

Correlation of Interleukin-10 and Interleukin-8 with Cytomegalovirus and Epstein–Barr Virus Infection in Hemodialysis Patients

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Abstract

Background: Herpes viruses like cytomegalovirus (CMV) and Epstein–Barr virus (EBV) can cause serious illness in those who already have impaired immune systems. **Objectives:** The purpose of this research was to examine the impact of CMV and EBV infection on specific immunological markers in individuals undergoing hemodialysis. **Materials and Methods:** Blood sample was collected from 91 hemodialysis patients and 50 healthy individuals as a control group for comparison. Serum was separated and examined for the confirmation of CMV and EBV infection, and then the sera were tested by using specific ELISA kits (human interleukin-10 and human IL-8, Sunlong Biotech Co., HangZhou, China). **Results:** Highest mean of IL-8 and IL-10 was obtained in CMV IgM positive patients in comparison with IgG positive and control group with P value = 0.00002, 0.0008, respectively. The results in patients with EBV IgM positive were also highly significant in comparison with control, P value for IL-8 was 0.0002 and for IL-10 was 0.00004. **Conclusion:** The study concluded that, the level of IL-10 and IL-8 was higher among hemodialysis patients with acute EBV and CMV infection, and this indicated that the ability of CMV and EBV to enhance IL-8 and IL-10 production which may play an important role in immune inflammatory states associated with CMV and EBV infection.

Keywords: CMV, EBV, hemodialysis, immunological markers

INTRODUCTION

Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are Herpesviridae viruses, having subfamilies Betaherpesvirinae as well as Gammaherpesvirinae. These viruses share structural characteristics and are members of the herpes virus family. The virus particle is composed of a large linear double-stranded DNA genome surrounded with an icosahedral nucleocapsid and an integument composed of an amorphous layer containing viral proteins and viral mRNAs.^[1] CMV can induce a wide variety of clinical syndromes, including hepatitis, pneumonitis, enterocolitis, and encephalitis, in its host when the immune system is functionally impaired, especially in immunocompromised patients.^[2] Upon initial infection, the virus enters a state of immunoevasion called latency, during which it prefers to reside in myeloid cells. Sickness and the recurrence of viruses are two potential

outcomes of immune suppression.^[3] Infections with EBV have the potential to cause serious morbidities and even result in death in healthy individuals. In addition, there is evidence that the virus plays a role in the development of other forms of cancer, such as Burkitt's lymphoma, Hodgkin lymphoma, nasopharyngeal carcinomas, and leukemia.^[4]

Hemodialysis and transplantation are both potential avenues for the spread of human CMV and EBV between patients suffering from renal failure. Patients undergoing

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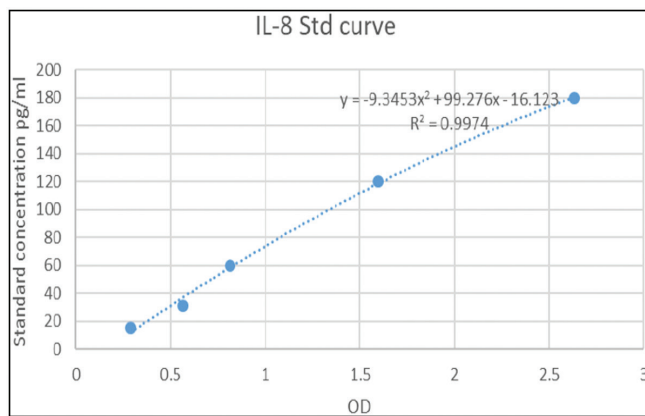


Figure 1: Standard curve of the human IL-8

hemodialysis have a significantly increased risk of coming into close contact with human CMV.^[5] IL-8, also known as interleukin-8, is a type of chemokine that is produced by macrophages as well as other cell types such as epithelial cells.^[6]

The primary function of IL-8 in neutrophils is to stimulate chemotaxis. IL-8 also causes the release of lysosomal enzymes, the overexpression of adhesion molecules, as well as an increase in intracellular calcium, and the start of the oxidative bursts.^[7] The pleiotropic cytokine IL-10 has potent anti-inflammatory and immunosuppressive effects. Now known to be produced by a range of immune cells with myeloid and lymphoid origins that are engaged in both innate and adaptive immunity, IL-10 was previously considered to exclusively be produced by T helper 2 cells. IL-10 during infection inhibits the host immune system's defense against pathogens and microbiota, which lessens tissue damage and immunopathology.^[8] The transmembrane receptors complex composed of IL-10R1 and IL-10R2 regulates the actions of macrophages, lymphocytes, and other cell types.^[9,10] IL-10 is made by Th2 cells. Increased IL-10 signaling, in turn, can block the release of proinflammatory cytokines by going after immune effectors. By impeding macrophage and dendritic cell development, it may indirectly alter immune response by decreasing the host's capacity for antigen presentation and chemokine release.^[11] With a worldwide prevalence of 9.1%, chronic kidney disease (CKD) is a major issue for public health on a global scale.^[12] CKD is characterized by the presence of structural along with functional renal damage for three months or longer with adverse health consequences. In general, it is progressive, irreversible, and affects numerous metabolic pathways. The severity of decreased kidney function, as measured by glomerular filtration rate (GFR), and the severity of albuminuria are used to divide CKD into five stages.^[13] Patients with end stage renal disease (ESRD) having chronic hemodialysis frequently have immunological abnormalities involving both the adaptive and innate immune systems that are unrelated to the basic renal illness.^[14]

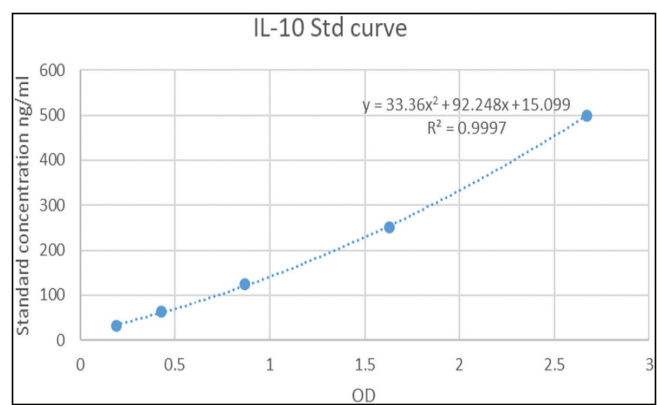


Figure 2: Standard curve of the human IL-10

MATERIALS AND METHODS

Study design

The study includes 91 hemodialysis patients who were treated at the Kirkuk general hospital/dialysis unit, as well as 50 healthy individuals who served as the control group.

Setting and time of the study

The research was carried out in Kirkuk/Iraq from November 2022 to March 2023.

Study samples and methods

Five milliliters of blood were taken in total. Following coagulation, the blood specimen was subjected to centrifugation at a rate of 3000 revolutions per minute for a duration of 15min, thereby facilitating the segregation of the concentrated red blood cells from the serum, serum sample was tested for the detection of antibodies (IgG and IgM) specific to CMV and EBV using ELISA technique. And then after the confirmation of the presence of CMV and EBV infection, serum sample was used for determining the level of IL-10 and IL-8 in CMV and EBV infection and also in hemodialysis patients by using ELISA kits involving human IL-8 and human IL-10 (Sunlong Biotech Company for Research, China).

Calculation of IL-8 results

Human IL-8 standard concentrations and optical density (OD) readings are displayed on logarithmic (x and y) scales. On the Y -axis, the sample's OD determines the human IL-8 concentration. Multiplying the diluting factor by the initial concentration yields the initial concentration.

Calculation of IL-10 results

Human IL-10 standard concentrations and OD reading are shown on log scales (x and y). The sample's OD on the Y -axis determines human IL-10 concentration. Multiplying the dilution factor yields the original concentration.

Table 1: The levels of IL-8 and IL-10 in hemodialysis patients with EBV infections

Level of		Patient with EBV infection		Control (n: 50)	P value (ANOVA)
		IgM (n: 7)	IgG (n: 39)		
IL-8 (pg/mL)	Mean	43.41	28.30	3.64	0.00002
	SD	5.50	4.78	1.31	
IL-10 (pg/mL)	Mean	78.50	29.90	5.49	0.0004
	SD	7.80	3.81	1.57	

Table 2: Levels of (IL-8) and (IL-10) in hemodialysis patients with CMV infection

Level of		Patient with CMV infection		Control (n: 50)	P value (ANOVA)
		IgM (n: 5)	IgG (n: 46)		
IL-8 (pg/mL)	Mean	153.30	23.31	3.64	0.00002
	SD	39.0	4.25	1.31	
IL-10 (pg/mL)	Mean	127.20	15.89	5.49	0.0008
	SD	39.7	3.19	1.57	

Statistical analysis

The data were analyzed by using *t* test and Chi-square test to obtain *P* value (significant > 0.05) of each group sample in this research.

Ethical approval

For performing this study, ethical approval was obtained from the directory of health/Kirkuk. The information of each participant was taken and local ethics committee reviewed and approved the study protocol as well as the data on the subjects and permission November 10, 2022 (764).

RESULTS

The present investigation revealed that individuals who experienced acute EBV infection exhibited the most elevated average concentrations of IL-10 and IL-8, measuring 78.50 and 43.41 pg/mL, respectively, as it shown in Table 1.

Patients who had acute CMV infection had the highest mean levels of IL-8 and IL-10 (153.30 and 127.20) pg/mL, respectively. The participants who had been infected with CMV in the past came next, and then the group that acted as the control. As it can be seen in Table 2, the results were highly significant from a statistical point of view.

DISCUSSION

CMV infection can increase the recruitment of neutrophil by upregulation of IL-8 gene expression. Before DNA synthesis, IL-8 can increase CMV late antigen protein synthesis and transcription. IL-8 may increase CMV replication in fibroblasts by interacting with CXCR-1.^[15,16] Qian *et al.*^[17] showed that the level of interleukin-8 was higher and significantly correlated with the level of CMV DNA. Another study showed that elevated IL-8 and IL-10

were associated with development of CMV reactivation.^[18] Chinta *et al.*^[19] suggested that human cytomegalovirus (HCMV) causes an increase in IL-10 during both the lytic and latent phases of infection. During the lytic phase, ULIII A gene of CMV, which can encode ortholog of hIL-10, known as cmvIL-10, is expressed, during the latent phase, LAcmvIL-10 stimulates the production of hIL-10 by CD34+ myeloid progenitor cells and CD14+ macrophages. As LAcmvIL-10 is unable to attach to the IL-10R, the cellular cytokines is recruited to offer additional immune suppression for HCMV latency maintenance. As a result, hIL-10 activation is important. Dendritic cells and macrophages were the most prominent cell types whose hIL-10 production was enhanced in response to treatment with cmvIL-10, indicating that reactivation of latent HCMV virus in these cells may be a source of cmvIL-10-induced hIL-10 secretion.^[20] Data of other study showed that IL-8 is increased in patients with reactivation and decreased in patients without reactivation.^[21] Yue *et al.*^[22] suggested that significant association of EBV infection with IL-8 and EBV can enhance the recruitment of lymphocytes to the site of infection by stimulating IL-8 release. EBV also can regulate NF- κ B signal to establish latent infection in NPC and this (NF- κ B) can regulate the releasing of (IL-8). Another study showed that mRNA expression of CXCL8 (IL-8) in EBV gastric carcinoma was significantly upregulated.^[23] In order to avoid or inhibit host anti-viral responses and establish latency, EBV encodes homologs of cellular cytokines. One of these proteins is viral IL-10, a human interleukin 10 (hIL-10) homolog. It inhibits the maturation of dendritic cells and the expression of major histocompatibility complex (MHC) and co-stimulatory molecules on myeloid cells, making it a unique class II cytokine. For B-cells, mast cells, and thymocytes, human IL-10 is a potent growth and differentiation factor.^[24] Both EBV-induced cIL-10 and ebvIL-10 work together to assist the pathogen in establishing latency in B cells and

in maintaining the equilibrium of antiviral T cells. This is accomplished by a coordinated action. As a direct result of this, the load of EBV, that is, always present in the immune system is kept at a level that is, both consistent and distinct for each individual [Figures 1 and 2].^[25]

CONCLUSION

According to the study's findings, IL-10 and IL-8 levels were higher in hemodialysis patients who had acute EBV and CMV infections. This suggests that CMV and EBV have the ability to increase IL-8 and IL-10 production, which may be crucial in the immune inflammatory states connected to CMV and EBV infection.

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Conflicts of interest

There are no conflicts of interest.

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