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Prevalence of Cytomegalovirus and its Roles in Cytokines Stimulation in Immunocompromised Patients in Mosul City, Iraq

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ABSTRACT

Cytomegaloviruses (CMV) cause different infections in humans all over the world with a prevalence exceeds 70% in adults and 90% in poorer communities and developing countries. Two hundred immunocompromised patients (cancer, dialysis, thyroid gland, and thalassemia) infected with CMV were subjected to determine CMV seroprevalence and its effect on cytokines expression using advance molecular test (Real time PCR) and Serological ELISA test. The results showed high CMV seroprevalence rate in immunocompromised patients but in low rate in thalassemia patients in Mosul city compared with other cities near Iraq. CMV stimulates upregulation in expression (mRNA transcripts) of three cytokines genes (IL-10, TNF, and CCL2) which affect four key immune pathways which in turn may cause severe complication on patients such as asthma and cytokine storm.

Keywords: Cytomegaloviruses, immunocompromised patients, Real time PCR.

INTRODUCTION

Cytomegaloviruses (CMV) cause high rate of infections all over the world with 45% to 100% (Lachmann *et al*., 2018), whereas seropositivity rates in the US adult population ranging between 40 and 90%. CMVs prefer monocytes and other haematopoietic progenitor cells as a good site to survive and stimulate important changes in immune gene expression (Staras *et al.*, 2006). CMV usually infect the patients whom suffer from other chronic diseases that cause weakness in immune system such as cancer, dialysis, thyroid gland and thalassemia (Fulop *et al*., 2013). CMV virus seems infects more than 70% of the human population worldwide, and it is responsible for high morbidity and mortality in immunocompromised individuals (Perotti and Perz, 2020; Goodman *et al.*, 1979).

Cytokines are soluble factors produced by one cell that acts on another cell. Cytokines can also function as integral membrane proteins and some of them are never released from the cell (Roshene *et al.*, 2017).

Chemokines are a group of cytokines includes 28 distinct members of this subgroup reported for mammals, called CC ligand chemokines ligand (CCL-1,2, 3) (Laing, 2004). For chemokines L-2 (CCL2) induce the migration of monocytes, NK cells and dendritic cells against inflammatory infections (Fernandez and Lolis, 2002).

IL-10 can modify the response of immune cells to prevent immuno pathology through inflammatory responses so the virus uses this pathway to escape from host immunity to establish latent or persistent infection (Rojas *et al*., 2017). It coordinates the migration of these cell types both through physiological immune defense and in pathological circumstances, like autoimmune diseases and infectious disease makes it an important therapeutic target (Gschwandtner *et al*., 2019).

Tumor necrosis factors (TNF-α, TNF-β) are produced from cells of the innate immune system such as macrophages in response to infection (Mehta *et al.*, 2003; Alberts *et al.*, 2002). The aims of this study are to determine the level of gene expression of important cytokines that stimulated by CMV infection and detect the prevalence of IgM-CMV, IgG-CMV and DNA-CMV in patients with different level of ages and suffer from different chronic diseases (Cancer, dialysis, thyroid gland and thalassemia).

MATERIALS AND METHODS

Sampling

This study was set out to determine the seroprevalence of CMV in four immuno compromised groups of patients. From September 2019 to February 2020, 200 blood samples were subjected to study. A group of (200) serum samples have been randomly collected from different immune compromised groups of patients (Cancer patients, Hemodialysis patients, Thyroid disorder patients, Thalassemia patients and control), (132 females and 68 males). The samples include (94) cancer patients, (59) hemodialysis patients, (41) Thyroid disorder patients, (6) thalassemia patients, and (50) controls. Their ages are ranging from (10-89) years.

Blood sample collection

A sample of (5) ml of fresh blood has been drawn from each patient and collected in a sterile plastic tube, left to clot at room temperature then centrifuged at (3000) rpm for 10 minutes, and then serum has been collected in sterile tube and stored at -20 ˚c.

Cytomegalovirus IgG detection by ELISA test:

Cytomegalovirus (CMV) IgG ELISA Kit has been used in this study and all instruction were followed according to the manufacturer (bioactiva diagnostic, GmbH, Homburg) including; Collect blood specimens, Reagent Preparation, Assay Procedure, and Calculation of Results

Cytomegalovirus IgM detection by ELISA test:

Cytomegalovirus (CMV) IgM ELISA Kit has been used in this study and all instruction were followed according to the manufacturer company (bioactive diagnostic, GmbH, Homburg,

Germany) including; Collect blood specimens, Reagent Preparation, Assay Procedure, and Calculation of Results.

Estimation of cytokines:

Estimation of the three cytokines was carried out using three kits: CCL2/MCP-1 (human) ELISA Kit (Mybiosource, USA), Human IL-10(Interleukin 10) ELISA Kit (Mybiosource, USA), and Human Tumor Necrosis Factor Alpha (TNF-α) ELISA Kit (Mybiosource, USA). The steps of all tests performed according to the manufacturer company (Mybiosource, USA)

Molecular Detection of CMV

Viral DNA extraction

Isolation of CMV DNA carried out using (QIAGEN Blood DNA Kits).

Real Time PCR test

CMV DNA was amplified using artus® CMV RG PCR technique kit**.** All steps of the technique were carried out according to the manufacturer company (artus® CMV RG PCR technique kit, USA).

RESULTS AND DISCUSSION

The results showed that prevalence of IgG - CMV was 36 % from 200 subjected samples distributed in male and female with 12% and 24% respectively. IgM-CMV Virus prevalence with 2.5% distributes in male and females with 1% and 1.5 % respectively. The total samples include 34% males and 66% females infected with CMV respectively. Real-Time-PCR test revealed the prevalence of CMV DNA with 8.5% (in all 200 samples) distributed in males and females with 5% and 3.5% respectively.

According to the marriage state, the prevalence of IgM-CMV and IgG-CMV in married was 2.5% and 33.5% respectively. For IgG –CMV presents only in not married patient with 2.5% Results from Real-Time-PCR revealed positivity for CMV-DNA with 22.2% and 1.3% in married and not married respectively.

The results recorded that the 200 subjected samples classified into 4 categories according to medical history of patients including four immunocompromised groups represented as cancer group with 47%, dialysis with 29.5 %, thyroid gland with 20.5%, and thalassemia with 3% (Table 1), Fig. (1).

Table 1: Groups of samples subjected to the study according to medical history

Medical history	No.	%
Cancer	94	47%
Dialysis	59	29.5%
thyroid gland	41	20.5%
Thalassemia	6	3%

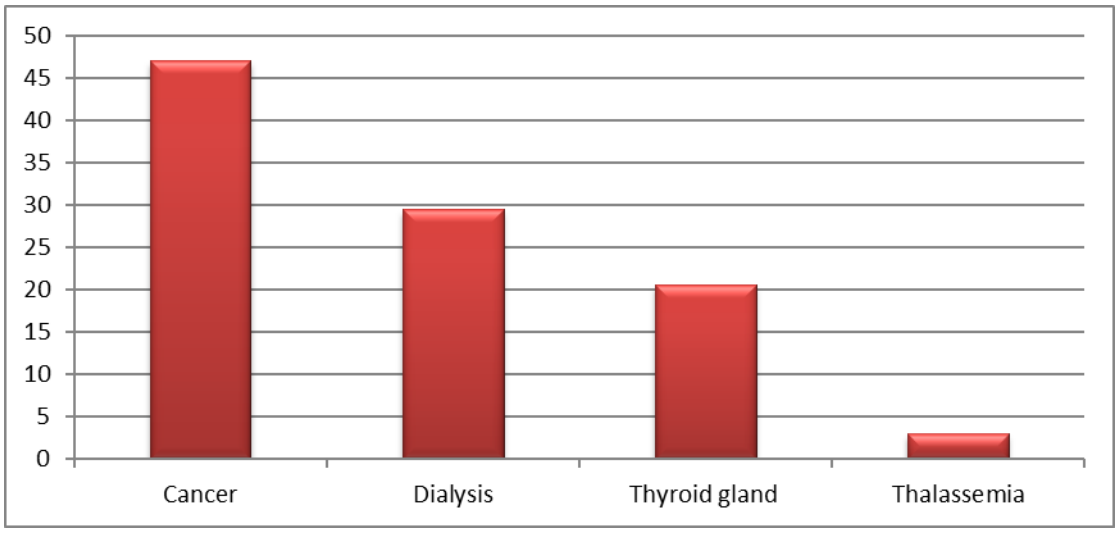

Fig. 1: CMV infections according to medical history.

First group include cancer patients showed 1%, 16.5% and 18% for IgM-CMV, IgG-CMV and Real-Time-PCR-DNA-CMV respectively. For the second group in dialysis patients the IgM-CMV and IgG-CMV present with 0.5 and 8.5% whereas DNA-CMV present in 10%. Third group (thyroid -gland patients) include 1%, 10% and 4% prevalence of IgM-CMV, IgG-CMV and Real-Time-PCR-DNA-CMV respectively. Fourth group with thalassemia showed prevalence with 1% and 2% for IgG-CMV and Real-Time-PCR-DNA-CMV respectively (Table 2), Fig. (2).

Table 2: IgM and IgG-CMV prevalence and positive DNA-CMV- Real-Time-PCR results according to medical history of patients

Medical History of patients	Total No. (%)	IgM +ve No. (%)	IgG +ve No. (%)	Real-Time-PCR +ve +ve No. (%)
Cancer	94 (47%)	2 (1%)	33 (16.5%)	9 (18%)
Dialysis	59 (29%)	1 (0.5%)	17 (8.5%)	5 (10%)
thyroid -gland	41(20.5%)	2 (1%)	20 (10%)	2 (4%)
Thalassemia	6 (3%)	0	2 (1%)	1 (2%)
Control	50	0	18 (36%)	0

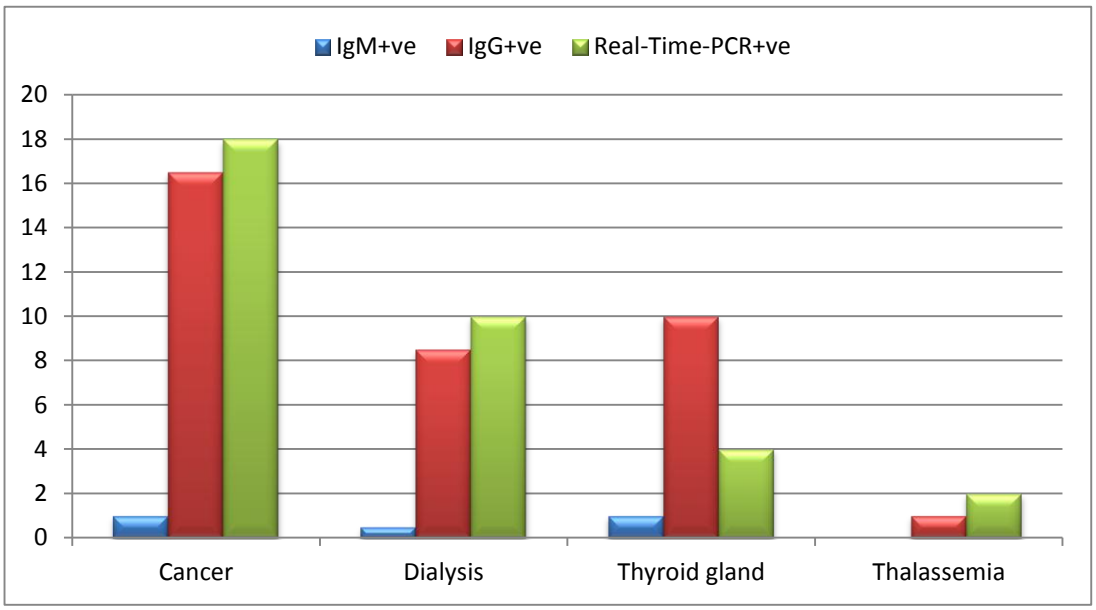

Fig. 2: IgM and IgG-CMV prevalence and positive DNA-CMV- Real-Time-PCR results according to medical history of patients.

The results revealed 9 various groups of age (10-fold years increasing) among the 200 samples. First group (1-9 years) was free from IgM-CMV, IgG-CMV and Real-Time-PCR-DNA-CMV. Second group (10-19 years), showed prevalence of 5% IgG and Real-Time-PCR-DNA-CMV with 1.5% and 1.3%. Third group (20-29 years), gave 7.5% prevalence of IgM-CMV, IgG-CMV and Real-Time-PCR-DNA-CMV with 0.5%, 2% and 1.3%. Fourth group (30-39 years), 13.5% of IgG-CMV and Real-Time-PCR-DNA-CMV appeared with 5% and 1.3%. In fifth group (40-49 years), gave 19% prevalence of IgM, IgG and Real-Time-PCR-DNA-CMV with 0.5%, 7% and 5.55. The group with 50-59 years old showed 30.5% prevalence of IgM-CMV, IgG-CMV and Real-Time-PCR-DNA-CMV with 1%, 11% and 8.3% respectively. Older group (60-69 years) showed prevalence of 18.5% of IgM-CMV (0.5%), IgG-CMV (8.5%) and Real-Time-PCR-DNA-CMV (4.1%). The group with 70-79 years old showed prevalence of 4.5% of IgG-CMV (0.5%) and Real-Time-PCR-DNA-CMV (1.3%). The oldest group (80-89 years) showed prevalence of IgG (0.5%) only (Table 3), Fig. (3).

Table 3: IgM and IgG-CMV prevalence and positive-CMV-RT-PCR test according to age group for patients

Groups	Number (%)	IgM +ve, Nu. (%)	IgG +ve, Nu. (%)	Real-Time-PCR-DNA-CMV,No. (%)
1-9	0	0	0	0
10-19	10 (5%)	0	3 (1.5%)	1 (1.3%)
20-29	15 (7.5%)	1 (0.5%)	4 (2%)	1 (1.3%)
30-39	27 (13.5%)	0	10 (5%)	1 (1.3%)
40-49	38 (19%)	1 (0.5%)	14 (7%)	4 (5.5%)
50-59	61 (30.5%)	2 (1%)	22 (11%)	6 (8.3%)
60-69	37 (18.5%)	1 (0.5%)	17 (8.5%)	3 (4.1%)
70-79	9 (4.5%)	0	1 (0.5%)	1 (1.3%)
80-89	3 (1.5%)	0	1 (0.5%)	0
Total	200	5	72	17

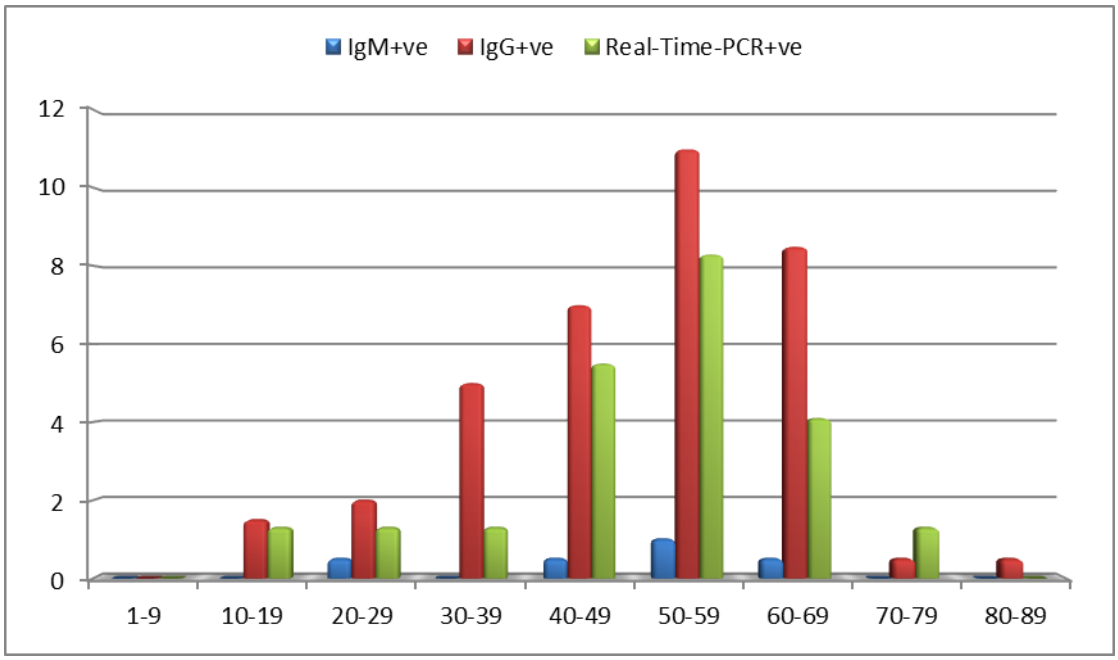

Fig. 3: Distribution of IgM, IgG-CMV and CMV-DNA in age groups

Viral infections regard the most common infectious illnesses in all organisms and human, but in spite of that they are usually self-limiting and limited to the respiratory tract. The early diagnosis of viruses is very important to control viral impact on human. Cytomegaloviruses (CMV) cause high rate of infections all over the world with 45% to 100% (Lachmann *et al.,* 2018), whereas seropositivity rates in the US adult population ranging between 40 and 90%. CMVs prefer monocytes and other haematopoietic progenitor cells as a good site to survive and stimulate important changes in immune gene expression (Staras *et al.,* 2006; Udeze, *et al.,* 2018).

CMV infect with high probability patients suffer from other diseases that cause weakness in immune system such as cancer, dialysis, thyroid gland and Thalassemia and other diseases (Fulop *et al.,* 2013; Rafailidis *et al.,* 2008; Pérez-Solaa *et al.,* 2008).

This study showed that CMV seroprevalence in Mosul city/Iraq is relatively high compared to other countries. The percentage distribution of CMV in females (66%) was more than in males (34%) in this study, this variation may be because females undergoing more CMV contamination during and after delivery especially in rural area. The prevalence of both IgM-CMV and IgG-CMV in males were 1% and 12 % respectively whereas in females they were 1.5 % and 24% respectively.

Previous studies showed gender was main factor effect on the number of immune cells because males who CMV is positive carried less number of total $CD_4^{+,}$ CD_4^{+} central memory (CM) and follicular helper T-cell than females (van der Heiden *et al.,* 2016; Haloschan *et al.,* 2014).These results are also coincide with another study which revealed that seroprevalence of CMV was 6.5% and 7.7% in males and females respectively (Eggert-Kruse *et al.,* 2009).

In this study using Real-Time-PCR-DNA-CMV test the total positive CMV DNA (from 200 patient) was 8.5% (5% in male and 3.5 % in females). To make more assurance of CMV prevalence for patients who are positive to IgG-CMV (72 patients), Real-Time-PCR-DNA-CMV test was done and showed different prevalence of DNA-CMV in both sexes (13.8% in males and 9.7% in females). The different results in both tests (serology and DNA) may belong to high sensitivity and accuracy to Real-Time-PCR.

In previous study in Germany used Real-Time Quantitative PCR for 194 samples revealed higher positive CMV-DNA reached 33.5%. This variation in results may belong to variation in social behavior between Iraq and Germany society (Nitsche *et al.,* 2000). The 200 samples of this study include various groups of patients (47% cancer, 29.5% dialysis, 20.5% thyroid gland and 3% thalassemia). The results of this study showed 36% of seroprevalence of CMV in patients suffer from cancer, dialysis, thyroid gland and Thalassemia with high significance ($P>0.05$) (Table 2), Fig. (2).

The results revealed that 47% of the subjected patients were suffer from cancer. this percentage was the highest within all other sample groups represented with dialysis group, 20.5% thyroid gland group and 3% thalassemia group. Cancer group includes 1% seroprevalence of IgM-CMV, 16.5% of IgG and 18% positive DNA-CMV- Real-Time-PCR (Table 2). Another study showed high percentage (27.5%) of the infected patients with CMV were suffer from cancer (tumor tissue) (Bai *et al.,* 2016; Pacsa *et al.,* 1975).

For patients infected with CMV and suffer from dialysis their total percentage reached 29% (IgM 0.5 %, IgG 8.5% and Real –Time DNA-CMV 10%). Another study recorded that CMV infects immunocompromised persons such as those whom suffer from thalassemia (Manandhar *et al.,* 2019; Cavdar *et al.,* 2008). Other studies revealed that Seroprevalence of CMV in hemodialysis patients varies in different area such as Italy with 67% (Spisni *et al.,* 1992), Czech Republic 80%, Croatia 75.3% (Korcakova *et al.,* 1988), Germany 83% (Sibrowski *et al.,* 1990), in Serbia 99.3% (Trkulic *et al.,* 2000), in Netherlands 68.7% (Betjes *et al.,* 2007).

Previous specific studies on relationship between cancer and CMV were performed and recorded that CMV has the ability to stimulates the infected cells to be tumor cells by modulating the cell signal pathways, transcription factors and tumor suppressor proteins (Cinatl *et al.,* 2004; Michaelis *et al.,* 2009). Other studies recorded relationship between CMV genomes or gene

products with many types of cancers such as breast cancer, cervical carcinoma malignant glioma and Kaposi's sarcoma (Richardson *et al.,* 2015).The relationship between CMV and cancer may be due to the ability of CMV to block the cell proteins that control the cell division to allow the continuous replication of CMV-DNA.

This study revealed a significant relationship between CMV infection and thyroid gland pathogenicity represented with 20.5% of all other samples including IgM-CMV seroprevalence (1%), IgG-CMV (10%), and 4% of DNA-CMV- Real-Time-PCR. These results came in agreement with previous study which showed that CMV infection can induce infected thyroid cells to be cancerous with high significance (Bricout *et al.,* 2013; Zheng *et al.,* 1987; Tidir *et al.,* 1978).

For thalassemia group the patients showed 3% infection with CMV including IgG-CMV seroprevalence with 1% and DNA-CMV- Real-Time-PCR with 2% (Table 2). Previous study revealed significant correlation between CMV infection and β-thalassemia major as red blood cells transfusions in beta-thalassemia major patients increase the probability of CMV infection which in turn cause severe thalassemia complications such reduction of phagocytic and chemotaxis activity of macrophages and neutrophils, reduction in the activity of lymphocytes, and changes in cytokines stimulation (Balouchi *et al.,* 2014). Another study showed significant seroprevalence of CMV with high incidence infection (Liatsos *et al.,* 2017; Nigro *et al.,* 1990).

Concerning the distribution of CMV seroprevalence according to age groups this study revealed that the highest infections of CMV were in three main groups (40-49, 50-59 and 60-69 years). For 40-49 group the prevalence of CMV was 19% (IgM, IgG and Real-Time-PCR-DNA-CMV with 0.5%, 7% and 5.55). The group with 50-59-year-old shoed 30.5% prevalence of IgM-CMV, IgG-CMV and Real-Time-PCR-DNA-CMV with 1%, 11% and 8.3% respectively. Group (60-69 year) showed prevalence of 18.5% of IgM-CMV (0.5%), IgG-CMV (8.5%) and Real-Time-PCR-DNA-CMV (4.1%) (Table 3), Fig. (3).

Other study recorded that CMV infection cause extension of CMV –specific T-cell especially in older individual so this is supposed to suppress immunity to other pathogens and to accelerate immune response (Bajwa, *et al.,* 2017). CMV has wide distribution in the population and its replication is suppressed via the immune system of the host, CMV infection increase the risk of mortality from vascular disease in older people (Firth *et al.,* 2016). From the results of this study it is clear that older patients are more susceptible to CMV infection and this is coincided with another study showed that older people with bladder carcinoma usually associated with viral infections (Saeed *et al.,* 2016). Same results were recorded in previous study as the rate of CMV infection increase with age and that may be impact on survival in the elderly people indirectly (Pawelec *et al.,* 2012).

Another study showed high significant infection of CMV in age less than 1 year (Shohei *et al.,* 2019). Previous studies revealed seroprevalence of CMV in different ration according to age as 34.9% with patient at 20 years old and 72% seroprevalence at 50 years old (Munro *et al.,* 2005; Wang *et al.,* 2011). In Khartum another study recorded seroprevalence of 30 % IgM-CMV classified as 3.6 %, 18% and 8.4% at group age 1-18, 19-30 and > 30 years old respectively. For IgG-CMV the patients showed 81% positivity classified as 5%, 28.75% and 67.5% at groups age ranged between 1-18, 19-30 and >30 years old respectively. Using PCR test, 60 % of patients gave positive CMV-DNA classified as 6.1%, 20.4% and 73.46 % for age groups with 1-18, 19-30 and > 30 years old (Mohammed *et al.,* 2017). In Netherland previous study subjected 6386 persons to investigate seroprevalence of CMV among the age and showed seroprevalence of 45.6% in age ranged between 6 months and 79 years (Korndewal *et al.,* 2015)

Another study recorded gradual increasing of CMV infection with age progressive. Patients with 0-20 years old showed CMV prevalence with 13.88% for females and 13.84 % for males. From 20-40 yr. old gave prevalence with 15.02% (females) and 9.80% (females). From 40-60 yr old revealed prevalence with 13.68% (females) and 9.80% (females). From 60-80 yr old revealed prevalence with 12.20 (females) and 11.60% (males) (van Boven, *et al.,* 2017).

From this study and others previous studies it is clear that the high seroprevalence of CMV was in elder persons (from 40 to 80 years old). In 2018 (Lachmann *et al*., 2018) recorded that CMV Seroprevalence increased with age: from 31.8% to 63.7% in men and from 44.1% to 77.6% in women when comparing the 18–29 with the 70–79 year age-group, respectively. This may belong to activity reduction of immunity in older patients which may increase the viral infection especially in those whom suffer from other diseases.

CONCLUSION

CMV seroprevalence in Mosul city is relatively high when compared to other countries. The percentage distribution of CMV in females was more than in males. Real-Time PCR is more sensitive and accurate than ELISA test. CMV prevalence in married persons is more than in singles. Females are more susceptible to the DNA of CMV than males. CMV prevalence is scattered with high rate in chronic patients (cancer, dialysis, thyroid gland) but in low rate in thalassemia patients. CMV almost infects low educational persons especially those with older age. CMV induce increasing of expression of important cytokines which cause high impact on four key immune pathways in infected cells.

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انتشار فايروس المضخم الخلوي ودوره في تحفيز السايتوكينات في المرضى المنقوصي المناعة في مدينة الموصل، العراق

الملخص

الفيروس المضخم للخلايا يسبب اصابات مختلفة في الانسان حول العالم بنسبة انتشار تتجاوز 70% في البالغين و90% في المجتمعات الاكثر فقرا والبلدان المتطورة، مئتان من المرضى المنقوصي المناعة (اورام، ديلزة، اضطرابات الغدة الدرقية، التلاسيميا) المصابين بالفايروس المضخم للخلايا كانوا هدفا لتحديد انتشار الفايروس المضخم للخلايا وتأثيره على تعبير السايتوكينات باستخدام تقنية جزيئية متقدمة (تقنية التفاعل الحلقي المتسلسل الاني) وتقنية الاليزا السيرولوجية. النتائج اظهرت معدل انتشار واسع للفايروس المضخم للخلايا في المرضى المنقوصي المناعة ولكن بمعدل واطئ في مرضى التلاسيميا في مدينة الموصل مقارنة مع المدن الاخرى في العراق. الفايروس المضخم للخلايا يحفز زيادة في التعبير الجيني (نسخ الحامض النووي الرايبوزي المراسل) لجينات ثلاث سايتوكينات هي (IL-10 , TNF , CCL2) والتي تؤثر على اربع مسارات مناعية رئيسية والتي بدورها ربما تسبب تعقيدات حادة في المرضى مثل الربو وعاصفة السايتوكينات.

الكلمات الدالة: الفايروس المضخم الخلوي، المرضى المنقوصي المناعة، تفاعل البلمرة المتسلسل بالزمن الحقيقي.