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Original Article

Possible Roles of Human Cytomegalovirus Immunoglobulin G and Its Avidity to Specific Human Cytomegalovirus Antigens in the Prevention of Abortion among Pregnant Women

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Abstract

Background: The human cytomegalovirus (HCMV) is a widespread viral pathogen characterized by strict host specificity and is limited to humans. It has been described as an important etiological agent of intrauterine infection during the pregnancy, that causes lifelong infection and may lead to some serious results such as miscarriage, cerebellar malformation stillbirth, and fetus developmental retardation. **Objectives:** The study was carried out in Kirkuk governorate from the August 2021 to April 2022 to analyze the seroprevalence of HCMV-immunoglobulin G (IgG) against some HCMV antigens and its relation to the history of abortion. **Materials and Methods:** A total of 220 pregnant women were examined for the seroprevalence of HCMV-IgG by using electro-chemo-luminescence technique and then examined their reactivity and avidity for specific HCMV antigens using line immune assay. **Results:** The findings of the study showed that among 120 HCMV-IgG seropositive pregnant women, the rates of IgG antibodies were 161 (73.18%). In terms of reactivity and avidity of HCMV-IgG against different HCMV antigens, the rates were as follows: 67 (55.83%) for HCMV IE1, 52 (43.33%) for CM2, 116 (96.66%) for p150, 68 (56.66%) for p65, 117 (97.5%) for gB1, and 82 (68.33%) for gB2 antigens. Among pregnant women with no previous history of abortion, the prevalence of HCMV-IgG reactivity against gB2 was 75.60%. Furthermore, the rates of HCMV-IgG avidity for HCMV antigens were 90.24% for CM2 and 83.05% for p65 antigens. **Conclusions:** This finding may refer to the possible role of the specificity of HCMV-IgG and its high avidity for specific HCMV antigens in the prevention of abortion among pregnant women infected with HCMV infection.

Keywords: Avidity, CM2, ECLIA, gB, HCMV, p150

Introduction

Human cytomegalovirus (HCMV) is one of the eight human herpesviruses that belong to the family Herpesviridae. It is the prototype of the subfamily—Herpesviridae and is described as an important etiological agent of intrauterine infection in pregnant women. This infection can cause a woman to miscarry, stillbirth, or a fetus to have developmental retardation.[1,2] Herpesvirus particles are characterized by three main components: a linear double-stranded DNA (dsDNA) genome packaged within an icosahedral capsid, tegument, and a viral envelope. These components are essential and unique to HCMV virions.[3] Many glycoproteins, including structural tegument and non-structural proteins, are encoded by the HCMV genome. These glycoproteins are essential for cell entrance, regulate cellular tropism, and most likely function as receptor-binding proteins, such as glycoprotein B (gB).[4] The phrase "Immediate Early proteins" (IE) pertains to a set of proteins that not only oversee innate immune responses and various cellular processes but also hold significant importance in the initial phases of lytic HCMV infection.[5] It has been discovered that a large number of tegument proteins accumulate during the infection, which highlights the

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importance of their participation in virion formation. Tegument proteins are involved in multiple different stages of the life cycle of viruses, in addition to their role as constituents of the virion's structural makeup. These processes include the commencement of viral replication as well as its regulation, the release of viral DNA into the nucleus, immune evasion, the intracellular trafficking of virus particles, and the assembly of infectious offspring.[6] The humoral responses to HCMV encompass a variety of proteins, including structural tegument proteins like pp65 and pp150, envelope glycoproteins with a primary emphasis on gB, as well as non-structural proteins such as IE1 and CM2.[7] The advancements in diagnostic techniques, which can have direct implications for the development and implementation of screening programs, as well as the available therapeutic strategies to prevent mother-to-child transmission and to improve the long-term outcomes of infants who are symptomatic have been taken into consideration.[8] It is possible to say that lowering the viral load in the maternal blood, preventing viral entry into the cell by blocking the various viral surface receptors, and forming robust antibody-virion complexes that are then phagocytosed and degraded are all the effects of HCMV-specific immunoglobulins and their avidity on the prevention of congenital HCMV infection.[9] Thus, the current study aims at the effecting of HCMV infection on human immune system and antibodies avidity in pregnant women.

Materials and Methods

A cross sectional study was carried out in Kirkuk city from August 2021 to April 2022. The number of pregnant women understudy were 220 whose age ranged from 18 to 42 years . These women presented in some private medical laboratories in Kirkuk province. An interview was conducted with these pregnant women using a questionnaire form created by the investigator. The variables that were covered in the interview were as follows: age, residency, number of children, history of abortion, and so on. The veins of each woman who participated in this research were punctured with a sterile syringe of 10 mL capacity in order to withdraw 7.50 mL of blood from each participant. Blood samples were placed into two sterile test tubes and left for 30 min at 37°C. After that, they were centrifuged at 3000 rpm for 15 min, after which the clot was removed and the remaining blood was re-centrifuged at 3000 rpm for 10 min twice. Finally, the obtained sera were aspirated using an automatic micropipette and transferred into a clean test tube. Each test tube was stuck with a label, and then placed in the deep freeze at –20ºC until it was time for the subsequent serological tests.

Using an electro-chem-luminescence assay (ECLIA), the detection of specific HCMV-immunoglobulin G (IgG) was carried out.

Using the RecomLine approach, determine the reactivity of the specific HCMV-IgG that was discovered as well as its avidity to the six specific HCMV antigens that were tested (IE1, CM2, p150, p65, gB1, and gB2).

Ethical approval

Approval permission was presented to the director of Kirkuk Health Directorate according to the document number 21247 (including the number and the date in September 8, 2020). An interview was conducted with these patients using a questionnaire form created by the investigator, which included demographic information such as age, sex and so on.

Results

A total 220 pregnant women were examined, and their ages ranged from 18 to 42 years , for detection of specific HCMV-IgG antibody by using ECLIA technique. The overall prevalence of HCMV-immunoglobulin G (IgG) for the 220 pregnant women was 161 (73.18%) [Table 1].

The rates of HCMV-IgG against HCMV antigens among the total 120 seropositive pregnant women were 67 (55.83%), 52 (62.04%), 116 (96.66%), 68 (56.66%), 117 (97.5%), and 82 (68.33%) positive for HCMV IE1, CM2, p150, p65, gB1, and gB2 antigens respectively [Table 2].

Regarding the avidity of HCMV-IgG among pregnant women to specific HCMV antigens, the rates of high avidity was higher than low and intermediate avidity, so the highest rate of high avidity was 92.30% for gB1

Table 1: Overall rates of HCMV-IgG specific antibody among pregnant women by using ECLIA technique

Results	Seroprevalence of HCMV-IgG	
	No.	%
Positive	161	73.18
Negative	59	26.82
Total	220	100

HCMV: human cytomegalovirus, IgG: immunoglobulin G

Table 2: Rates of specific HCMV-IgG in pregnant women against various HCMV antigens by using line immunoassay

HCMV antigens	HCMV-IgG (+)					
	Positive		Negative		Total	
	No.	%	No.	%	No.	%
IE1	67	55.83	53	44.17	120	100
CM2	52	43.33	68	56.67	120	100
p150	116	96.66	4	3.34	120	100
p65	68	56.67	52	43.33	120	100
gB1	117	97.5	3	2.5	120	100
gB2	82	68.33	38	31.67	120	100
$X^2 = 23.571$	$P = 0.00026$		$P < 0.01$ H.S.			

HCMV: human cytomegalovirus, IgG: immunoglobulin G

Table 3: The avidity of HCMV-IgG to various HCMV antigens

HCMV antigens	HCMV-IgG avidity							
	IgG avidity							
	High		Low		Intermediate		Total	
	No.	%	No.	%	No.	%	No.	%
IE1	61	91.04	4	5.98	2	2.98	67	100
CM2	41	78.84	8	19.51	3	5.76	52	100
p150	106	91.37	8	11.60	2	1.73	116	100
p65	59	86.74	7	10.29	2	2.97	68	100
gB1	108	92.30	7	5.98	2	1.72	117	100
gB2	75	91.46	5	6.09	2	2.43	82	100
$X^2 = 13.023$	$P = 0.222$			$P > 0.05$ N.S.		N.S.		

HCMV: human cytomegalovirus, IgG: immunoglobulin G

Table 4: Relation HCMV-IgG against various HCMV antigens with the history of abortion and abortional frequency among pregnant women

HCMV antigens	HCMV-IgG									
	History of abortion									
	No abortion		One abortion		Two abortions		Three abortions or more		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
IE1	48	71.76	9	13.43	6	10.46	4	5.98	67	100
CM2	37	71.15	4	7.69	5	9.61	6	11.55	52	100
p150	86	74.13	13	11.20	10	8.62	7	6.03	116	100
p65	49	72.05	8	11.76	6	8.82	5	7.35	68	100
gB1	86	73.50	12	10.25	11	9.40	8	6.83	117	100
gB2	62	75.60	11	13.41	6	7.31	3	3.65	82	100
$X^2 = 7.942$			$P = 0.023$		$P < 0.05$		Significant			

HCMV: human cytomegalovirus, IgG: immunoglobulin G

antigen, while the highest rates of low and intermediate avidity were 19.51% and 5.76%, respectively, seen for CM2 antigen [Table 3].

Among women with HCMV-IgG antibodies, the reactivity to various HCMV antigens was examined in relation to their history of abortion and abortional frequency. It was observed that the highest rate of women with IgG antibodies showed reactivity against the gB2 antigen (75.60%), and notably, these women did not have a history of abortion [Table 4].

Regarding to the correlation the avidity of HCMV-IgG seropositive to various HCMV antigens with the history of abortion and abortional frequency, the highest rate of HCMV-IgG avidity (90.24%) was for CM2 antigen seen within pregnant with no history of abortion, whereas different rates of low and intermediate of HCMV-IgG avidity to most HCMV antigens were seen among different abortional frequency groups [Table 5].

Discussion

Human-CMV is the most frequent congenitally transmitted disease found everywhere in the world. It is also a key contributor to long-term neurologic impairments, such as deafness, microcephaly, and neuro-developmental delay, in addition to fetal loss and occasional newborn mortality.[1] As a result, having an understanding of the prevalence state of HCMV antibodies among pregnant women as well as the maternal immunity that correlates with protection against congenital HCMV is essential for informing the design of an effective maternal and considering the significance of intrauterine HCMV infection transmission and its associated complications, it appears necessary to investigate the prevalence of HCMV infection during pregnancy and interpret the results in order to know the history and the current status of the disease. In addition, no study of a comparable nature has been published among pregnant women in Iraq or in many other countries; hence, the purpose of this study was to determine the humeral immune response, its avidity to several HCMV antigens, and its link to maternal immunoglobulins.

Although the present study recorded the rate of HCMV-IgG prevalence close to the world prevalence ranges of HCMV-IgG 40%–100%, and regardless to the different serological tests may be used in other studies in Iraq and

Table 5: Correlation the HCMV-IgG avidity to various HCMV antigens with the history of abortion and abortional frequency among pregnant women

HCMV-Ag (No.)	Avidity	HCMV-IgM(–)/IgG (+)									
		History of abortion									
		No abortion		One abortion		Two abortions		Three abortions or more		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
IE1 (67)	High	48	78.68	8	13.13	4	6.55	1	1.64	61	100
	Low	0	0	1	25.00	1	25.00	2	50.00	4	100
	Intermediate	0	0	0	0	1	50.00	1	50.00	2	100
CM2 (52)	High	37	90.24	2	4.88	1	2.44	1	2.44	41	100
	Low	0	0	1	12.50	3	37.50	4	50.00	8	100
	Intermediate	0	0	1	33.33	1	33.33	1	3.33	3	100
p150 (116)	High	86	81.14	12	11.32	6	5.66	2	1.88	106	100
	Low	0	0	1	12.50	3	37.50	4	50.00	8	100
	Intermediate	0	0	0	0	1	50.00	1	50.00	2	100
p65 (68)	High	49	83.05	7	11.86	2	3.38	1	1.69	59	100
	Low	0	0	1	14.28	3	42.85	3	42.85	7	100
	Intermediate	0	0	0	0	1	50.00	1	50.00	2	100
gB1 (117)	High	86	79.64	12	11.11	7	6.48	3	2.77	108	100
	Low	0	0	0	0	3	42.86	4	57.14	7	100
	Intermediate	0	0	0	0	1	50.00	1	50.00	2	100
gB2 (82)	High	62	82.66	9	12.00	4	5.34	0	0	75	100
	Low	0	0	1	20.00	2	40.00	2	40.00	5	100
	Intermediate	0	0	1	50.00	0	0	1	50.00	2	100
		$X^2 = 54.367$		$P = 0.0014$		$P < 0.01$		H.S.			

HCMV: human cytomegalovirus, IgG: immunoglobulin G

other countries which mainly used ELISA technique so the ECLIA is a powerful tool and is highly amenable to the study. These studies showed occasionally the same or closed results as in Kenya 77.3%, whereas others revealed higher rates including; in Iraq (Diylah) 100% and (Sulaymaniyah) 90.2%, in Egypt and Turkey were 100%, in Yemen 99.0%, in Iran 98.8%, in China 98.7%, in Sudan 97.5%, in Palestine 96.6%, in Nigeria 94.8%, and in Ethiopia 88.5%, but higher than that recorded by other studies; in Japan 69.1%, in Mexico 65.5%, in Australia 57.0%, in the United Kingdom 49.0%, and in France 43.7%.[2-15] Also the IgM antibodies present in the sample mainly bind to few number of HCMV antigens, while IgG antibodies mainly react with the total viral particle and majority of the commercial serologic tests are capable of detecting antibody responses to viral lysates covering a large repertoire of HCMV epitopes.[16,17] The HCMV virus encodes two type I transmembrane receptors with Fcγ-binding properties, namely gp34 and gp68. These receptors, encoded by independent genes TRL11/IRL11 and UL119-UL118 respectively, are known as vFcγRs. They are capable of recognizing the Fc domain of IgG antibodies and have the ability to trigger both humoral and cellular immune responses. These receptors specifically bind to human IgG but not IgM, and they can bind all four subclasses of human IgG (IgG1, IgG2, IgG3, and IgG4). The shared binding properties of gp34 and gp68 for human IgG make them important components of HCMV's ability to interact with the immune system.[18,19]

Regarding to the lowest rate of the reactivity of determined HCMV antibodies to various examined HCMV antigens were 43.33% for CM2 antigen especially with HCMV-IgG seropositive with highly significant relation ($P < 0.01$). It has been demonstrated through research that reactivity against the CM2 antigens is definitely associated with primary infections and increases with them.[17] This discovery might be because not all components or sequences of CM2 antigen activate or stimulate the immune system, particularly the humeral immune response. It is common knowledge that the core of pUL57 contains a major reactive protein, which is active in the cases of acute HCMV infection.[18] A reactivity against CM2 was able to be detected a couple of months after the starting point for a few months into the infection. There is a possibility that the earlier reactivity with CM2 for this patient was caused by a stronger reactivity against the midsequence of the pUL57 protein that is found in the CM2 antigen.[19] Additionally, human-CMV displays high levels of genetic diversity even within a single infected individual (intrahost diversity). In a manner analogous to that of interhost variability, the majority of the data on intrahost diversity have concentrated on the HCMV

glycoproteins.[20] In point of fact, a level of intrahost genetic diversity that is measurable was observed in nearly every open reading frame (ORF) of the HCMV genome. As a result of these studies, it has become abundantly clear that HCMV exhibits an extremely diverse genetic makeup within humans.[21] It was hypothesized, based on the functions of gB, that any change in the gB gene could make a person more susceptible to HCMV disease, either by facilitating viral replication or by eliciting a severe immunopathological response. However, this hypothesis was disproved.[15] When looking at the avidity of HCMV-IgG among pregnant women who tested positive for HCMV-IgG, the current study found that the rates of high avidity were higher than the rates of low and intermediate avidity; consequently, the highest rate of high avidity was 92.30% for gB1 antigen with a relation that was not significant ($P > 0.05$). This finding may be due to the fact that the majority of cases of HCMV infection among pregnant women were infections that occurred in the past. It is also possible that these women were exposed to the source of HCMV transmission and were infected before becoming pregnant, despite the fact that there was a recent and reactivation infection found. The results may not be statistically significant because the rates of high avidity for all antigens are significantly higher than the rates of low and intermediate avidity with the same and closed rates. The research done on the 3D structural domain of gB showed that it contains the homologous domain that shares an epitope with a virus-neutralizing antibody. This domain has been described as being highly immunogenic.[20] Given that gB plays such a central role during the fusion process, host defense mechanisms are likely to focus their attention on this protein. Indeed, gB was found to be a primary target for virus-neutralizing antibodies, and gB-specific antibodies may be found in practically all people who are infected with HCMV.[21] However, gB is also responsible for the production of a significant number of antibodies that do not neutralize the virus.[22,23] The structural integrity of AD-1 is determined by a disulfide bond between cysteine residues 573 and 610 of gB, and the establishment of this bond is necessary for the binding of conformation-dependent neutralizing antibodies. Two distinct antibody binding sites are found on the AD-2, which results in the production of neutralizing antibodies.[24] Except for the fact that 100% of HCMV-convalescent sera contain AD-3-reactive antibodies, the AD-3 is composed of gB residues that are located in the cytoplasmic/intraviral region of gB. There are largely conformational epitopes for neutralizing antibodies located in the AD-4 domain, which is a discontinuous domain. More than 90% of people who are infected with HCMV have AD-specific antibodies.[25] In addition to being a target for antibodies that neutralize viruses, the AD-5 protein, which corresponds to structural domain I.[26,27] Taking into account the avidity of HCMV-IgG seropositive pregnant women, the current study found that the rates of high avidity were higher than the rates of low and intermediate avidity; consequently, and the highest rate of high avidity was 92.30% for gB1 antigen with a relation that was not significant ($P > 0.05$). It has been demonstrated through research that reactivity against the CM2 antigens is definitely associated with primary infections and increases with them.[17] This discovery might be because not all components or sequences of CM2 antigen activate or stimulate the immune system, particularly the humeral immune response. 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primary target for virus-neutralizing antibodies, and gB-specific antibodies may be found in practically all people who are infected with HCMV.[21] However, gB is also responsible for the production of a significant number of antibodies that do not neutralize the virus.[22,23] The structural integrity of AD-1 is determined by a disulfide bond between cysteine residues 573 and 610 of gB, and the establishment of this bond is necessary for the binding of conformation-dependent neutralizing antibodies. Two distinct antibody binding sites are found on the AD-2, which results in the production of neutralizing antibodies.[24] Except for the fact that 100% of HCMV-convalescent sera contain AD-3-reactive antibodies, the AD-3 is composed of gB residues that are located in the cytoplasmic/intraviral region of gB. There are largely conformational epitopes for neutralizing antibodies located in the AD-4 domain, which is a discontinuous domain. More than 90% of people who are infected with HCMV have AD-specific antibodies.[25] In addition to being a target for antibodies that neutralize viruses, the AD-5 protein, which corresponds to structural domain I.[26,27] Taking into account the avidity of HCMV-IgG seropositive pregnant women, the current study found that the rates of high avidity were higher than the rates of low and intermediate avidity; consequently, the highest rate of high avidity was 92.30% for gB1 antigen with a relation that was not significant ($P > 0.05$).

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Conflicts of interest
There are no conflicts of interest.

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