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Original Article

Prevalence of Anti-Human Herpes Virus Type 7 IgG Positivity Rate among Children with Fever and Skin Rash in Diyala Province, Iraq

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Abstract

Human herpesvirus 7 (HHV-7) is a T-lymphotropic virus isolated from peripheral blood mononuclear cells as beta herpes viruses. It is a highly prevalent virus since over 90% of adults are seropositive. The majority of primary infection occurs in early childhood, and its prevalence peaks at 60 % in 11–13-year-old. This study was designed to investigate the seroprevalence of HHV- 7 infections among apparently healthy children as well as child patients with fever and skin rash in the Diyala community and its association with certain socio-demographic variables. The current study is a cross-sectional study conducted in Diyala province-Iraq, extending from July 2020 to March 2021. A total of 180 child patients with fever and skin rash were included. Their age range was 1-14years. Additionally, 60 healthy age-matched children were enrolled as a control group. A special questionnaire was prepared for this study, including socio-demographic information, clinical notes and the results of a complete blood count. Human privacy was esteemed by obtaining parents' verbal approval. Blood specimen was aspirated from all study groups. Sera were separated and kept at -20 ^{0}C until tested. Enzyme-linked immunosorbent assay (ELISA) kits for the detection of anti-HHV-7 IgG were used (Mybiosource-China). Statistical analysis was done using Statistical Package of Social Science (SPSS) version 27, and the P value was considered significant wherever it was less than 0.05. The anti-HHV-7 IgG positivity rate in patients was 19.4%, and that in healthy individuals was 31.7%, with an insignificant difference (*P*=0.051). The highest HHV-7 IgG positivity rate was found among patients 1-4 years old, matching that in the healthy group with a statistically insignificant difference (*P*=0.675). The gender, residence and number of children/ family insignificantly affect the distribution of HHV-7 IgG in the control group. The mean±SD of hemoglobulin (Hb) concentration among participants with negative anti-HHV-7 IgG was insignificant compared to their positive counterparts (*P*=0.987). The mean±SD of total WBC count among those positive for anti-HHV-7 IgG was insignificantly higher than their negative counterpart (*P*=0.945). The mean±SD lymphocyte count in patients and healthy control positive for anti-HHV-7 IgG were insignificantly higher (*P*=0.241) and (*P*=0.344), respectively. Lastly, healthy control positive for anti-HHV-7 IgG had insignificantly higher lymphocyte count (*P*=0.710). About one-third of healthy children in our community were seropositive for anti-HHV 7 IgG antibodies that are most prevalent at 1-4 years old and are insignificantly associated with gender, residence, and the number of children per family. Furthermore, the HHV-7 infection is insignificantly associated with alterations of complete blood count parameters.

Keywords: Human herpesvirus-7, Roseola infantum, Diyala province

1. Introduction

The HHV-7 is a member of the *Roseolovirus* genus within the Betaherpesvirinae subfamily of *the herpesviriodae* family. It was first detected from purified, activated $CD4^+$ T lymphocytes from the peripheral blood of a healthy individual (1). HHV-7 is

closely related to human herpesviruses-6 (HHV-6). HHV-7 infection occurs in early childhood and causes a short febrile disease frequently associated with a skin rash called exanthema subitum or roseola infantum (2). HHV-7 infection also leads to or is associated with a number of other symptoms, including acute febrile respiratory disease, vomiting, diarrhea, low lymphocyte counts, and febrile seizures (3). The clinical manifestations of primary and reactivated HHV-7 infections are similar, except those seizures occurred more frequently in reactivated infections. These findings, previously unrecognized in otherwise healthy children, suggest that HHV-7 viremia can represent primary or reactivated infection and may be affected by the interaction between HHV-6 and HHV-7 (4). It has been found that HHV-7 is associated with the classic fever of unknown origin (FUO) (5).

The HHV-7 is ubiquitous and is responsible for lifelong latent infections in macrophages and T-lymphocytes, most often asymptomatic. It resides primarily in $CD4^+$ T cells since it uses the CD4 and possibly some cell-surface glycoproteins to enter $CD4^+$ T cells (6). Reactivation of latent HHV-7 may cause a mononucleosis-like syndrome. HHV-7 is highly prevalent in the healthy population, with over 90% of adults being seropositive to the virus (7). Primary infections frequently occur in early childhood. Anti-HHV-7 antibodies were detected in infants under 2 years old or later. Seroconversion occurs in 3- to 4-year-old (8): the HHV-7 infects T cells, monocytes-macrophages, epithelial cells, and central nervous system cells. The latent viral persistent infection is established in salivary glands, and the virus is continuously shed through the saliva (9). So, it has been readily detected in the saliva of healthy adults, suggesting that saliva plays a role in the horizontal transmission of the virus via close contact between parents and children (2). Additionally, breastfeeding may be a possible route of transmission (10).

The seroprevalence of HHV-7 reaches 75% in 3- to 6-year-old children and 98% in adults (11). Anti-HHV-7 antibody titers are high (94.4%) in children in the first 2 months, possibly due to maternal antibodies, followed by a reduction to 30% between 6-7 months. Then re-increased after 8 months (8). The prevalence of antibodies to HHV-7 increases with age; 60% of young adolescents have detectable titers. The anti-HHV-7 antibodies are sustained into adulthood, as sera from 92% of healthy adults are seropositive (12).

Most of the studies affirm the higher role of HHV-6 in the causation of roseola infantum in children compared to HHV-7 (13). In this regard, it has been found that more than half of the children were infected with HHV-6B prior to HHV-7 (14). However, the distinction between the primary role in the causation of roseola infantum, whether HHV-6 or HHV-7 and the cross-reactivity of these viral antibodies are still puzzling worldwide (15).

2. Materials and Methods

2.1. Study Design and Sampling

The current study is a cross-sectional conducted in Diyala province from July 2020 to March 2021. A total of 180 child patients with fever and skin rash were included. Their age range was 1 -14 years. Additionally, 60 healthy children were enrolled as the control group aged 1-14. Patients were allocated and collected from Al-Batool Teaching Hospital for Maternity and Children and other Healthcare centres in the Diyala Directory of Health. A special questionnaire form was reconstructed for this study which includes socio-demographic information plus clinical notes and the results of a complete blood count. Blood specimen was aspirated from all patient and control groups. Sera were separated and kept at -20 ^{0}C until testing. An ELISA kit for the detection of anti-HHV-7 (Mybiosource-China) was used.

2.2. Statistical Analysis

Statistical analysis was done using Statistical Package of Social Science (SPSS) version 27, and the *P*-value was considered significant wherever it was less than 0.05.

3. Results

Concerning the any-HHV-7 IgG positivity rate, the results showed that 33 (19.4%) of the patients were positive versus 137 (80.6%) were negative, while in the healthy group, 19 (31.7%) were positive for anti-HHV-7 IgG and 41 (68.3%) were negative. However, the difference between the two groups was insignificant statistically (*P*=0.051) (Table 1).

The results in a table 2 found that one patient who was positive for anti-HHV-7 IgM was also positive for anti-HHV-7 IgG against 26 (96.3%) who were negative for anti-HHV-7 IgM but positive for anti-HHV-7 IgG. So, the difference was statistically significant (*P*=0.038). In the healthy group, only one individual who was positive for anti-HHV-7 IgM was also positive for anti-HHV-7 IgG, while 18 (94.7%) were negative for anti-HHV-7 IgM but positive for anti-HHV-7 IgG, with a statistically insignificant difference (*P*=0.405).

Data in table 3 found that the HHV-7 IgG positivity rate (20.0%) among patients 1-4 years old was insignificant higher compared to other age groups (*P*=0.678). In the control group, the HHV-7 IgG positivity rate among those 1-4 years old was insignificantly higher (*P*=0.675). Regarding gender, the anti-HHV-7 IgG positivity rate was insignificantly different between male and female patients (16.7% Vs 21.7%, *P*=0.405) and between healthy males and females (34.5% Vs 29.0%, *P*=0.650). Concerning the residence, the HHV-7 IgG positivity rate among urban patients (20.1%) was insignificantly higher (*P*=0.463). Among the healthy, only those residing in the urban areas had a 31.7% positivity rate of anti-HHV-7 IgG. Concerning the number of children in the family, the results of patients revealed that families with four children had the highest anti-HHV-7 IgG positivity but with an insignificant difference (*P*=0.124). In the healthy control group, families with 5 or more children had the highest anti-HHV-7 IgG positivity (35.0%) but with an insignificant difference (*P*=0.839).

Table 1. Distribution of anti-HHV-7 IgM and IgG in study groups

Variables	Patients		Control		*P*-value
	No.	%	No.	%	
Anti-Human Herpes Virus 7 (Anti-HHV-7) IgM					
Positive	22	17.1	6	10.0	0.204 *
Negative	107	82.9	54	90.0	
Anti-Human Herpes Virus 7 (Anti-HHV-7) IgG					
Positive	33	19.4	19	31.7	0.051 *
Negative	137	80.6	41	68.3	

*Insignificant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level

Table 2. Association of anti-HHV-7 IgM with anti-HHV-IgG in study groups

Anti-HHV-7 IgG	Patients				Controls			
	Anti-HHV-7 IgM				Anti-HHV-7 IgM			
	Positive		Negative		Positive		Negative	
	No.	%	No.	%	No.	%	No.	%
Positive	1	3.7	26	96.3	1	5.3	18	94.7
Negative	21	20.6	81	79.4	5	12.2	36	87.8
P-value	0.038*				0.405 *			

*Insignificant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level

Table 3. Association of anti-HHV-7 IgG positivity with social variables of study groups

Variables	Patients				Controls			
	Anti-HHV-7 IgG				Anti-HHV-7 IgG			
	Positive		Negative		Positive		Negative	
	No.	%	No.	%	No.	%	No.	%
Age (Ys)								
1---4	12	20.0	48	80.0	7	36.8	12	63.2
5---9	16	21.3	59	78.7	8	33.3	16	66.7
10---14	5	14.3	30	85.7	4	23.5	13	76.5
P-value	0.678 *				0.675 *			
Gender								
Male	13	16.7	65	83.3	10	34.5	19	65.5
Female	20	21.7	72	78.3	9	29.0	22	71.0
P-value	0.405 *				0.650 *			
Residence								
Rural	2	12.5	14	87.5	-	-	-	-
Urban	31	20.1	123	79.9	19	31.7	41	68.3
P-value	0.463 *				-			
No. children/family								
One	1	16.7	5	83.3	1	25.0	3	75.0
Two	10	27.8	26	72.2	3	30.0	7	70.0
Three	6	17.1	29	82.9	5	41.7	7	58.3
Four	11	28.2	28	71.8	3	21.4	11	78.6
≥ Five	5	9.3	49	90.7	7	35.0	13	65.0
P-value	0.124 *				0.839 *			

*Insignificant difference among percentages using Pearson Chi-square test (χ^2-test) at 0.05 level

The Association of anti-HHV-7 IgG with CBC parameters is shown in table 4. Regarding the mean±SD concentration of hemoglobulin (Hb), there was a slight insignificant increase of Hb in patients with negative anti-HHV-7 IgG compared to their positive counterparts (11.7±15 *Vs* 11.2±1.2) (*P*=0.746). Similarly, in the healthy, there was a slightly increased in the mean ± SD of Hb concentration among individuals with negative anti-HHV-7 IgG compared to their positive counterparts (11.9±1.1 *Vs* 11.3±0.9) (*P*=0.987). Concerning the mean±SD of PCV, the patients' results showed an insignificant increase in patients with negative anti-HHV-7 IgG compared to their positive counterparts (36.8±3.7 *Vs* 35.6±3.6) (*P*=0.821). In the healthy group, individuals with negative anti-HHV-7 IgG had higher PCV than their positive counterparts (37.7±1.2 *Vs* 35.9±1.4), but the difference was statistically insignificant (*P*=0.088).

In connection with the total WBC count, patients with positive anti-HHV-7 IgG had higher but insignificant mean±SD of WBC count compared to their negative counterparts (8.7±1.4 *Vs* 7.6±1.6) (*P*=0.975). Similarly, individuals in the healthy group with positive anti-HHV-7 IgG had insignificantly higher counts than their negative counterparts (6.8±2.6 *Vs* 6.4±2.3) (*P*= 0.945). Concerning the lymphocyte count, the mean±SD count in patients with positive anti-HHV-7 IgG was insignificantly higher than in their negative counterparts (3074.4±1302 *Vs* 2914.2±1194) (*P*=0.241). In the healthy group, individuals positive for anti-HHV-7 IgG had insignificantly higher than their negative counterparts (2914.2±1194 *Vs* 2640.1±891), (*P*=0.344). Lastly, patients with positive anti-HHV-7 IgG had insignificantly lower platelet counts than their negative counterparts (302.9±82.8 *Vs* 302.9±82.8) (*P*=0.328). In comparison, healthy individuals with positive anti-HHV-7 IgG had insignificantly higher than their negative counterparts (338.9±94 *Vs* 310.5±82) (*P*=0.710).

Table 4. Association of anti-HHV-7 IgG positivity with CBCs in study groups

CBC Parameters	Anti-Human Herpes Virus 7 (Anti-HHV-7) IgG			
	Patients		Controls	
	Positive	Negative	Positive	Negative
Haemoglobin (g/dL)	11.2±1.2	11.7±15	11.3±0.9	11.9±1.1
P-value	0.746 *		0.987 *	
PCV (%)	35.6±3.6	36.8±3.7	35.9±1.4	37.7±1.2
P-value	0.821 *		0.088 *	
WBC ($\times 10^3$ cell/cu.mm)	8.7±1.4	7.6±1.6	6.8±2.6	6.4±2.3
P-value	0.975 *		0.945 *	
Lymphocytes	3074.4±1302	2914.2±1194	2763.6±852	2640.1±891
P-value	0.241 *		0.344 *	
Platelets count ($\times 10^3$ plate. l/cu.mm)	302.9±82.8	287.3±70.0	338.9±94.	310.5±82
P-value	0.328 *		0.710 *	

4. Discussion

This study is emerging from the importance of roseola infantum, a common illness in childhood caused by a primary infection by HHV-6 and/or HHV-7. It is also known as exanthema subitum or the sixth disease because it ranks as the sixth condition, following measles, scarlet fever, rubella, Duke's disease, and parvovirus B19, causing skin rash in infants (3).

To explore the prevalence of roseola infantum among Diyala children, the contribution of both causative viruses, HHV-6 and HHV-7, should be investigated. We started with the HHV-6 in 2018; at that time, the anti- HHV-6 IgM positivity rate among children 6-24 months who complained of fever and skin rash was 45.6%, and the highest positivity rate was among the age group 1-6 months. Additionally, the anti- HHV-6 IgM positivity was higher among children with breast milk and those whose mothers complained of infection during pregnancy (16). On the other hand, the anti-HHV6 IgG positivity among apparently healthy infants was 43.9%. The highest positivity was among those 19-24 months old, and a significantly higher anti-HHV6 IgG positivity was found among infants whose families had a recent history of positive cases (9). After that, to complete the epidemiological picture of roseola infantum, the prevalence of HHV-7 was explored in the present study.

The current study found that the anti-HHV-7 IgG positivity rate among child patients with fever and skin rash was 19.4% versus 80.6 % who were negative, while among healthy control, the positivity rate was 31.7% and 68.3% were negative. It was well documented that the seroprevalence of HHV-7 and HHV-6 was greatly variable worldwide and that almost all people are exposed firstly to HHV-6 and secondly to HHV-7 during childhood (17). Because HHV-6 and HHV-7 are closely related in genome organization and sequence, the cross-reactive antibody responses between HHV-6 and HHV-7 have been reported.

In a study that included sera of healthy blood donors from nine countries using indirect immunofluorescent assays, Lan and Luo (17) reported that the prevalence of anti- HHV-7 antibodies is high (75–98%) in all countries except for Northern Japan (44%). There were regions of low, intermediate and high mean antibody titers against HHV-7 such as 78.5–91.3 for Belgium, Israel, Japan, USA and Australia, 175.4–182.6 for Mexico and Cologne/Germany, and 389.2 for South Africa for which geographic characteristics may be responsible, suggesting that HHV-7, similar to HHV-6, is a widespread human herpesvirus with elevated antibody titers in the healthy human population. Additionally, among Mexican blood donors using the indirect immunofluorescence test, the anti-HHV-7 positivity rate was 98.5%, and nearly 85% had high

titers (18). Therefore, a future study to explore the anti-HHV-7 titers among the general population is recommended to recognize which region Iraq belongs to.

Among healthy Hungarian children aged 6 - 18 months, the anti- HHV-7 was found in 19.0% of children before 12 months, but the majority were infected after that age. More than half of the children were infected with HHV-6B prior to HHV-7. Anti-HHV-7 antibodies were higher in girls compared to boys (15). The present study found that 20% of children had anti-HHV-7 IgG at 1-4 years old, and females and urbanites had insignificantly higher HHV-7 IgG positivity than their counterparts. Thus, a comprehensive study is suggested to address the seroprevalence of all betaherpesviruses among Iraqi children.

Furthermore, in a seroprevalence study, children aged 3 months to 6 years and from cord blood were tested. The HHV-6 seropositivity rate increased from 19% to 79.3% in the first eighteen months of life, while the HHV-7 seroprevalence reached a similar level (75.9%) in children aged 3-6 years. These results show that HHV-7, like HHV-6, is a prevalent virus in infancy. In cord blood sera, a similar value for the two viruses (78.9% for HHV-6 and 76.3% for HHV-7) was found, affirming that HHV-6 primary infection generally precedes that by HHV-7 (11). It was found that the HHV-7 prevalence in the USA population was >85%; however, in Japan, a low prevalence was reported. The primary infection of HHV-7 appears later in life than HHV-6, while HHV-7 can be more readily isolated from the saliva than HHV-6 (19).

Molecular and epidemiological analysis revealed that HHV-7 was transmitted horizontally from grandparents to parents and children through close contact within a household. Of note, either parent can transmit HHV-7 to the children. A follow-up study on saliva samples revealed that the titer of HHV-7 DNA differed in each individual and that "high producers" and "low producers" can be recognized. Maternal antibodies against HHV-7 tended to be higher and remain longer after birth than those of HHV-6. Thus, these findings are consistent with the clinical observation affirming that HHV-6 infection occurs earlier than HHV-7 infection (20). This is very important in our community since kissing of newly born or infants by his/her parents, grandparents, brothers/sisters, or even relatives is an inherited custom among Iraqi families. These may form the main route for transmission of all betaherpesviruses to offspring. Another important clinical feature of HHV-7 infection is that most infections during childhood remain apparent (21). Although it was insignificant, the results in this study found that the presence of four children in the family increases the chance of infection by HHV-7, suggesting that siblings in the family may infect each other.

In Japan, the positivity rate of anti-HHV-7 antibody was 40% in the first 2 months of life, which declined during the first 6 months, then gradually increased to 45% at 1-4 years till it reached the highest level (60%) at 11-13 years of age that was maintained until the end of the third decade, then decreased after that (22). In the present limited study, the highest ant-HHV-7 positivity rate was among those 5-9 years old. Thus, more extensive studies are required among immunocompetent or immunocompromised people to clarify this feature more precisely.

Numerous neurological manifestations have been associated with HHV-7 primary infection in children and occasionally in immunocompromised adult patients (22). Additionally, reactivation of latent HHV-7 may cause CNS disease in immunocompetent adults, as detected by the presence of HHV-7 DNA in CSF (23). Besides the possible role of HHV-7 in certain myelo radiculo neuropathy and malignancies (24) and hemiconvulsion-hemiplegia-epilepsy syndrome. Collectively, these observations make this virus of serious concern, and thus future molecular or immunological studies are recommended to address these query points in the community.

There are several reports on the association of roseola viruses and the development of drug-induced hypersensitivity syndrome or some tines called drug

reaction with eosinophilia and systemic syndrome (24). Additionally, lymphadenopathy was found in 54% of patients with drug-induced hypersensitivity syndrome (25). It is well known that HHV-7 is a lymphotropic virus that infects and resides in $CD4^+$ T lymphocytes using the $CD4^+$ molecule. At the same time, HHV-7 has a number of effects on these cells, including membrane leaking, lytic syncytia, occasional apoptosis, supporting of latent infection, up or downregulating levels of specific cytokines and enhancement of natural killer cell cytotoxicity (26). These effects collectively and gradually decrease the number of circulatory lymphocytes affirming the lymphopenia found in this study.

Another result obtained by this study is the significantly lower mean platelets count (thrombocytopenia) in patients compared to the control. This result is consistent with a fact reported that the HHV-7 has the potential to infect hematopoietic stem and progenitor cells and impair hematopoietic stem and progenitor cells' survival and proliferation, presumably *via* lysis or induced cell death. Since all blood cells develop from the hematopoietic stem cells in the bone marrow through a process called hematopoiesis. Notably, hematopoietic stem cells give rise to red and white blood cells and platelets in a tightly regulated process (26). These mechanisms are responsible for the significant drop down of platelets and insignificant decrease in hemoglobin concentration (Hb) obtained in this study (27). The HHV-6 infection suppressed the three lineages of hematopoiesis; erythroid, granulocyte/macrophage, and megakaryocyte using the hematopoietic colony assays (22).

Authors' Contribution

Study concept and design: A. SH. H.
Acquisition of data: S. A. A.
Analysis and interpretation of data: K. L.
Drafting of the manuscript: A. SH. H.
Critical revision of the manuscript for important intellectual content: A. SH. H.
Statistical analysis: S. A. A.
Administrative, technical, and material support: K. L.

Ethics

The study was scientifically and ethically approved by the Committees in the College of Medicine-Diyala University and Diyala Directory of Health. Human privacy was esteemed by obtaining the parent's verbal approval.

Conflict of Interest

The authors declare that they have no conflict of interest.

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