inflammatory axis and not an independent activator of cytokines. Mechanistically, these cytokines interact with each other at the transcriptional level, stabilising mRNA of proinflammatory genes and enhancing downstream mediators such as IL-6, GM-CSF and matrix metalloproteinases [7, 10]. This interaction results in a self-sustaining inflammatory loop that could be one of the explanations of the level of cytokine upregulation that was measured in the present study. This axis has been found to contribute to chronic inflammatory and autoimmune disease indicating that there is a common pathogenic pathway that is shared between infection-induced and immune-mediated inflammation.

The increase of CRP also indicates the presence of a systemic inflammatory process and reflects the activation of the IL-6-mediated acute-phase response of the liver. In addition to playing a passive role as a biomarker, CRP can also play an active role in the immune responses by being actively involved in the complement activation process and opsonization [9]. Its rise in CMV seropositive females is in line with epidemiological evidence of CMV seropositivity with chronic low-grade inflammation and cardiometabolic susceptibility.[18]

Even though no statistically significant differences were reported in terms of age distribution between CMV-infected patients and healthy controls, the dominance of the participants in the younger age group (20-30 years) might be related to a more active and responsive immune system that could have contributed to the observed high cytokine levels. Conversely, people of the older age group (41-55 years) might show some age-related immune modulation, such as low-grade chronic inflammation, which may have an impact on the dynamics of cytokines.

These results imply that, age, despite a lack of statistical significance, may be a modulatory factor when it comes to CMV-associated immune responses.[21]

One of the strongest points of the study is that it only looked into female subjects, but this gives a good understanding of the sex-specific immune responses. Women have been known to be highly immune reactively in part because estrogen mediates a series of changes in immune cells and the expression of immune genes X-linked [11]. It has been demonstrated that under specific conditions estrogen can promote Th17 differentiation, which may be the reason why Th17 levels were so high in this cohort. Additionally, hormonal effects can also impact CMV latency and reactivation dynamics, indicating that female-specific immune regulation can contribute to both heightened antiviral responses and increased inflammatory burden.

In a pathophysiological perspective, the IL-17/TNF-α axis, which was identified in this study, may be a central mechanism that links CMV infection to chronic inflammation and the complications that it entails. Repeated activation of this axis can play a role in endothelial dysfunction, oxidative stress and tissue remodeling, processes that are becoming increasingly appreciated in CMV-associated comorbidities [22]. Hence, the cytokine profiles observed could not only be an indication of acute immune activation, but it also may indicate long-term clinical outcomes.

These results demonstrate the possible value of IL-17 and TNF-α as composite biomarkers of immune activation in CMV infection. Their joint estimation might enhance the sensitivity of the inflammatory status assessment as compared to the analysis using single markers. Moreover, therapeutic benefits might be gained by attacking this cytokine axis. In spite of the well-established use of biological agents targeting TNF-α or IL-17 pathways in autoimmune diseases, the application of such agents in viral infections necessitates careful consideration of the problem to balance the control of inflammation with the maintenance of antiviral immunity.

Although such insights have been made, a number of limitations must be realized. The causal inference is limited by the relatively small sample size and the cross-sectional research design. Moreover, the lack of quantification of the viral load and clinical severity limit the possibility to correlate the level of cytokines with the progression of the disease. Future research must consider the use of longitudinal designs that incorporate virological, immunological and clinical parameters to further clarify the mechanism of CMV-induced immune activation.

Conclusion

Summing up, this present study shows that the cytomegalovirus (CMV) infection in females is related to a significant proinflammatory immune response, as indicated by significantly higher serum levels of IL-17, TNF-α and C-reactive protein (CRP). These findings suggest the engagement of a coordinated inflammatory network, where IL-17/TNF-α axis plays a central role in enhancing immune signaling and maintaining systemic inflammation.

The observed cytokine interaction not only reflects a dynamic immune response to the viral infection, but also indicates a mechanistic relationship to inflammatory complications associated with CMV infection.

Their regular upregulation indicates their possible use as combined measures of immune response in CMV infection. Collectively, these findings provide important insights into the immunopathogenesis of CMV and highlight the value of cytokine profiling in both clinical and research settings. The prognostic value of these biomarkers and their potential as therapeutic targets should be studied further to validate their prognostic importance and their possible application as targets of therapeutic intervention.

Limitations

Although this study has some strengths, there are some limitations that one should take into consideration when interpreting the findings of this study. To begin with, the sample size used is relatively small, which could restrict the external validity of the findings to larger populations, thus the need to conduct larger, multicenter studies to confirm these results. Also, the cross-sectional design excludes the opportunity to define cause-effect relationships between CMV infection and cytokine elevation, as well as does not allow assessing temporal dynamics in the immune responses. The other crucial limitation is the lack of CMV viral load quantification or the extensive molecular confirmation (e.g., polymerase chain reaction), which could have given a deeper insight into the correlation between the viral activity and the expression of the cytokines. On the same note, the absence of standardized clinical severity indices prevents the possibility of correlating the levels of biomarkers with the progression of the disease and burden of symptoms.

Moreover, no additional immunological parameters (e.g., IL-6, IL-10, or regulatory T-cell markers) were addressed by the study and would provide a more comprehensive picture of the equilibrium between proinflammatory and anti-inflammatory responses. Lastly, the use of potential confounding variables such as hormonal status, nutritional condition, and subclinical infections had not been completely controlled and could have been a source of influence on the cytokine levels.

Future studies are necessary to overcome these limitations through the adoption of longitudinal designs, use of more comprehensive immunological panels, and the integration of virological and clinical data to give a more comprehensive picture of CMV-induced immune activation.

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