

# Association of HHV6 infection with neuroinflammatory diseases Patients in Najaf/Iraq: (cross sectional study\_

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## Abstract

**Background:** A wide range of illnesses that have an impact on brain function are called neuroinflammatory diseases. 37 million people around the world suffer from neurodegenerative disorders (Karim et al., 2014), The development of specific pathological changes in the brain, such as extracellular protein deposits, cellular inclusions, and alterations in cell morphology, characterizes neurodegenerative disorders (Armstrong et al., 2005) including Alzheimer's disease (Sorbi & Ferrari, 2021) Parkinson disease (Tolosa et al., 2021) Epilepsy (Manford, 2017) Wilson (Członkowska et al., 2018) stroke (Iadecola et al., 2020) multiple sclerosis (Kamińska et al., 2017). The sixth herpes virus in the family, human herpes virus 6, was discovered in 1986. HHV 6A and HHV 6B are the two HHV-6 subtypes that are most prevalent.(Abdel-Haq & Asmar, 2004) It exhibits a broad cell tropism in vivo and, like other herpesviruses, causes a latent infection that lasts the rest of a person's life. HHV-6 DNA is covalently integrated into the subtelomeric region of cell chromosomes in about 1% of the general population (ciHHV-6)(Agut et al., 2016).**Methods:** In the study, 200 patients with neuroinflammatory disease (clinically determined by neurologists) took part. There were 200 patients in total, with an average age ranging from well under 20 to well over 80, and 120 girls and 80 men. The investigation took place between November 2020 and May 2021. HHV6 IgM and IgG levels were assessed using an enzyme-linked immunosorbent assay (ELISA). **Results:** The results of Anti-HHV6 IgM Antibodies were 78 (39%) positive case while the rest 122 (61%) gave negative results and the results of Anti-HHV6 IgG Antibodies were 152(76%) positive cases while the rest 48(24%) gave negative results. **Conclusions:** A significant number of individuals with neuroinflammatory diseases are infected with the HHV6 virus and Activation of HHV6 viral infection may be responsible for neuroinflammatory disorders or aggravation of a pre-existing condition, since the IgG and IgM levels of many individuals increased simultaneously. A low percentage of individuals with negative results still have positive IgG, which might suggest a past infection. **Keywords:** neuroinflammatory diseases, HHV6, Anti -HHV6 IgM, Anti -HHV IgG.

## 1. Introduction

An inflammatory response that develops within the central nervous system is referred to as neuroinflammation. The production of cytokines, chemokine, reactive oxygen species, and secondary messengers is what leads to this systemic inflammation. These mediators are produced by endothelial cells, microglia, and astrocytes in the central nervous system, as well as immune cells from the periphery. These neuroinflammatory responses affect the body's physiology, biochemistry, and psychology in addition to the immune system (Wohleb & Godbout, 2013) The type of the primary stimulus or injury, as well as its severity, duration, and progression, all affect the degree of neuroinflammation (Jassam et al., 2017)

The central immune system is made up of immune cells such as neurons, glial cells, and others. as stated by(Jeon et al., 2021) The most common type of all neuroinflammatory diseases, stroke is a cerebrovascular disorder characterized by the

sudden onset of symptoms and clinical signs. Ischemic stroke is the most common type of stroke, followed by hemorrhagic stroke (Boursin et al., 2018) Another neuroinflammatory disease is Alzheimer's disease, a genetic and sporadic neurodegenerative condition that, in its prototypical presentation, results in amnesic cognitive impairment and, in less common variants, non-amnesic cognitive impairment (Knopman et al., 2021) A serious condition that affects the central nervous system is meningitis. It is an inflammation of the meninges, the membrane that encases the spinal cord and the brain. Infections that are bacterial, viral, or fungal can result in meningitis (Kohil et al., 2021) One of the most prevalent and incapacitating neurological conditions is epilepsy (Stafstrom & Carmant, 2015) An extremely serious brain condition (Schmidt & Schachter, 2014) Multiple sclerosis (MS) is a long-lasting inflammatory demyelinating condition that affects the CNS and causes gray and white matter in the brain to degenerate (Lassmann, 2018) Numerous neurological conditions, such as ischemic stroke, traumatic brain injury, Alzheimer's disease (AD), and

Parkinson's disease, are linked to neuroinflammation (PD) (Jiao & Gong, 2020).

Human herpes virus 6 (HHV-6) is a beta herpes virus family that currently includes two distinct species, HHV-6A and HHV-6B. These viruses share genetic similarities with HCMV, a common beta herpes virus. HHV-6, like other herpes viruses, can infect a wide variety of cells and can remain dormant in the human body for the rest of the host's life (Agut et al., 2016). Patients in North America with AIDS-related lymphomas, lymphadenopathies, and other lymphoproliferative disorders were the first to be isolated from their samples in 1986, HHV-6 infects and replicates in lymphocytes, with a preference for CD4+ T cells (Pantry & Medveczky, 2017). Over 36% of all cases of acute fever in children aged 12 to 15 months are caused by primary HHV-6 infection, which is almost always caused by HHV-6B rather than HHV-6A (Tesini et al., 2014). Herpes viruses are DNA viruses with two strands that infect humans and a variety of other hosts (Zmasek et al., 2019). All herpes viruses have the same three structural components: A virus's DNA genome is encased in an icosahedral nucleocapsid with a diameter of 90-110 nm; the envelope encloses the nucleocapsid and contains the viral glycoproteins; and the tegument, a protein combination, bridges the gap between the nucleocapsid and the envelope (De Bolle et al., 2005). Human herpes virus 6 (HHV-6) can live in the salivary glands and be transmitted to offspring through maternal or inter-child saliva transmission (Mukai et al., 1994). Glycoproteins B (gB), H (gH), and L (gL) are all essential for entry and are shared by all herpes viruses (Maeki & Mori, 2012). Human herpes virus 6 (HHV-6) can cause a variety of neurological diseases (Yamashita & Morishima, 2005). When there is detectable viremia, a systemic active infection is suspected (Flamand et al., 2010) creates a dormant infection in the central nervous system (CNS) (Fotheringham et al., 2008). Persistent infections occur when the virus is able to evade the adaptive immune response and remain dormant in the infected person's target cells (Sampaio et al., 2011). The presence of HHV-6 neutralizing antibodies before, during, and after the rash stage of primary infection (rather than the fever stage) suggests that maternal antibodies help prevent viral infection (Kawabata et al., 2011). Two symptoms that appear within the first four to six weeks after initial infection are seroconversion from IgG-negativity to IgG-positivity and the presence of IgM to HHV-6 (Zerr et al., 2005). However, IgM antibodies found during the first week of infection were completely gone within one month, whereas IgG antibodies emerged later and have lasted for the rest of one's life (Agut et al., 2015).

## 2. Materials and Methods

**Patients:** Two hundred patients with neuroinflammatory disease, who had been clinically diagnosed by neurologists, took part in the study. The 200 patients ranged in age from well under 20

to well over 80, with an average of 120 girls and 80 men. The investigation will run from November 2020 to May 2021. In addition to demographic questions about name, gender, age, smoking history (yes/no), type of heart disease, and laboratory examination (WBC, PLT, Lymphocytes), each patient was asked about their medical conditions, such as hypertension (high blood pressure) and diabetes (diabetes mellitus). In this study, patients with congenital neurological disorders, accident-related nerve damage, and covid19 were not included.

**Material:** the tools used in this search included disposable gloves, disposable pipette tips, plastic EDTA tubes, sterile syringes 5 ml, disposable glass gel serum tubes, Eppendorf Tubes –Sterile, alcohol for sterilization, cotton, deep freezer, filter paper, Tourniquet, computer, centrifuge and incubator. and the following equipment's were used in our study: ELISA automated washer, ELISA kit (Anti-HHV6 IgG, Anti-HHV6 IgM) sunlong, ELISA printer, ELISA reader. **Methods** "Blood samples were taken only after participants gave their verbal and written consent. The Kufa College of Medicine's ethics board approved the research plan, and 5 ml of vein blood was also included. Before taking blood samples, we cleaned the area with alcohol at a 70% strength. Separated swatches were put in separate gel tubes. Before blood can be used to create serum, it must first coagulate for about an hour at room temperature. The serum was divided into new plain tubes for immunological assays (HHV-6 IgG and HHV-6 IgM), centrifuged at 3000 rpm for 15 minutes, and then stored at (-20 °C) until analysis.

**Ethical Approval:** After gaining both verbal and written agreement from the participants, blood samples were collected. The research plan has been given the go light by the Kufa College of Medicine's ethics board.

**Statistical Analysis:** Version 24 of the software for the social sciences was used to enter, manage, and analyze the data. Variables were displayed as means, standard deviations, frequencies, and percentages. All continuous variables' assumed normality was examined. The Chi-square test is one tool for determining the significance of a relationship between two category variables. To evaluate lab variables and parameters, use the Welch's t-test. Bivariate Pearson correlation and spearman correlation are used to compare the correlation of demographic, clinical, and laboratory data. The significance level for all statistical tests was set at 5%. The tables and figures were produced using Word 2016 and Excel, and an explanation paragraph was added.

## 3. Results

Anti-HHV6 IgG Antibodies and Anti-HHV6 IgM antibodies seropositivity according to age groups. Table 1 shows the results of Anti-HHV6 IgG Antibodies and Anti-HHV6 IgM antibodies in regard to age group. as the table revealed in age group (< 20) the results of Anti-HHV6 IgG Antibodies were 11

(55%) positive and 9 (45%) negative and the results of Anti-HHV6 IgM antibodies were 4 (20%) positive and 16 (80%) negatives. in age group (21 – 40). The results of Anti-HHV6 IgG Antibodies were 38 (59.6%) positive and 9 (19.1%) negative and the results of Anti-HHV6 IgM antibodies were 12 (25.5%) positive and 35 (74.5%) negatives in age group (41 - 60) the results of Anti-HHV6 IgG Antibodies were 43 (72.9%) positive and 16 (27.1%) negative and the results of Anti-HHV6 IgM antibodies were 22 (37.3%) positive and 37 (62.7%) negative in age group (61-80) the results of IgG were 48(80%) positive and 12 (20%)

negative and the results of Anti-HHV6 IgM antibodies were 31 (51.7%) positive and 29 (48.3%) negative in age group (> 80)) the results of IgG were 12(85.7%) positive and 2 (14.3%) negative and the results of Anti-HHV6 IgM antibodies were 9 (64.3%) positive and 5 (35.7%) negative. Male Female 0 20 40 60 80 100 120 Total Anti-HHV6 IgG + Anti-HHV6 IgG - 80 63 17 120 89 31 No. of cases Anti-Human herpes virus 6 IgG results Male Female 86.A statistically significant difference between a p-value of 0.04 and 0.05 was found.

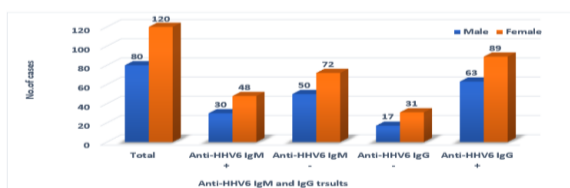
**Table 1: Anti-HHV6 IgG Antibodies and Anti-HHV6 IgM antibodies seropositivity according to age groups**

p-value	No. of cases	Anti-HHV6 IgM +ve	Anti-HHV6 IgM -ve	Anti-HHV6 IgG +ve	Anti-HHV6 IgG -ve	Age groups years
0.04	20	4(20.0%)	16(80.0%)	11(55.0%)	9(45.0 %)	< 20
	47	12(25.5%)	35(74.5%)	38(59.6 %)	9(19.1 %)	21 – 40
	59	22(37.3%)	37(62.7%)	43(72.9%)	16(27.1%)	41 - 60
	60	31(51.7%)	29(48.3%)	48(80.0%)	12(20.0%)	61 - 80
	14	9(64.3%)	5(35.7%)	12(85.7%)	2(14.3%)	> 80
	200	78 (39%)	122 (61%)	152 (76%)	48(24%)	Total

p-value = 0.04 (a statistically significant difference exists when p-value is less than 0.05), X<sup>2</sup> = 21.507, df = 12

Anti-HHV6 IgG and Anti-HHV6 IgM antibodies seropositivity according to sex

Figure 1 explains the results of Anti-HHV6 IgG and Anti-HHV6 IgM antibodies seropositivity according to sex. As shown in this figure below, the results of Anti-HHV6 IgG antibodies in male group included 63 (78.8%) positive and 17 (21.1%) negative while in female the result included 89 (74.1%) positive and 31 (25.8%) the result of Anti-HHV6 IgM antibodies in male group was 30 (62.5%) positive and 50 (37.5%) negative while in female group 48(40%) positive and 72 (60%) negatives at p-value = 0.87 p-value > 0.05 statistically was not significant.



**Figure 2: Anti-HHV6 IgG and Anti-HHV6 IgM antibodies seropositivity according to sex**

Positive serology for anti-HHV6 IgM antibodies; median of anti-HHV6 IgG findings

Table 2 explains the Chi-square analysis of the relationship between anti-HHV6 IgM seropositivity and the mean of anti-HHV6 IgG test results. The results of the present study, together with an examination of the link between the detection of antiviral IgM antibodies and the identification of Anti-HHV6 IgG, revealed the following: Among the 78 samples that tested positive for Anti-HHV6 IgM antibodies, only 8 samples (4%) tested positive for Anti-HHV6 IgG antibodies. Of the remaining samples, researchers discovered that 82 (41%) of those that tested negative for Anti-HHV6 IgM antibodies also tested positive for Anti-HHV6 IgG, whereas 40 instances (20%) tested negative for both Anti-HHV6 IgM antibodies and the presence of Anti-HHV6 IgG. Patients with a positive Anti-HHV6 IgG also had very high levels of Anti-HHV6 IgM antibodies, as shown in the table (p0.00001). The average levels of Anti-HHV6-IgG antibodies in individuals who tested positive for Anti-HHV6 IgM were also statistically significant.

**Table 2: Positive serology for anti-HHV6 IgM antibodies; median of anti-HHV6 IgG findings**

Parameter	Anti-HHV6 IgM +ve	Anti-HHV6 IgM -ve	Total	P-value
Anti-HHV6-IgG +ve	70 (35%)	82 (41%)	152 (76%)	< 0.00001*
Anti-HHV6-IgG -ve	8 (4%)	40 (20%)	48 (24%)	
Total	78 (39%)	122 (61%)	200 (100%)	
Mean± SD (ng/L)	1.05±0.77	0.18±0.12		< 0.00001*

Seropositivity of Anti-HHV6 IgM antibodies According to the type of Neuroinflammatory disease:

Figure 2 revealed the Seropositivity of Anti-HHV6 IgM antibodies According to the type of Neuroinflammatory disease. In the below listed figure, we can see the Neuroinflammatory disease were categorized along with total number of each disease. Among the first group of disease (Parkinson) with total number of 8 (4%) cases the results of Anti-HHV6 IgM antibodies were 0 positive and 8 (100%)

negatives. Among the second group of disease (neuropathy) with total number of 47(23.5%) cases the results of Anti-HHV6 IgM antibodies were 32 (68%) positive and 15(32%) negatives. Among the third group of disease (stroke) with total number of 87(43.5%) cases the results of Anti-HHV6 IgM antibodies were 23 (26.4%) positive and 64 (73.5%) negatives. the fourth group of disease (Meningitis)

with total number of 13 (6.5%) cases the results of Anti-HHV6 IgM antibodies were 6 (46.1%) positive and 7 (53.8%) negatives. fifth group of disease (epilepsy) with total number of 10 (5%) cases the results of Anti-HHV6 IgM antibodies were 1 (10%) positive and 9(90%) negatives. Among the sixth group of disease (MS) with total number of 28 (14%) cases the results of Anti-HHV6 IgM antibodies were 16 (57.1%) positive and 12(42.9%). And lastly among the seventh group (Wilson) with total number of 7 (3.5%) cases the results of Anti-HHV6 IgM antibodies were 0 (0%) positive and 7 (100%) negatives.

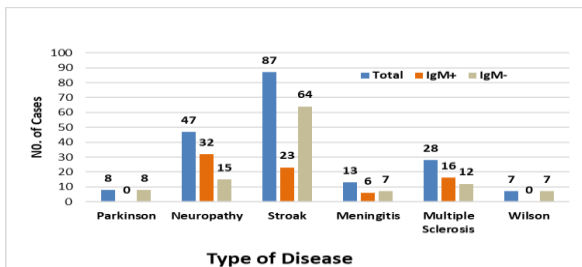


Figure 2: Seropositivity of Anti-HHV6 IgM antibodies According to the type of Neuroinflammatory disease Seropositivity of Anti-HHV6 IgG antibodies According to the type of Neuroinflammatory

Figure 3 explains the Seropositivity of Anti-HHV6 IgG antibodies According to the type of Neuroinflammatory disease. In the below listed table, we can see the Neuroinflammatory disease were categorized along with total number of each disease. Among the first group of disease (Parkinson) with total number of 8 (4%) cases the results of Anti-HHV6 IgG antibodies were 5 (62.5%) positive and 3 Table 3 explains the Correlation between the levels of white blood cells, platelets and lymphocytes according to the results of Anti-HHV6 IgM results (A statistical comparison by chi- square method). As we can see in this table, the level of WBCs among HHV6 IgM + group was (high = 45 (63.4%), normal = 20 (17.5%), low = 5 (33.3%) ) and the their level among Anti-HHV6 IgM - was (high = 26 (36.6%), normal = 94 (82.5%), low = 10 (16.9%), while the level of platelets among Anti-HHV6 IgM + group was (high=49(83.1%), normal = 21 (15.4%), low = 0 (0.0%) and their level among Anti-HHV6 IgM - group was (high = 10 (16.9%), normal = 115 (100.0%), low = 5 (100.0%) and lastly the level of lymphocytes among Anti-HHV6 IgM + group was (high = 54 (80.6%),

(37.5%) negatives Among the second group of disease (neuropathy) with total number of 47(23.5%) cases the results of Anti-HHV6 IgG antibodies were 32 (68%) positive and 15(32%) negatives Among the third group of disease (stroke) with total number of 87 (43.5%) cases the results of Anti-HHV6 IgG antibodies were 69(79%) positive and 18(21%) negatives Among the forth group of disease (Meningitis) with total number of 13 (6.5%) cases the results of Anti-HHV6 IgG antibodies were 13 (100%) positive and (0%) negative. Among the fifth group of disease (epilepsy) with total number of 10 (5%) cases the results of Anti-HHV6 IgG antibodies were 4 (40%) positive and 6 (60%) negatives. Among the sixth group of disease (MS) with total number of 28 (14%) cases the results of Anti-HHV6 IgG antibodies were 26 (92.9%) positive and 2 (7.1%) negatives. And lastly among the seventh group (Wilson) with total number of 7 (3.5%) cases the results of Anti-HHV6 IgG antibodies were 3 (42.9%) positive and 4 (57.1%) negatives.

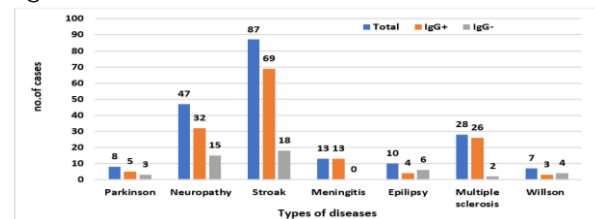


Figure 3: Seropositivity of Anti-HHV6 IgG antibodies According to the type of Neuroinflammatory disease

Correlation between the levels of white blood cells, platelets and lymphocytes according to the results of Anti-HHV6 IgM

normal = 4 (3.4%), low = 12 (70.0%) and their level among Anti-HHV6 IgM - group was (high = 13 (19.4%), normal = 112 (98.2%), low = 5 (29.4%)) eventually resulting in a total number of cases with high WBCs in both positive and negative Anti-HHV6 IgM groups was (71), and a total number of normal WBCs was (114), a total number of low WBCs was (15), and total number of cases with high PLT in both positive and Anti-HHV6 IgM groups was (59), a total number of normal PLT was (136), a total number of low PLT was (5), and last the total number of high lymphocytes in both positive and negative Anti-HHV6 IgM groups was (67), a total number of normal lymphocytes was (116), a total number of low lymphocytes was (17) at a P value = 0.0001

IgM results Hematological Levels	Anti-HHV6 IgM Positive %	Anti-HHV6 IgM Negative %	No. of cases %	P-value
High WBCs	45(63.4%)	26(36.6%)	71	0.0001
Normal WBCs	20(17.5%)	94(82.5%)	114	
Low WBCs	5(33.3%)	10(16.9%)	15	
High PLTs	49(83.1%)	10(16.9%)	59	
Normal PLTs	21(15.4%)	115(100.0%)	136	
Low PLTs	0(0.0%)	5(100.0%)	5	
High lymphocyte	54(80.6%)	13(19.4%)	67	
Normal lymphocyte	4(3.4%)	112(98.2%)	116	
Low lymphocyte	12(70.0%)	5(29.4%)	17	

X<sup>2</sup>=247.31, df=8, p0.0001 (p0.05 was considered statistically significant).

Correlation between the levels of white blood cells, platelets and lymphocytes according to the results of Anti-HHV6 IgG

Table 4 explains the Correlation between the levels of white blood cells, platelets and lymphocytes according to the results of Anti-HHV6 IgG results (A statistical comparison by chi- square method). As we can see in this table, the level of WBCs among Anti-HHV6 IgG + group was (high = 45 (63.4%), normal = 20 (17.5%), low = 5 (33.3%) ) and the their level among Anti-HHV6 IgG - was (high = 26 (36.6%), normal = 94 (82.5%), low = 10 (16.9%), while the level of platelets among Anti-HHV6 IgG + group was ( high=49(83.1%), normal = 21 (15.4%), low = 0 (0.0%) and their level among Anti-HHV6 IgG - group was ( high = 10 (16.9%), normal = 115 (100.0%), low = 5 (100.0%) and lastly the level of lymphocytes among Anti-HHV6 IgG + group was (high = 54

(80.6%), normal = 4 (3.4%), low = 12 (70.0%) and their level among Anti-HHV6 IgG - group was (high = 13 (19.4%), normal = 112 (98.2%), low = 5 (29.4%)) eventually resulting in a total number of cases with high WBCs in both positive and negative Anti-HHV6 IgG groups was (71), and a total number of normal WBCs was (114), a total number of low WBCs was (15), and total number of cases with high PLT in both positive and negative Anti-HHV6 IgG groups was (59), a total number of normal PLT was (136), a total number of low PLT was (5), and last the total number of high lymphocytes in both positive and negative Anti-HHV6 IgG groups was (67), a total number of normal lymphocytes was (116), a total number of low lymphocytes was (17) at a P value = 0.0001.

**Table 4: Correlation between the levels of white blood cells, platelets and lymphocytes according to the results of Anti-HHV6 IgG**

IgG results Hematological Levels	Anti-HHV6 IgG Positive %	Anti-HHV6 IgG Negative %	No. of cases %	P-value
High WBCs	45(63.4%)	26(36.6%)	71	0.0001
Normal WBCs	20(17.5%)	94(82.5%)	114	
Low WBCs	5(33.3%)	10(16.9%)	15	
High PLTs	49(83.1%)	10(16.9%)	59	
Normal PLTs	21(15.4%)	115(100.0%)	136	
Low PLTs	0(0.0%)	5(100.0%)	5	
High lymphocyte	54(80.6%)	13(19.4%)	67	
Normal lymphocyte	4(3.4%)	112(98.2%)	116	
Low lymphocyte	12(70.0%)	5(29.4%)	17	
p-value=0.0001(p-value ≤ 0.05 statistically was significant), X2=247.31,df=8				

### 4. Discussion

The Human Herpes virus 6 test searches for IgG antibodies, which normally form a few weeks after infection and can last a person's whole lifetime. A positive test often indicates prior illness, but not always a present infection. There were 119 (77%) of CFS patients were positive for HHV-6 EA IgG or IgM (or both), whereas only 12% (20/165) of the controls exhibited IgG or IgM to HHV-6 EA (Picard et al., 2015). More CFS patients than controls reported increased levels of HHV-6 EA-specific IgM, which may imply active replication of HHV-6 in CFS. According to the results of the study by Hasan et al., 2019, 43.9% of otherwise healthy newborns tested positive for anti-HHV6 IgG. The positive rate was slightly higher among males than females (44.0% vs. 43.8%, P = 0.973), and the greatest rate was seen in the 19–24-month age group compared to other age groups. The positive rate was also somewhat higher among infants who were mixed-fed (55.3 vs. 54.2, P = 0.083). Additionally, the data showed that the positive rate was greater but not statistically significant among babies who did not have a history of hospitalization (46.8% vs. 26.9%, P = 0.065). Anti-HHV6 IgG positivity was observed to be considerably greater among newborns whose families had a current history of positive case (62.2% vs. 35.8% or 50.0%, P = 0.006). They reported that the occurrence of an intrafamilial primary HHV-6 positive case was substantially associated with an enhanced incidence of anti-HHV6 IgG among siblings in the Diyala community, even among those who were born

healthy. Females had a higher seropositive rate and GMT than men (X2 = 7.05, P 0.01 and F = 7.23, P 0.01, respectively) of the 430 serum samples examined for HHV-6 IgG by Wu and Wang (1998). Young children had a higher titer than adults, and there was a statistically significant difference in the frequency of HHV-6 antibodies between age groups and genders (X2 = 20.08 and 20.28, P = 0.04, respectively). However, there was no noticeable difference in incidence across genders or age groups among blood donors. Mays 2021 study showed that According to the age groups of cancer patients with lymphocytopenia and leucopenia, the age group (60-41) had the highest percentage of positive results (32.7%), followed by the age group (21-40) with 27.8%. Positive results for HHV6 were highest in the age group (41-60), at 35.2%, followed by the age group (61-80), at 31.3%. According to research published by Lene et al., 1996, the seropositive rate was 78% in children younger than 1 year old. The results showed that all 120 (3-and-older) kids were seropositive. By collecting 83 blood samples from 65 Danish patients, they compared the sensitivity of the ELISA to that of the indirect immunofluorescence test (IFA) (aged 4 weeks to 72 years). In contrast to the 69% of patients whose sera were positive by ELISA, all of those patients' sera were positive by this method. In a study conducted by Marianna et al. in 2014, the seroprevalence of HHV6 was determined to be 78.75% (126/160) among blood donors. There was no statistically significant difference in seroprevalence between men and females (77.68%:

94/121) or between various age groups (82.61: 19-30, 81.82: 31-40, 69.76: 41-50, 81.48%: 51-64). There were no statistically-significant variations in height between HHV-6 Ag-positive males and females, as discovered in Mays' 2021 study, suggesting a strong correlation between these two factors. Since HHV-6 Ag is present when latent infection exists, patients have been exposed to the virus in the past and since this virus is a part of the herpesviridae family, it may integrate and reactivate, which is why IgG is linked to the existence of HHV-6 Ag.

According to Freitas et al. (2003), between January 1996 and December 2001, 323 patients in Belém, Brazil, who had been diagnosed with lymphadenopathy, were chosen and tested for the presence of (HHV-6) IgG and IgM antibodies. The sero-prevalence test revealed that the prevalence percentage is almost the same for both males (55.9%) and females (60.6%). IgM and IgG levels for HHV 6 were positive in 77 people (23.8%), with females being more likely to test positive (29.7%) than males (17.7%) ( $p = 0.0007$ ). This community of persons categorized Sera ( $n = 120$ ) based on elevated HHV-6 antibody levels (IgM+ or IgG+ reactivities) tested for the presence of HHV-6 DNA. A total of 120 people were given effective infectious diseases after being suspected of having a recent HHV-6 infection; this number includes 20/77 (20.0%) and 8/43 (18.6%) cases. Researchers such as Mays 2021 found that, among the 41% of men with lymphocytopenia and leukopenia, 63.4% were IgM positive and 56.4% were IgG positive. Among the 45.7% of women with same conditions, 63.4% were IgM positive and 64.4% were IgG positive. Based on the combined percentage of IgM (53%) and IgG (61%). However, among those who didn't have lymphocytopenia or leukopenia, men made up 48% of the total, and IgM positivity among this group was at 10.4% and IgG positivity among this group was at 12.5%. Despite the fact that the results were only found in females (out of a total of 52%), the IgM positive percentage was 13.4% and the IgG positive percentage was 17.3%. A lower percentage of IgG indicates that the virus has been reactivated from a dormant infection. Furthermore, IgM manifests during initial infection and reactivation. Fox et al., (1990) shown the presence of HHV6 IgM after both initial infections and reactivations. We find no statistically significant age differences in herpes infection, and this is because all patients undergoing prolonged therapy are vulnerable to a reduction in immunity, and immunodeficiency is a primary factor for the reactivation of the virus Anti-HHV6 IgG antibodies showed that forty percent of people with the seventh group of illness (epilepsy) out of a total of five percent of cases were positive, whereas sixty percent of people were negative. Anti-HHV6 IgG antibodies showed a positive response in 87.9% of instances involving the eighth type of illness, which was a cerebral thrombus, accounting for 29% of all cases. The remaining 12.1% of cases showed a

negative response. Anti-HHV6 IgG antibodies showed a positive response in 92.9% of people suffering from the ninth category of diseases (MS), which accounted for 14% of all cases, whereas only 7.1% of people had a negative response.

The findings of testing for Anti-HHV6 IgG antibodies showed that 62.5% of patients with Parkinson disease, which accounted for 4% of all cases, had positive results, whereas 37.5% had negative results. And finally, the findings of the test for anti-HHV6 IgG antibodies in the tenth group (Wilson), which included a total of 3.5% cases, showed that 42.9% of the samples were positive while 57.1% were negative. The entry points of HHV-6 into the central nervous system are poorly understood, as stated by Caserta et al. (1994). Following primary infection, HHV-6B is thought to rapidly spread throughout the brain and create a persistent infection. Herberts et al. (2011) found that HHV-6A had an affinity for infecting certain glial cells in the nasal cavity, suggesting that it could be able to use the olfactory pathway to gain access to the brain.

Numerous clinical research, such as Chapenko et al., 2003 and Garcia-Montojo et al., 2011, have demonstrated a link between MS and a number of HHV-6 infection assessment criteria. Specifically, the amounts of HHV-6 DNA in the serum, which are indicative of a continuing infection, are much higher in MS patients than in healthy donors or patients with other disorders. Ablashi et al. (1998) determined that MS patients' CSF and peripheral blood mononuclear cells contained elevated levels of HHV-6 DNA. In addition, Friedman et al. (1999) observed that MS patients had elevated levels of HHV-6-specific IgG and IgM in both blood and CSF.

Increased levels of HHV-6-specific IgG were also identified in MS patients experiencing clinical aggravation by Simpson et al. (2012) and Alvarez-Lafuente et al. (2004). Levels of HHV-6B-specific IgM were found in MS patients, and these levels were considerably greater than HHV-6A-specific IgG levels. Patients with MS had significantly greater amounts of HHV-6B IgG than HHV-6A IgG in their intrathecal fluid, and only HHV-6B-specific IgM was found (Ongrádi et al., 1999). One-third of instances of febrile status epilepticus (which raises the risk of epilepsy) appear to be caused by HHV-6 and HHV-7 (Epstein et al., 2012). The finding that HHV-6 infection can change astrocytic absorption of glutamate in primary cultures (Fotheringham et al., 2007) raises the possibility that HHV-6 contributes to the disruption of the neuronal excitatory balance seen in epilepsy. Recent research evaluated IgG reactivity against the very dissimilar coding regions U90-U89 and U11 between HHV-6A and HHV-6B in the serum and plasma of over 16,000 MS patients and controls (Engdahl et al., 2019). Since high doses of chemotherapy induce immunodeficiency, we show that patients with cancer have a latent infection with HHV6 and that the immunological status and the action of particular medications plays an essential role in reactivating the illness. We now know that

HHV6 may integrate into chromosomes, and that lowered immunity was a major element in the virus's resurgence. The ability of the HHV-6 virus to create latent infection has been noted, and viral reactivation in the central nervous system (CNS) may be associated to the pathophysiology of epilepsy, as stated by Jiaqi et al., 2021. Epilepsy patients' tissue samples show that HHV-6 causes a variety of inflammatory responses and preferentially boosts neuronal excitability.

## 5. Conclusion

A significant number of individuals with neuroinflammatory diseases are infected with the HHV6 virus. Activation of HHV6 viral infection may be responsible for neuroinflammatory disorders or aggravation of a pre-existing condition, since the IgG and IgM levels of many individuals increased simultaneously. Negative findings for anti-HHV6 IgM antigen do not rule out HHV-6 viral infection, as a tiny percentage of individuals with negative results still have positive IgG, which might suggest a past infection. There is no relationship between a particular kind of neuroinflammatory diseases and HHV6 infection.

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