Prevalence of Human Herpes Virus Type 7 among Children with Skin Rash in Diyala Province

A thesis

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بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

﴿ يَٰٓأَيُّهَا ٱلَّذِينَ ءَامَنُوٓاْ إِذَا قِيلَ لَكُمۡ تَفَسَّحُواْ فِي ٱلۡمَجَٰلِسِ فَٱفۡسَحُواْ يَفۡسَحِ ٱللَّهُ لَكُمۡۖ وَإِذَا قِيلَ ٱنشُزُواْ فَٱنشُزُواْ يَرۡفَعِ ٱللَّهُ ٱلَّذِينَ ءَامَنُواْ مِنكُمۡ وَٱلَّذِينَ أُوتُواْ ٱلۡعِلۡمَ دَرَجَٰتٍۚ وَٱللَّهُ بِمَا تَعۡمَلُونَ خَبِيرٌ ۝١١ ﴾

صدق الله العظيم

Dedication

To the soul of my father …… Allah overwhelmed him with his mercy .

To my mother ……………….. God extended her life.

To the one who inhabits my heart and fills my life with joy and pleasure … who supported me with all strength, always stood by my side and bears the hardships of my studies………my dear husband.

To the shining stars in the sky of my life ….. my brothers and sisters.

To the pure, kind hearts and the innocent souls, and the wind of my life, my heart and happen ……... My dear my sons.

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Summary

Human Herpesvirus type- 7 (HHV-7) is a T-lymphotropic virus that was first isolated from mononuclear cells of peripheral blood as well as detection from saliva of healthy individuals. It was then recognized as a new lymphotropic herpesvirus belonging to subfamily Beta herpesviridinae of Herpesviridae family. HHV-7 utilizes CD4 as its essential receptor to enter the target cells, The CD4+ T lymphocytes, in which it reside during its latency period. Reactivation of HHV-7 may cause mononucleosis like syndrome. In its primary infection, the HHV-7 causes roseola infantum or exanthem subitum, which is a classical early childhood disease with skin rash with a high fever that appears suddenly lasts 3–4 days, as well as a maculopapular rash that appears when the child's temperature drops.

Although there is considerable variance in the sero-prevalence of HHV-7 infection, more than 95 percent of adults have been infected with the virus and are immune to it, with more than three quarters of those infected before the age of six. Primary HHV-7 infection in children occurs most commonly between the ages of 2 and 5, which indicates it occurs after primary HHV-6 infection.

This cross-sectional serological study included 180 patient with skin rash and fever. Their age range between (1 -14) years old. Additionally, 60 apparently healthy individuals were enrolled as control group with an age range of (1-14) year. The research was carried out in the Diyala province . For the period from (1 st) July 2020 to (31th) March 2021. Blood samples were collected from Baladrose General Hospital, Khan Bani Saad Healthcare Center and Al-Batool Teaching Hospital for Maternity and Children.

Serum anti-HHV-7 IgG and IgM were determined by use of enzyme linked immunosorbant assay (ELISA) technique (Mybiosource-China). The participant's privacy was protected by receiving verbal agreement from their

parents. Statistical analysis was done using Statistical Package for Social Science (SPSS) version 25 and P values less than 0.05 was considered significant.

The outcomes of this revealed that the anti-HH V-7 IgM positivity rate among patients was 11.7% versus 82.9% who were negative. On the control side, 10% of the controls were positive versus 90% were negative. The difference among the two groups was statistically significant (P=0.0204). The anti-HHV-7 IgG positivity rate, the results showed that 19.4% of the patients were positive versus 80.6% were negative, while in the control group, 31.7% were positive and 68.3% were negative.

However, the difference between the two groups was failed to reach the level of statistically unsignificant (P= 0.051). The higher positivity rate of anti-H H V-7 IgM was among those 10-14 years old. The highest anti-HHV-7 IgG positivity rate was among those 5-9 years. No significant association was found between anti-HHV-7 IgM or anti-HHV-7 IgG and gender, residence, parent's education, number of children in family, vaccination status, site and duration of rash.

Patients positive for anti-HHV-7 IgM has unsignificantly lower mean ± SD of hemoglobin concentration compared to those negative for anti-HHV-7 IgM (11.3 ± 1.1 *Vs* 11.7 ± 1.5) (P= 0.151). Patients with positive anti-H HV-7 IgM had significantly higher WBC count compared to their counterpart (9.8 ± 2.2 *Vs* 6.6 ± 1.6), (P= 0.035). The patients with positive anti-HHV-7 IgM had higher lymphocyte count compared to those with negative anti-HHV-7 IgM (4874.9 ± 1258 *Vs* 2735.0 ± 1100), (P= 0.049), the results also found that patients with positive anti-H HV-7 IgM had significantly higher platelets count compared to their counterpart (431.5 ± 80.6 *Vs* 295.4 ± 83.6), (P= 0.028).

There was a slight insignificant increase of Hb in patients with negative anti-HHV-7 IgG compared to their positive counterpart (11.7 ± 15 *Vs* 11.2 ± 1.2), (P= 0.746). Patients with positive anti-H H V-7 IgG had higher but

insignificant mean ± SD of WBC count compared to their negative counterpart (8.7 ± 1.4 Vs 7.6 ± 1.6), (P= 0.975). the results showed that the mean ± SD lymphocyte count in patients with positive anti-HHV-7 IgG was insignificantly higher than in their negative counterpart (3074.4 ± 1302 *Vs* 2914.2 ± 1194), (P=0.241). Patients with positive anti-HHV-7 IgG had insignificantly higher platelet count compared to their negative counterpart (302.9 ± 82.8 *Vs* 287.3 ± 70), (P= 0.328).

It can be concluded that the contribution of HHV-7 in causation of fever and skin rash among Diyala children was low, while the seroprevalence of HHV-7 among apparently healthy population was moderate. The total WBC count, lymphocyte count and platelets count were elevated during acute HHV-7 infection and renormalize later on.

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List of Abbreviations

Abbreviation	Meaning
CBC	Complete blood count
CFS	Chronic fatigue syndrome
CMV	Cytomegalovirus
CPE	Cytopathic effect
DIHS	Drug-induced hypersensitivity
DNA	deoxyribonucleic acid
DRESS	Durg reaction with eosinophilia and systemic syndrom
EBV	Epstein-Barr virus
ELISA	Enzyme linked immune sorbent assay
ES	Exanthema submit
FUO	Fever unknown origin
FVO	Fever of viral origin
HB	Haemoglobin
HHV-6	Human herpes virus type-6
HHV-7	Human herpes virus type-7
HHV-8	Human herpes virus type-8
HIV	Human immunodeficiency virus
HRP	Horseradish peroxidase
HSV-1	Herpes simplex virus type-1
HSV-2	Herpes simplex virus type-2
IF	Immunofluorescence
IFA	Immunofluorescence assay
IgG	Immunoglobulin G
IgM	Immunoglobulin M
OD	Optical Density
PBMC	peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PCV	Packed cell volume
PR	Pityriasis Rosea
RK	HHV-7 strain RK
TNF	Tumor Necrosis Factor
TRAIL	T-Related Apoptosis inducing ligand
VZV	Varicella-Zoster virus
WBC	White blood count

Chapter One
Introduction

Chapter One

1. Introduction

Frenkel and colleagues discovered the human herpesvirus (HHV) -7 virus in 1990, who found that primary T-cells had an irregular cytopathic effect (CPE), taken from a healthy person's peripheral blood under T-cell activation circumstances. A hitherto unknown virus was isolated from the culture using an electron microscope, and typical herpes virus virons were exposed. The virion, which had a diameter of 170 nm and consisted of an electron dense cylindrical core, capsid, tegument, and envelope, (Frenkel *et al*., 1990; Secchiero *et al*., 1994). The genome of HHV-7 is closely related to that of HHV-6, although it is about 10% smaller (Nicholas and John, 2002).

Like HHV-6, the HHV-7 is belong to genus Roseolovirus, subfamily Betaherpesvirinae of herpesviriodae family which include HHV-6,7 and cytomegalovirus or HHV-5. The DNA genome of about 145,000 base pairs. There are a number of key differences between the genome of HHV-7 and that of HHV-6, but the importance of them for viral DNA replication is not yet known (Martin *et al*., 2020).

Exanthema subitum, or roseola infantum, is a skin disease caused by both H HV-6 and HHV-7 in babies, although HHV-7 is less frequently than HHV-6. (Arango and Jones, 2017). Fever, rash, vomiting, diarrhea, low lymphocyte counts, and febrile seizures are all symptoms of acute febrile respiratory illness. All of these symptoms are caused or connected to HHV-7 infection (Tesini *et al*., 2014).

The HHV-7 infect T cells, monocytes-macrophages, epithelial cells, and central nervous system cells. HHV-7 resides generally in $CD4^+$ T cells. HHV-7, different from H HV-6, uses $CD+^4$ and perhaps some cell-surface glycoproteins to come in $CD4^+$ T cells (Agut *et al.*, 2017). HHV-7 is ubiquitous and is responsible for life long latent infections, most often asymptomatic. Reactivation of latent HHV-7 may cause mononucleosis like syndrome (Cherry, 2019).

The HHV-7 is a very common virus, with over 90% of people testing positive for the virus(Clark *et al.*, 1993; Otlib, 2015). Early childhood infection is considered to be the source of primary infection. Certain results showed that, similar to HHV-6, antibodies against HHV-7 were found in infants under the age of two (Clark *et al.*, 1993). Others believe that sero-conversion happens later in childhood, between the ages of three and four (Wyatt and colleagues, 1991).

Another study found that the prevalence of HHV-7 increases by 60% in (11-13) year olds (Yoshikawa *et al.*, 1993). HHV-7 virus has been isolated from the saliva of a healthy adult (Wyatt and Frenkel, 1992; Yoshikawa *et al.*, 1993), showing that saliva has a role in viral spread The restriction patterns of viral DNA isolated from children's saliva were found to be similar to those of their parents(Wyatt and Frenkel, 1992; Yoshikawa *et al.*, 1993) .

Furthermore, because viral DNA has been discovered in breast milk, and the sero-positive level in breast-fed infants is somewhat higher than in bottle-fed children,breast feeding may also be a viable transmission method (Fujisaki *et al.*, 1998).

Human herpesvirus (HHV)-6 and HHV-7 are ubiquitous T- lymphotropic viruses that infect most humans. Infections with either agent occur primarily during childhood. Viral persistent infection is established in salivary glands and the virus continuously shed through the saliva (Stone *et al.*, 2014). Seroprevalence of HHV-6 reaches > 80% in children >2 years. Antibody prevalence for HHV-7 reaches 75%

in 3- to 6-year-old children and 98% in adults (Valeria *et al*., 2017). It is worthy to mention that most of studies are affirming the higher role of HHV-6 in the causation of roseola infantum in children compared to that of HHV-7 (Galama, 1996; Suga *et al*., 1998). In this regard, it has been found that more than half of the children were infected with HHV-6B prior to HHV-7 (Cermelli *et al*., 1996; Ongradi *et al*., 1999). However, the distinction between the primary role in causation of roseola infantum whether HHV-6 or HHV-7 and the cross-reactivity of these viruses antibodies are still puzzling worldwide (Yoshida *et al*., 2002).

1.2. Aims of the study:

The present study was designed to achieve these following goals:

1. Detection of the Prevalence rate of infection by HHV-7 among children with fever and rash in Diyala Province by useing ELISA.

2. Explore the seroprevalence of HHV-7 among children clinically presented with rash as well as apparently healthy children.

3. To Figure out the role of socio-demographic or other risk factors.