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Determination of the Cytomegalovirus (CMV) infection Role with the Disturbances of Immunoglobulin E (IgE) and Interleukin-33 (IL-33) Concentrations in the Pathogenesis of Asthma and Atherosclerosis in a Sample of Iraqi Patients

Jasim Mohammed Muhsin[1]*, Sura O. Yousif[2], Ameer M. Hadi[3] and Ahmed Rahman Rawdhan[4]

[1]Middle Technical University, Health and Medical Technology College, Baghdad, Iraq. [2]Technical Institute, Suwaira, Middle Technical University, Wasit, Iraq. [3]University of Babylon, DNA Research Center, Babylon, Iraq. [4]Shiekh Zayed Hospital, Baghdad, Iraq.

Abstract

Subsequently, the early reactivation or old human cytomegalovirus (HCMV) infection may be interfere with IgE and interleukin-33 (IL-33) levels disturbances throughout the life intervals and act as synergistic factors to play a significant role in the pathogenesis of various diseases; like asthma or coronary heart diseases (CHD). The main subject of the current study was to determine the role of CMV infection onto IgE levels and IL-33 disturbances in the pathogenesis of asthma and atherosclerosis as a case-control study. A total of 175 participants were with a mean age of 38.17 ± 7.51 years [age range: 26–52] years, which were distributed as patients with atherosclerosis (n=50) and asthmatic patients (n=50) as the cases of our study and 75 healthy subjects as a control group. Both groups of asthmatic and atherosclerosis patients show a significant association with the seropositivity of CMV-IgG which was detected in 33 (18.9%) and 30 (17.1%). While, CMV-PP65 Ag which was detected in 26 (14.9%) and 28 (16.0%) respectively (P < 0.0001). High level of abnormal IL-33 was detected in 36 (20.6%) with 45 (25.7%) of abnormal IgE was determined in patients with asthma followed by 26 (14.9%) and 44 (25.1%) for abnormal levels of IL-33 and IgE respectively in patients with atherosclerosis. Furthermore, there was a positive significant association between the seropositivity of CMV-IgG and CMV-PP65 Ag with abnormal IgE and IL-33 levels in the pathogenesis of asthma and atherosclerosis (P < 0.0001), and impact of our study support the hypothesis that previous cytomegalovirus infection or early reactivation with unregulated IL-33 expression or high IgE level play a significant role in the pathogenesis of coronary heart diseases and asthma.

Keywords: Allergy, Coronary heart diseases (CHD), Cytomegalovirus (CMV), Interleukin (IL-33), IgE.

***Correspondence:** Jasim.muhsin99@gmail.com; Phone: 009647735414764

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INTRODUCTION

Human cytomegalovirus (HCMV) or human herpesviruses 5, (HHV-5) is a genus of DNA virus of *Herpesviridae* family and *Betaherpesvirinae* subfamily, with primary asymptomatic infection, a virus with latency cycle, also it's one of the causative agents of infectious mono-nucleosis[1]. The primary infection of CMV characterized by the presence of IgM immuno-globulins or another indicator of active infection more than CMV IgM antibody which is phosphoprotein 65 (pp65); the most copious constituent of the virion tegument of human cytomegalovirus (HCMV) protein. The positive CMV pp65 antigen in patient serum appeared on average of nine days earlier of serologic evidence of primary active infection. Therefore, detection of CMV pp65 antigens consider earlier and has been a valued tool for detection of early disease progression (active CMV disease)[3]. Later, the existence of immunoglobulin G (IgG) antibodies for a lifetime (seropositivity) its evidence of previous (old CMV infection)[2].

A study revealed the prevalence of CMV DNA increasing in the blood of asthmatic patients throughout the lifetime; proposes that disorder associated with latent CMV infection and may contribute to asthma pathogenesis[7]. Furthermore, some studies linked between CMV IgG sero-positivity or CMV reactivations with cardio-vascular disease progression that assumed to increase mortality risk[4]. Other herpesviruses or papilloma viruses maybe also of importance with the heart diseases interferences, but the possibility of interaction has been explored to a limited extent[5-6].

Asthma and coronary heart disorders are represented by excessive inflammatory dysregulation processes which occur in developing countries. They lead to serious health problems and affect negatively the quality of life. Studies suggested an association between allergy and an increased risk of coronary heart disease (CHD), resulting by over synthesis of pro-inflammatory cytokines in allergic diseases and disturbances of immune reactions, which has been interfered in the pathogenesis of atherosclerosis mechanisms[8].

The aim of this article, to explore CMV infection by; whether seropositivity for CMV IgG antibody (past infection) or CMV pp65 antigens (recent infection) are related to asthma and coronary heart diseases among participants in case-control study and whether the pro-inflammatory and immune reaction have any association with the pathogenesis of these disorders.

MATERIALS AND METHODS

Participants

A (case-control) study was established from the first of August till to the 30th of September (2018), with 175 serum samples of adult participants (aged 26 – 52), which distributed into (75) a healthy subjects as controls and (50) individuals had been with asthma which collected from Specialized Center of Allergy and Asthma, Baghdad. Furthermore, another fifteen individuals who admitted to Ibn al-Bitar for Cardiac Surgery Hospital, Baghdad, for coronary heart diseases such as; atherosclerosis. All cases diagnosed with specialized physician and some laboratory tests. The study protocols approved by the local Ethics Committee.

Measurement of CMV-IgG, CMV-PP65 Ag, IgE and IL-33 serum levels

The commercial ELISA of CMV/IgG (Diagnostic Automation/ Cortez Diagnostics, Inc., USA / HCMV-IgG) was used for estimation of CMV IgG antibodies. All analysis steps were performed according to the instructions of the manufacturer, (Cut-off Index = 1.0).

(MyBioSource Inc., USA / CMV-PP65 Ag) Commercial (ELISA) kit was used to detect CMV-PP65 Antigens in serum samples. (Cut-off Index ≥1.0).

(Diagnostic Automation / Cortez Diagnostics, Inc., USA / IgE) commercial ELISA IgE kit was used to detect the IgE levels according to the manual instructions (Range: 0 – 800IU/mL; sensitivity: 5 IU/mL).

(MyBioSource Inc., USA / IL-33) Commercial (ELISA) kit was applied to detect IL-33 serum concentration levels. The interleukin assay was conducted using the instruction manual which is recommended by the manufacturers (standard range: 15.6–1000 pg/ml; sensitivity: < 9.375 pg / ml).

Statistical analysis

All statistical analysis was accomplished with (SPSS, Inc., Chicago, IL USA, ver.19.0). The results of quantitative data were expressed as

mean ± standard deviation (mean ± SD) for all continuous variables and compared with one-way ANOVA and independent t-Test. Pearson's correlation was applied to examine the relation between dependent and independent variables. Furthermore, qualitative data were compared with the chi-square test. *p-value* <0.05 was considered statistically significant.

RESULTS

In this study, 50 (28.6%) patients with allergic disorders 17 (9.7%) males and 33 (18.9%) females, with a mean age of 37 ± 7.4 years [age range: 24–26] and 50 (28.6%) patients with cardiovascular diseases 35 (20.0%) males and 15 (8.6%) females, with mean age 39 ± 7.2 years [age range of 26–52]. In addition to, 75 (42.9%) participants as healthy subjects 49 (28.0%) males and 26 (14.9%) females, with a mean age of 37.3 ± 7.6 years [age range: 26–49] were scanned.

Table (1) explored the demographic characteristics of all participants, 44 (25.1%) of allergic disorders patients had abnormal (High) IgE levels with abnormal IL-33 expression in 36 (20.6%), 33 (18.9%) of them had been with a positive CMV-IgG. While, cardiovascular diseases patients 44 (25.1%) had been with a high level of IgE and 26 (14.9%) expressed abnormal IL-33 concentration with the seropositivity of CMV-IgG it was in 30 (17.1%) of them, with highly significant differences (P < 0.001).

The mean comparisons of serological markers of (CMV-IgG, IgE and IL-33) concentration according to the study groups in the table (2) which shows high significant differences between variables (P < 0.001). High levels of IL-33 were detected in allergic disorders patients compared with controls (584.6±298.9 vs. 184.1±95.0). Moreover, the patients with CVD had a high level of IgE than healthy control (145.6±43.8 vs. 46.4±19.0).

The correlation between CMV-IgG Seropositivity with IgE and IL-33 exposed high significantly positive associations between them (*P* = 0.001, *R* = 0.48) and (*P* = 0.001, *R* = 0.47) respectively. Furthermore, with age showed that a large proportion had been with old infection had significantly higher levels of CMV-IgG (*P* = 0.15, *R*

Table 1. Baseline data of study population characteristics

Characteristics N (%)		Control N=75 (42.9%)	asthmatics N=50 (28.6%)	*CHD N=50 (28.6%)	*p. value*
Genders	Male	49 (28.0%)	17 (9.7%)	35 (20.0%)	< 0.001
	Female	26 (14.9%)	33 (18.9%)	15 (8.6%)	
Age (Years)	(26- 40)	31 (17.7%)	20 (11.4%)	14 (8.0%)	0.28
	≥ 41	44 (25.1%)	30 (17.1%)	36 (20.6%)	
Diseases History	Yes	0 (0.0%)	30 (17.1%)	37 (21.1%)	< 0.001
	No	75 (42.9%)	20 (11.4%)	13 (7.4%)	
Smoking status	Smoker	5 (2.9%)	40 (22.9%)	32 (18.3%)	< 0.001
	Non-smoker	70 (40.0%)	10 (5.7%)	18 (10.3%)	
*BMI (kg/m^2)	Normal weight	75 (42.9%)	3 (1.7%)	2 (1.1%)	< 0.001
	Over weight	0 (0.0%)	47 (26.9%)	48 (27.4%)	
CMV-IgG	Negative	65 (37.1%)	17 (9.7%)	20 (11.4%)	< 0.001
	Positive	10 (5.7%)	33 (18.9%)	30 (17.1%)	
*CMV-PP65 Ag	Negative	67 (38.3%)	24 (13.7%)	22 (12.6%)	< 0.001
	Positive	8 (4.6%)	26 (14.9%)	28 (16.0%)	
*IgE Levels	Normal	75 (42.9%)	5 (2.9%)	6 (3.4%)	< 0.001
	Abnormal	0 (0.0%)	45 (25.7%)	44 (25.1%)	
*IL-33 Levels	Normal	71 (40.6%)	14 (8.0%)	24 (13.7%)	< 0.001
	Abnormal	4 (2.3%)	36 (20.6%)	26 (14.9%)	

Chi-square test was conducted to test the association between demographic characters and study groups* BMI (kg/m^2)= Body mass index (Kilogram/meters squares)*CHD = Coronary heart diseases * CMV-PP65 Ag = phosphoprotein 65 antigens*IgE= Immunoglobulin E*IL-33 = Interleukin 33

Table 2. Comparison association of the mean levels among studied serological markers according to the study groups

Groups (mean±SD)	CMV-IgG	CMV-PP65 Ag	IgE Levels	IL-33 Levels	*p.value*
Asthmatics (n=50)	1.54±0.88	1.06±0.84	145.5±37.2	584.6±298.9	< 0.001
CHD (n=50)	1.49±0.90	1.23±0.87	145.6±43.8	438.5±289.4	< 0.001
Control (n=57)	0.5±0.4	0.52±0.46	46.4±19.0	184.1±95.0	< 0.001
Total (n=175)	1.11±0.87	0.88±0.78	103.1±59.2	371.2±286	< 0.001

One-way ANOVA test was conducted to test the mean levels comparison serological markers and study groups

= 0.01) and concerning to the BMI, reveled high significant positive association with abnormal; weight (*P* = 0.001, *R* = 0.49) and significant negative association (*P* = 0.001, *R* = - 0.26) with smoking status, but there was no association with genders and CMV-IgG seropositivity as represented in table (3).

Furthermore, there was a significantly positive associations between CMV-pp65 Ag with IgE and IL-33 exposed high them (*P* = 0.001, *R* = 0.36) and (*P* = 0.001, *R* = 0.26) respectively. Besides, there was positive significant relation with age and BMI (*P* = 0.01, *R* = 0.16, *P* = 0.001, *R* = 0.32) and significant negative association (*P* = 0.02, *R* = - 0.15) with smoking status, table (4).

Table (5) demonstrate the comparison association of the mean level of IL-33 concentration, it was with the high significant difference among all demographic characteristics (P < 0.001) except with age it was a non-significant difference (*P* = 0.95). The level of IgE and CMV-IgG did not show significant differences with age and genders but both of them show a higher significant difference with the diseases history, smoking status and BMI (P < 0.001).

Table 3. Correlation of CMV-IgG Seropositivity with overexpression of interleukin-33, total IgE levels, and other demographic characters

Serological Markers	Pearson Correlation (r)	*p. value*
IgE Levels	0.48	0.001
IL-33 Levels	0.47	0.001
Age (Years)	0.15	0.01
Genders	0.08	0.12
BMI (kg/m^2)	0.49	0.001
Smoking status	- 0.26	0.001

Pearson Correlation test was applied to test the correlation of CMV-IgG with serological markers and demographic characteristics

Table 4. Correlation of CMV-PP65 Ag with overexpression of interleukin-33, total IgE levels, and other demographic characters

Serological Markers	Pearson Correlation (r)	*p. value*
IgE Levels	0.36	0.001
IL-33 Levels	0.26	0.001
Age (Years)	0.16	0.01
Genders	-0.35	0.32
BMI (kg/m^2)	0.32	0.001
Smoking status	-0.15	0.02

Pearson Correlation test was applied to test the correlation of CMV-PP65 Ag with serological markers and demographic characteristics

Recommendations

The current results may not be generalized to all diseases in the selected sample so it is useful to review a large sample size with other molecular markers in order to understand the biology of this issue. In addition to, estimate sST2 level concentration as a decoy IL-33 receptor.

DISCUSSION

The distinctiveness of the resent study was to estimate the interaction role of four serological markers (CMV-IgG, CMV-pp65, IgE and IL-33) in the pathogenesis of two inflammatory disorders which are; asthma and athero-sclerosis. However, this study has limitations, it's significant to interpret the recent outcomes in a larger sample size with multiple genetic markers for better understanding the biology of these disorders with further immunological and virologic markers.

Table 5. Comparison association of the mean levels of CMV-IgG, CMV-PP65 Ag, total IgE and interleukin-33 level in baseline data of study participants

Characteristics	N	Serological Markers (mean±SD)				
		(%)	CMV-IgG	CMV-PP65 Ag	IgE	IL-33
Genders	Male	101 (75.7%)	1.0±0.87	0.90±0.78	97.2±60.2	297.67±230.50
	Female	74 (42.3%)	1.2±0.86	0.84±0.77	111.17±57.2	471.66±324.22
	p.value	0.25	0.64	0.12	< 0.001	
Age (Years)	(26 – 40)	65 (37.1%)	0.95±0.85	0.75±0.77	98.7±-61.2	372.9±287.09
	≥ 41	110 (62.9%)	1.12±0.87	0.95±0.76	105.7±58.07	370.2±287.42
	p.value	0.06	0.10	0.45	0.95	
Diseases History	Yes	67 (38.3%)	1.45±0.93	1.09±0.86	136.6±41.8	491.3±320.9
	No	108 (61.7%)	0.90±0.76	0.74±0.69	82.3±58.9	296.7±235.1
	p.value	< 0.001	0.004	< 0.001	< 0.001	
Smoking status	Smoker	77 (44.0%)	1.38±0.90	1.01±0.83	141.7±47.8	509.9±309.2
	Non-smoker	98 (56.0%)	0.9±0.79	0.77±0.72	72.7±48.7	262.2±212.1
	p.value	< 0.001	0.04	< 0.001	< 0.001	
BMI (kg/m^2)	Normal weight	80 (45.7%)	0.62±0.51	0.56±o.52	52.4±30.0	198.5±132.4
	Overweight	95 (54.3%)	1.53±0.89	1.15±0.85	145.8±41.0	516.6±300.6
	p.value	< 0.001	< 0.001	< 0.001	< 0.001	

Independent *t*-Test test was applied to test the mean comparison of serological markers according to demographic characteristics, data were presented as mean ± SD.

Cytomegalovirus has a variable tissue tropism by its ability to infect different organs and interfere with many disorders such as; atherosclerosis, hypertensive blood pressure, cervical cancer and autoimmune diseases[9-12].

A study verified that the patient had been established hypersensitivity syndrome related to CMV reactivation by the increasing CMV-IgG accompanied by low CMV replication level was predominant among asthmatic participants[13]. Another study concluded that HCMV infection is related to asthma and may play a role in the pathogenesis of asthmatic inflammation by the detection of HCMV DNA in about 10.7% of the asthmatic patients[14].

Otherwise, a study was found CMV DNA increased by age with double IgE count to be connected with a risk of asthma traits comparing to controls. Nevertheless, herpesviruses infection has been measured to have a probable influence on the progression of the atopic disorder, so it cannot be omitted CMV chronic infection or reactivation that may have a fundamental influence on the traits of asthma progressing[15].

In addition, the relation of IL-33 with asthma and allergies is still uncertain. However, only a few studies have been conducted in humans and the impact of IL-33 has been proved in some allergic diseases such as; allergic rhinitis[15].

Furthermore, a number of candidate genes have identified by genome-wide association studies that contribute to asthma. Recently, studies suggested that variation in genes encoding IL-33 and IL-1 receptor-like 1 (IL-1RL1) has an association with asthma. IL-1RL1 is a part of the IL-33 receptor complex[16]. IL-33 is a member in the IL-1 family of cytokines such as IL-1ʎ and IL-18, but IL-33 promotes Th2 cells, unlike other members which mostly create TH1 inflammation[17]. After epithelial cell injury, IL-33 releases as an alarm signal and activates other immune cells such as basophils, Th2 cells and mast cells, leading to the secretion of other cytokines like as IL5 and IL13 which have a major role in starting allergic inflammation in asthma[18]. A recent study significantly found higher levels of IL-33 and total IgE were detected in asthmatic patients compared with controls[19].

Moreover, Interleukin-33 (IL-33) was connected to the progression of several allergic disorders such as atopic dermatitis (AD) and asthma and also assumed to participate in the acceleration of T-helper17 cell-mediated in mast

cells of airway inflammation process[20]. Therefore, it is obvious from previous immunological studies that IL-33 play both as T-helper2 inducing cytokines and pro-inflammatory cytokine as IL-1 and IL-18[20].

In 1987, Adam first stated that HCMV infection is associated with atherosclerosis: By significant detection of antibody in the case group more than in the control group[21]. Furthermore, HCMV IgG antibody levels are associated with ischemic heart disease (IHD) among organ transplant recipients compared to sero-negativity[21]. As atherosclerosis (AS) is an inflammatory disorder related to numerous risk factors with complex pathophysiology[23]. From various mechanisms associated atherosclerotic plaque, there was evidence propose that an allergic process plays a role in atherosclerosis pathogenesis[24,25].

A study detects a relation of CMV-DNA with a higher risk of atherosclerosis as detection of IgE with allergic immune responses, in patients with acute myocardial infarction or unstable angina pectoris; as double those in patients with stable angina pectoris or without coronary heart disease. Furthermore, CMV-DNA was present in 8 (14.5%) of the cases and 2 (4%) of the controls. (P = 0.03)[26].

The interaction between allergy, atherosclerosis and IgE have gradually come to light. Evidence from in vitro experiments using animal models suggests that the connections between IgE and mast cells trigger the release of a diversity of substances in a direct or indirect way[25,26]. A study was detected CMV DNA in patients with fatal myocarditis and exposed the detection of CMV DNA in cardiomyocytes in the most samples comparing to the control subjects[27]. Another study was revealed patients with coronary artery disease (CAD) had higher serum IgE levels than those without CAD (p = 0.003), so it proposed as Immunoglobulin E (IgE), play a significant role in allergic reactions, it can be involved in the atherosclerosis development[28].

There was a previous controversy hypothesis of the interrelationship between allergies and cardiovascular diseases problems[8]. So, the recent study added to the old hypothesis; it is possible that disorders, with continuous inflammation course, reflected by high levels of proinflammatory cytokines or secretion disturbances that induced by some viral agents throughout old or recent reactivation of viral infection maybe contribute to the pathological process and encourage to induce these disorders as co-factors in the pathogenesis. This problem needs more studies. Hopefully, in the future, they will deliver valuable visions into preventing or treated one disorder in order to prevent the other, by targeting the viral infection or dealing with some of the pro-inflammatory cytokines.

Finally, evidence has suggested IL-33 as therapeutic and beneficial effects as antagonist target in allergic disorders such as asthma, Studies suggesting IL-33 a potential therapeutic target against allergies in murine models of allergic rhinitis, lower airway inflammation, and allergic contact dermatitis[21].

CONCLUSION

The recent study has boundaries, but our outcomes had a statistically significant association in the pathogenesis of the two selected disorders with the studied serological markers, further exploration is needed to validate our recent outcomes. In addition, these finding proposed that interleukin-33 and IgE maybe dependently or independently play a role in the inflammatory process that leads to asthma or heart disorders. Finally, our recent results suggest, that CMV infection (or \ and) recent reactivation may be related to asthma or heart disorders, (and \ or) may contribute to the pathogenesis of them.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS' CONTRIBUTION

All authors have made substantial, direct and intellectual contribution to the work and approved it for publication.

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None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

The current study was approved by the Centre of Ethical Committee

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