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A Study of the Relationship Between CMV IgG Titers and Blood Pressure in Iraqi patients

Maryam Kamel Mohammed*
Department of Biology, College of Science, Baghdad University, Baghdad, Iraq

Abstract

Human cytomegalovirus (CMV) infection is associated with higher risk of cardiovascular diseases in immunocompromised organ transplant patients; it has been linked with the elevated arterial blood pressure. This study aimed to find a relationship between CMV antibody titers and blood pressure elevation by using the enzyme-linked immunosorbent assay (ELISA) to measure CMV IgG levels in the serum of 60 patients with high blood pressure, in comparison to 30 healthy persons with normal blood pressure as a control. All patients and control were 25-50 years old. The results showed that CMV antibody titers were higher in those who undergo blood pressure elevation. This finding supports the hypothesis that; the common CMV infection may leads to impaired vascular function.

Keywords: Cytomegalovirus, high blood pressure, enzyme -linked immunosorbant assay

دراسة العلاقة بين مستويات الاجسام المضادة من نوع IgG لفايروس CMV وارتفاع ضغط الدم في المرضى العراقيين

مريم كامل محمد*

قسم علوم الحياة، كلية العلوم، جامعة بغداد، بغداد، العراق

الخلاصـــة

لُوحظ وجود علاقة بين اصابات فايروس الـ CMV و امراض القلب في المرضى الخاضعين لعمليات نقل الاعضاء من ذوي المناعة المنخفضة مما يؤدي الى الاعتقاد بوجود علاقة اخرى بين الاصابة بهذا الفايروس وحدوث حالات ارتفاع ضغط الدم ، لذا يهدف هذا البحث لدراسة تلك العلاقة بين مستويات الاجسام المضادة من نوع IgG عند الاصابة بفايروس CMV وحالات ارتفاع ضغط الدم من خلال قياس مستوى او معدل هذه الاجسام المضادة في مصل 60 مصاب بالفايروس بواسطة طريقة الـ ELISA مقارنة بعدد السيطرة البالغين30 شخص طبيعي ليس له تاريخ مرضي او ارتفاع ضغط الدم وقد تراوحت اعمار الافراد قيد الدراسة (25–50) سنة، حيث اكدت النتائج العلاقة بين وجود هذه الاجسام المضادة وحدوث حالات ارتفاع ضغط الدم مما يؤكد نظرية خطورة الاصابة بفايروس CMV على وظائف القلب والشرايين .

Introduction:

Cytomegalovirus (CMV) is a member of the Herpesvirideae family, which includes herpes simplex virus types 1 and 2, varicella-zoster virus (which causes chickenpox), and Epstein-Barr virus (which causes infectious mononucleosis) they are of large enveloped DNA viruses. The definitive characteristic of the herpesvirus family is the ability of these viruses to cause both acute lytic infections, as well as long term persistent latent infections [1, 2]. These viruses share a characteristic ability to remain dormant within the body over a long period. Initial CMV infection, which may have few symptoms, is always followed by a prolonged, inapparent infection during which the virus resides

*Email: mmbio2003@yahoo.com

in cells without causing detectable damage or clinical illness. Sever impairment of the body's immune system by medication or disease consistently reactivates the virus from the latent or dormant state [1, 3].

Infectious CMV may be shed in the body fluids of any previously infected person, and thus may be found in urine, saliva, blood, tears, semen, and breast milk. The shedding of virus may take place intermittently, without any detectable signs, and without causing symptoms. Transmission of CMV occurs from person to person. Infection requires close, intimate contact with a person excreting the virus in their saliva, urine, or other body fluids. CMV can be sexually transmitted and can also be transmitted via breast milk, transplanted organs, and rarely from blood transfusions.

Most healthy people who acquire CMV after birth experience few or no symptoms and no long-term sequelae. Some experience a mononucleosis-like syndrome with symptoms including malaise, persistent fever, myalgia, cervical lymphadenopathy, and, less commonly, pneumonia and hepatitis. After the primary infection, defined as CMV infection in a previously seronegative person, the virus becomes dormant and exists in a latent state, from which it can be reactivated. This is designated as recurrent (secondary) infection [4]. In addition, there seem to be several strains of CMV that infect humans, so reinfection can occur, even in immunocompetent individuals. Therefore, secondary infection, defined as intermittent excretion of the virus in the presence of host immunity, may be due to either reactivation of an endogenous virus or exposure to a new virus strain from an exogenous source. Differentiation between these two kinds of secondary infection is not possible by serology but only by molecular analysis of virus isolates [5].

One of the initial correlates of HCMV with vascular disease was the finding of increased HCMV-specific antibodies in atherosclerosis patients who required surgery compared to those who did not, and various chronic inflammatory diseases, including cardiovascular disease (CVD) autoimmune diseases and certain cancers. Subsequently, HCMV DNA was detected in atherosclerotic coronary arteries [5-7]. Perhaps most importantly, anti-HCMV ganciclovir therapy was shown to lower atherosclerosis following heart transplants [6]. It should be noted that these early associations were not universally accepted, [7, 8].

Since that time, it has been realized that most clinical HCMV isolates replicate in cultured cells derived from the vasculature, including epithelial, endothelial, smooth muscle, and monocyte-derived macrophage cells [9, 10]. Recent studies have linked high CMV antibody titers with cardiovascular disease and total mortality among older people. It was hypothesized that CMV antibody titers, rather than seropositivity, might be more relevant markers of deleterious effects of CMV infection in young adults [5].

It remains an important investigational subject to define the role of CMV in vascular injury and atherosclerosis. This could also be mediated by CMV inducing vascular injury and causing hypertension, which serves as a cofactor to interact with other factors to induce atherosclerosis. As atherosclerosis is a complicated event with lipid metabolism, genetic factors and inflammatory pathways obviously playing crucial roles, it is important to define that a common widespread virus, such as CMV, might initiate atherosclerosis or inflammatory response resulting in vascular injury [11].

This has the potential to lead to new treatments for vascular disease directed at the antiviral therapy of CMV or prevention by a vaccine against CMV. Furthermore, distinguishing the role of CMV infection in vascular cells and atherosclerosis adds to elucidating the mechanism of CMV associated cardiovascular diseases (CV), since CMV infection is reported as a primary factor and directly linked to CV as in myocardial infarction, stroke, coronary restenosis, or CV death [12].

The direct mechanism through which viruses might cause pulmonary hypertension remains unknown. It is conceivable that the anti-viral inflammatory response against HCMV plays an important role in the process. In fact, inflammation-dependent hypertension has been validated in a mouse animal model system [13]. A recent analysis utilizing murine CMV (MCMV) in mice demonstrated that viral infection led to increased arterial blood pressure [14]. Coincident with MCMV replication was increased expression of proinflammatory cytokines.

The significance of these studies is their implication that management of CMV infection may limit development of atherosclerosis and hypertension in humans [3]. Therefore, the aim of this study was to try to find a kind of relationship between the presence of CMV and hypertension.

Material and Methods:

1. Study population

Sixty patients were recruited in this study, (males: 26; females: 34) along with (30) healthy controls (males 14; females:16). Ages of both groups were between (25-50) years, the individuals of this study were chosen randomly from community. Hypertension was detected by the specialists' physicians in private clinics for documentation of the status of patients (patients had high blood pressure from 14/10 to 16/12 while normal controls had 12/8).

2. Blood samples collection:

Blood samples were collected from patients and controls by blood derange using disposable syringes and blood volume collected was (5 ml), which was left to clot for 30 min. at room temperature then centrifuged at 3000 rpm for 5 min. and the serum was separated and kept in sterile plane tubes for further tests.

3. Detection of CMV IgG by ELISA techniques:

Specific IgG for CMV was detected qualitatively using enzyme immune sorbent assay depending on the instruction of the company kit (Human- Germany). The positively of results was compared with the cutoff value (0.560), only results under this value considered negative.

Results and Discussion:

In our study, all samples collected from the hypertension patients (both males and females) showed increase in CMV- IgG titer when compared with healthy control individuals who showed negative results, Table-1.

Table 1- CMV IgG Titer in patients (Men & Women) and Controls

CMV –IgG Titer in Male	CMV –IgG Titer in Female	Control
2.306	3.441	0.267
1.853	3.284	0.223
2.303	2.895	0.153
2.332	3.502	0.201
1.987	2.981	0.301
2.101	3.39	0.266
1.61	2.676	0.302
2.146	3.43	0.312
2.75	3.292	0.39
2.957	3.122	0.146
3.012	3.312	0.394
2.01	2.72	0.122
1.753	2.791	0.3
2.501	3.56	0.251
1.789	3.421	0.293
1.986	2.811	0.22
2.987	2.858	0.302
2.51	2.77	0.21
3.103	3.42	0.391
3.001	3.1	0.147
1.680	2.67	0.147
2.884	2.591	0.224
3.011	3.4	0.305
2.446	3.441	0.4
2.106	3.792	0.247
1.509	3.813	0.285
	2.65	0.310
	2.459	0.265
	3	0.113
	3.016	0.203
	2.5	
	1.99	
	2	
	2.11	

IgG-CMV titer percentage for females was (62.77 %) which was higher than males (37.23 %), Figure-1.

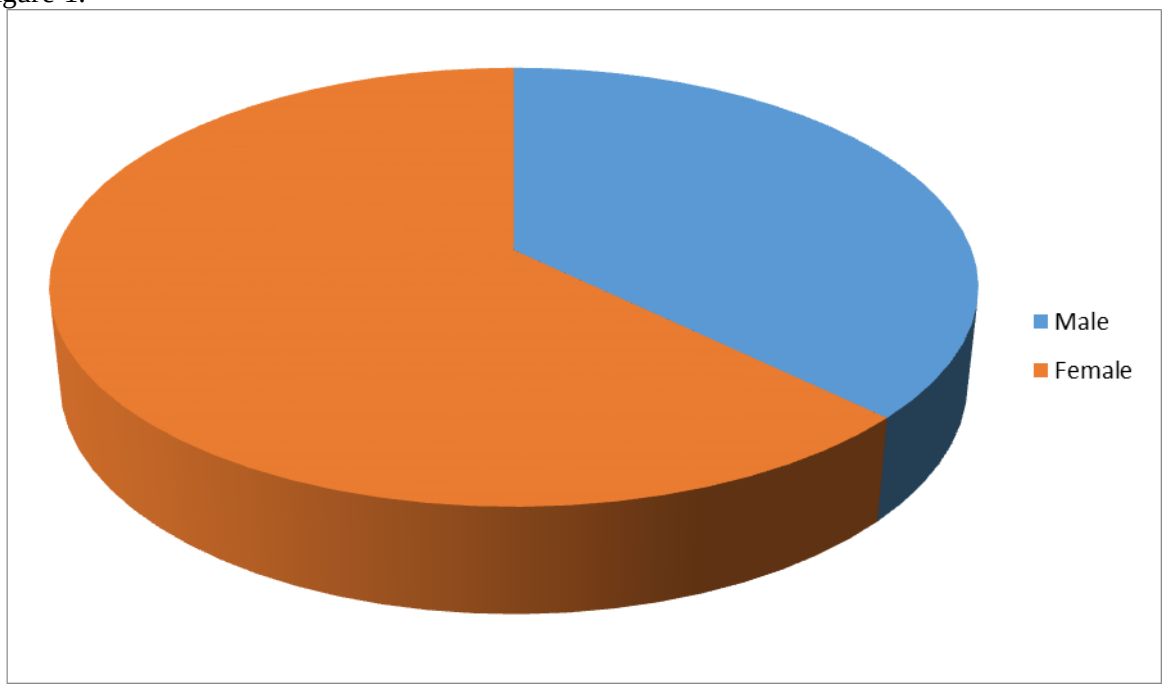

Figure 1- IgG-CMV titer percentage according to gender

The average of IgG-CMV titer in females was (3.01), while in males was (2.33) in this study. There was no correlation between the age of the hypertension patients and IgG-CMV titer in the collected samples.

In this study, we showed that high CMV-IgG titer are associated independently with high blood pressure. To our knowledge, there are few studies which demonstrate the relationship between CMV infection and blood pressure in humans. Recently, Haarala et. al showed that CMV antibody titers are associated independently with high blood pressure values and associated inversely with FMD (flow mediated dilution), [4]. Additionally, Li et.al have been showed that plasma CMV DNA copy number is associated with hypertension. Also, they showed that CMV-encoded micro RNA, hemv-miR-UL112, was highly expressed in hypertensive patients. Further they showed that heme-miR-UL112 could target interferon regulatory factor 1, which is related to up-regulation of angiotensin II type2 receptor, [15]. The relationship between CMV infection and increased arterial pressure also has been shown in mice [2].

In our study, differences were showed in CMV antibody titers between men and women, this observation has also been seen in other study [4, 16], this supports the hypothesis that immune response to CMV may differ according to gender; Zhu et. al proposed that the differences between the genders may be due to the association between CMV and C- reactive protein in men, but not in women [17], while Haarala et. al did not find any association with C- reactive protein.

In conclusion, this study showed that high CMV antibody titers associated with high blood pressure and this supported the idea that the CMV virus could be a risk factor for cardiovascular system.

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