

SEROPREVALENCE OF ANTI- HERPES SIMPLEX VIRUS TYPE2 IGG, IGM ANTIBODIES AMONG HOSPITALIZED CHILDREN UNDER FIVE YEARS

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(Accepted 2 March 2018)

ABSTRACT : Herpes simplex viruses are large, enveloped virions with an icosahedral DNA viruses subclinical or symptomatic infection of genital system with herpes viruses have nonspecific signs and symptoms and many women will be acquired infection during pregnancy and shedding it from labia, cervix or both so the most cases of neonatal infection occur from pregnant women who do not have history of herpes genital infection. To determine the seroprevalence of herpes simplex virus type 2 among hospitalized Children Under 5 years with the most risk factors. A total of 100 children under five years of age were enrolled in this study. Inclusion criteria for selecting children was the age group (from zero time to 60 months). Serological test to estimate the levels of Anti HSV (IgG) and (IgM) by Enzyme-Linked immunosorbent assay (ELISA). The principle demographic data were represented in Fig. 1. Male to female ratio was 1.7:1. Normal vaginal delivery was the mode of birth for 63 children versus 37 children who born with C/S. Three fourth (75%) of children had full gestational age, while 25% of children were preterm. Anti-HSV-2 IgG antibodies were detected in 35 (35%), while anti-HSV-2 IgM antibodies in 17 (17%) of children. High prevalence of HSV infection in Iraqi children under five, when compared with the rate of most neighboring developing countries. Immune suppression for different reasons play the crucial role in acquiring the infection especially postnatally.

Key words : Herpes viruses type 1 and type 2, risk factors, antenatal riskfactors, ceserean section, natal risk factors.

INTRODUCTION

Herpes simplex viruses are large, enveloped virions with an icosahedral DNA viruses under subfamily of Herpesviridae, two viruses belong to this family considered one of the most sexually transmitted disease in human, these viruses are Herpes viruses type 1 and type 2 (Elk Grove Village, 2009), both viruses have ability to transmitted through the skin abrasion as well as epithelial mucosal cell, where they persist in a latent state in nerve tissue, Perinatal transmission herpes virus from mothers who are infected with these viruses and shedding it during of delivery can causes life-threatening consequences in newborns (Xu *et al*, 2007) subclinical or symptomatic infection of genital system with herpes viruses have nonspecific signs and symptoms and many women will be acquired infection during pregnancy and shedding it from labia, cervix or both so the most cases of neonatal infection occur from pregnant women, who do not have history of herpes genital infection (Elk Grove Village, 2009) newborn can be acquired herpes simplex viruses through the utero, intrapartum and postnatally, Transplacental transmission or ascending infection from vagina or cervix either through intact amniotic membrane or due to leaks and reseals causes the infection (Xu *et al*, 2007).

Intrauterine viral transmission is highest during the first 20 weeks of gestation leading to abortion, still birth and congenital anomalies in infants (Jabbar *et al*, 2017). Recurrences are more common with HSV-2 infections than with HSV-1 infections Individuals with HSV-2 infection generally have high rates of recurrence in the first and second years followed by a substantial decrease in subsequent years. Most reactivations are asymptomatic (1% of individuals with previous HSV-2 infection have asymptomatic viral shedding on any given day). When symptomatic reactivation occurs, genital lesions are typically few. Tender lymphadenopathy, dysuria, vaginal discharge and systemic symptoms are less common (Schiffer and Corey, 2009).

MATERIALS AND METHODS

This cross-sectional study was conducted from September 2014 to March 2015. A total of 100 children under five years of age were enrolled in this study. Inclusion criteria for selecting children was the age group (from zero time to 60 months). A structured questionnaire was developed by the face-to-face interviews of child mother or child-caring relative that made by the investigator at the time when samples were taken. Included child information, maternal variables, parent's

demographic information and contact information while clinical manifestations were determined by consultation of a pediatric specialist and verification of the information in the medical record. The children labelled for blood transfusion had received blood or a blood product within (12-100 days) before sample collection.

Serum samples were collected from Children visited the emergency room, children admitted to the hospital, and neonates admitted to the neonatal intensive care unit (NICU) from Baghdad City hospital, Al-Yarmouk Teaching Hospital, AL-kadhimiya Teaching Hospital, Al-Elwia pediatrics hospital.

Two -three ml of venous blood was collected in plan tube from each participant; serum was obtained by centrifugation and stored at -20°C until used. The sera of study groups were subjected to serological test to estimate the levels of Anti HSV (IgG) and (IgM) by Enzyme-Linked immunosorbent assay (ELISA) according to manufacturing instructions (Human company).

RESULTS

The current study enrolled 100 children under 5 years old from 4 referral hospitals in Baghdad, Iraq. The principle demographic data were represented in Fig. 1. Male to female ratio was 1.7:1. Normal vaginal delivery was the mode of birth for 63 children versus 37 children who born with C/S. Three fourth (75%) of children had full gestational age, while 25% of children were preterm (Fig. 1).

Association of HVS-2 Infection with gender and age

Previous or current infection with HSV-2, as indicated by positive result for anti-HSV-2 IgG and IgM antibodies respectively, was reported in 52 children. Anti-HSV-2 IgG antibodies were detected in 35 (35%), while anti-HSV-2 IgM antibodies in 17 (17%) of children. Male showed non-significantly higher percentage of positive cases for both IgG and IgM antibodies (37.5% and 20.31%, respectively) than female (30.56% and 11.11%, respectively). Moreover, there was no significant difference in mean age between seropositive and

seronegative children for both IgG and IgM (Table 1).

Association of HVS-2 Infection with Antenatal risk factors

Five factors were chosen to represent antenatal factors for HSV-2 infection. These were father's and mother's educational level, father's and mother's occupation and number of abortions that the mother had experienced before the last birth. There were no significant differences between IgG and IgM seropositive and seronegative groups in respect of father's and mother's educational level, father's and mother's occupation (Table 2). Furthermore, the number of mother's abortion before the last delivery did not affect significantly the child's susceptibility to HSV-2.

Association of HVS-2 Infection with Natal risk factors

Natal factors selected in this study were mode of delivery, gestational age of the child and birth location. About two thirds (63%) of children were born by NVD, while 37% by S/C. Statistical analysis revealed non-significant effect of mode of delivery on seropositive for HSV-2 (Table 3).

Three-fourths of children had full term gestational age versus 25% preterm. Again, there was no significant difference in terms of seropositivity for IgG and IgM between the two categories.

The majority of children (80%) were born in hospital compared to 20% at home. The percentage of seropositive for both types of antibodies in the both locations were very close with no significant differences.

Table 4 shows the different postnatal factors and their association with HSV-2 infection. Fourteen children (14%) needed blood transfusion while 86% did not need such treatment. Both group showed close percentages of IgG and IgM seropositivity against HSV-2 without significant differences. More than three-fourths of children received breastfeeding during the first 72 hours of life, while 12% had only formula feeding, and 10% had mixed feeding. Statistical analysis did not reveal any significant differences between these groups in terms of antibody

Table 1 : HSV-2 infection among study group and relation with gender and age.

Variables	IgG		IgM	
	Positive(35)	Negative(65)	Positive(17)	Negative(83)
Age, months (mean±SD)	12.11±20.23	19.82±20.56	13.47±21.59	17.87±20.54
P-value	0.075		0.427	
Sex				
Male (64)	24(37.5%)	40(62.5%)	13(20.31%)	51(79.69%)
Female (36)	11(30.56%)	25(69.44%)	4(11.11%)	32(88.89%)
P-value	0.520		0.281	

Table 2 : The relation of Anti-HSV results with antenatal risk factors.

Variables	IgG		IgM	
	Positive(35)	Negative(65)	Positive(17)	Negative(83)
Father's education				
Illiterate (27)	5(18.52%)	22(81.48%)	3(11.11%)	24(88.89%)
Primary school (30)	14(46.67%)	16(53.33%)	4(13.33%)	26(86.67%)
Secondary school (28)	12(42.86%)	16(57.14%)	8(28.57%)	20(71.43%)
University and higher (15)	4(26.67%)	11(73.33%)	2(13.33%)	13(86.67%)
P-value	0.101		0.290	
Mother's education				
Illiterate (26)	9(34.62%)	17(65.38%)	4(15.38%)	22(84.62%)
Primary school (39)	15(38.46%)	24(61.54%)	8(20.51%)	31(79.49%)
Secondary school (22)	9(40.91%)	13(59.09%)	4(18.18%)	18(81.82%)
University and higher (13)	2(15.38%)	11(84.62%)	1(7.69%)	12(92.31%)
P-value	0.433		0.751	
Father's occupation				
Unemployed (4)	0(0%)	4(100%)	0(0%)	4(100%)
Private (60)	22(36.67%)	38(63.33%)	10(16.67%)	50(83.33%)
Governmental job (36)	13(36.11%)	23(63.89%)	7(19.44%)	29(80.56%)
P-value	0.325		0.614	
Mother's Occupation				
Unemployed (87)	28(32.18%)	59(67.82%)	15(17.24%)	72(82.76%)
Governmental job (13)	7(53.85%)	6(46.15%)	2(15.38%)	11(84.62%)
P-value	0.210		1.00	
Number of abortions				
≤2 (89)	34(38.2%)	55(61.8%)	15(16.85%)	74(83.15%)
≤3 (11)	1(9.09%)	10(90.91%)	2(18.18%)	9(81.81%)
P-value	0.663		0.404	

Table 3 : Relation between HSV-2 infection and natal risk factors.

Variables	IgG		IgM	
	Positive(35)	Negative(65)	Positive(17)	Negative(83)
Mode of delivery				
NVD (63)	22(34.92%)	41(65.08%)	14(22.22%)	49(77.78%)
C/S (37)	13(35.14%)	24(64.86%)	3(8.11%)	34(91.89%)
P-value	1.00		0.098	
Gestational age				
Full term (75)	24(32%)	51(68%)	13(17.33%)	62(82.67%)
Preterm (25)	11(44%)	14(56%)	4(16%)	21(84%)
P-value	0.335		1.00	
Birth location				
Hospital (80)	27(33.75%)	53(66.25%)	13(16.25%)	67(83.75%)
Home (20)	8(40%)	12(60%)	4(20%)	16(80%)
P-value	0.613		0.741	

NVD: normal vaginal delivery, C/S: Cesarean section.

response for HSV-2. Seven children were treated with immune suppressor drug for different reasons (particularly cancer), 4 of whom (57.14%) developed anti-HSV-2 IgG antibodies compared to 3(42.86%) of immunocompetent children who had these antibodies with no significant difference. On the other hand, 5(71.43%) of immunocompromised children developed IgM antibodies

compared to 2(28.57%) of immunocompetent who had these antibodies with significant differences (P=0.001)

Association of HVS-2 Infection with Clinical Findings

Out of 100 involved children, 58 (58%) children were symptomatic. Clinical manifestations included jaundice (22 cases), petechiae (9 cases), oral lesion (20 cases) and eye lesion (40 cases). Thirty-four cases had solitary

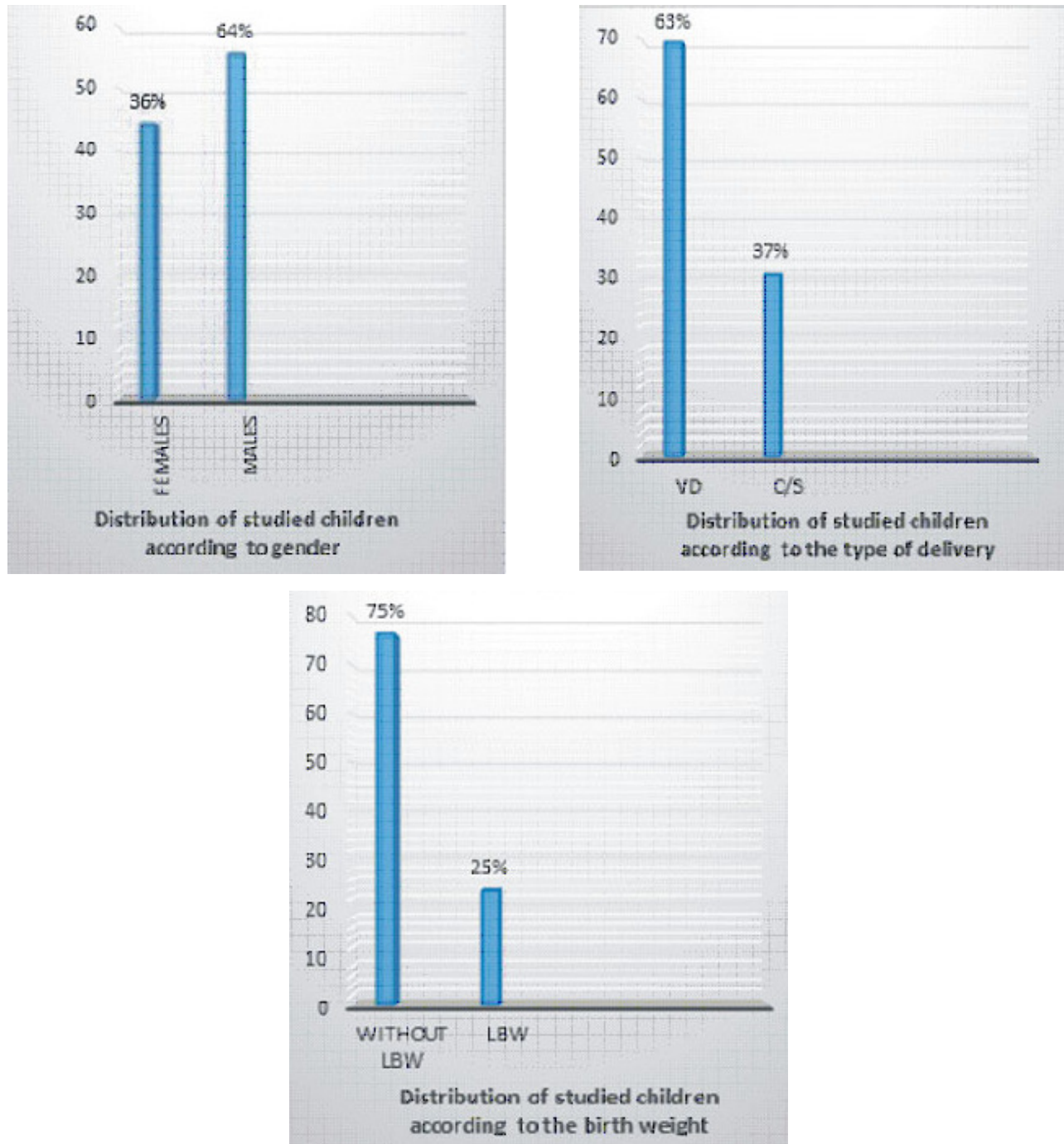


Fig. 1 : Studied children characteristics in percentage.

clinical symptom and 22 cases had mixed (two or more symptoms). Jaundice was significantly associated with anti-HSV-2 IgM antibodies; out of 22 children with jaundice, 8(36.36%) developed IgM compared to 9(11.54%) of non-icteric children, who developed the same Abs ($P=0.001$) as shown in (Table 5).

Relatively small number of children (only 9) had petechiae as a clinical symptom; 6 of them (66.67%) were positive for IgG versus 31.87% of non-petechial children

positive for these Abs ($P = 0.062$).

Twelve (60%) out of 20 children with oral lesions were positive for IgG compared to 28.75% of children without oral lesions with significant difference ($P=0.017$). Similarly, 35% and 12,5 of children with and without oral lesion were positive for IgM with significant difference ($P=0.04$).

Eye lesion was the most common lesions among the study population accounting for 40% of all cases.

Table 4 : Postnatal risk factors and HSV-2 Infections among study children's.

Variables	IgG		IgM	
	Positive(35)	Negative(65)	Positive(17)	Negative(83)
Blood transfusion				
Yes (14)	5(35.71%)	9(64.29%)	3(21.43%)	11(78.57%)
No (86)	30(34.88%)	56(65.11%)	14(16.28%)	72(83.72%)
P-value	1.00		0.702	
Breastfeeding				
Yes (78)	26(33.33%)	52(66.67%)	15(19.23%)	63(80.77%)
No (12)	4(33.33%)	8(66.67%)	1(8.33%)	11(91.67%)
Combination (10)	5(50%)	5(50%)	1(10%)	9(90%)
P-value	0.577		0.532	
Immune suppression				
Yes (7)	4(57.14%)	3(42.86%)	5(71.43%)	2(28.57%)
No (93)	31(33.33%)	62(66.67%)	12(12.9%)	81(87.1%)
P-value	0.236		0.001	

SD: standard deviation, **Combination:** both breastfeeding and bottle feeding were used.

Table 5 : HSV-2 infections and clinical findings.

Variables	IgG		IgM	
	Positive (35)	Negative (65)	Positive (17)	Negative (83)
Jaundice				
Yes (22)	11(50%)	11(50%)	8(36.36%)	14(63.64%)
No (78)	24(30.77%)	54(69.23%)	9(11.54%)	69(88.46%)
P-value	0.129		0.001	
Petechiae				
Yes (9)	6(66.67%)	3(33.33%)	2(22.22%)	7(77.78%)
No (91)	29(31.87%)	62(68.13%)	15(16.48%)	76(83.52%)
P-value	0.062		0.648	
Oral lesion				
Yes (20)	12(60%)	8(40%)	7(35%)	13(65%)
No (80)	23(28.75%)	57(71.25%)	10(12.5%)	70(87.5%)
P-value	0.017		0.040	
Eye lesion				
Yes (40)	17(42.5%)	23(57.5%)	8(20%)	32(80%)
No (60)	18(30%)	42(70%)	9(15%)	51(85%)
P-value	0.208		0.591	

However, there was no significant association of this symptom with neither anti-HSV-2 IgG nor IgM.

DISCUSSION

A relatively high rate of seropositivity to anti-HSV-2 IgG and IgM in children under 5 years old was recorded in this study. This result is compatible with that obtained by Abdullah *et al* (2003), who reported an increasing herpes virus infection rate in Iraqi population. Furthermore, the current result agrees with many global studies investigating Herpes virus infection in different countries (Katharine *et al*, 2017; Hemelaar *et al*, 2015).

In the presented study, the higher rate of males than females among children might be explained by the higher

number of males than females in children that was born during the study period.

In this study, the ratio of whom delivering at hospital is found to be higher than that recorded in 2014 by the Ministry of Health- Iraq and WHO-Iraq, which was 64.1% (Health Annual Report Iraqi, 2014). This variation in results may be due to the fact that, current data were collected in urban areas where hospital deliveries are higher than in rural areas. However, a considerable proportion of pregnant women still deliver at home in developing countries (Nazar, 2017).

Out of 100 participants enrolled in this study 37% born by Cesarean Section (C/S), which was higher than that reported by many studies in Iraq, Nazar P. Shabila (2017) found this rate was the highest in Baghdad (38.8%), between 2008 and 2012 while Al-Kubaisy *et al* reported 38% of C/S in 2014 (10). This variation may be due to that high hospital-based cesarean section rate might be indirectly attributed to having many low-risk pregnancies delivered at home, though the high-hazard pregnancies and the elective or arranged cesarean sections are referred to doctor's facilities. Accordingly, the rate of cesarean areas in clinics increments relatively. In addition, multiple global studies reported a trend of rising C/S rates (Tita, 2012; ACOG Committee on Practice Bulletins, 2007). Regarding mode of delivery, many studies suggest that delivery by elective Cesarean section markedly reduces but does not eliminate the risk for newborn infection and that might explain markedly increased rate of Cesarean section in seropositive HSV-2 (Royal College of Obstetricians and Gynaecologists, 2007).

Many factors influence the transmission of HSV infection to newborns, including education of parents as

a antenatal factors since good hygiene practices and attitudes that taught in school are likely to reduce the risk of transmission of many infectious agents, the mode of delivery and birth location because Obstetrical procedures and use of intrapartum instrumentation considered as a risk factors for transmitted HSV to children and gestational age of the child however many studies suggest that the duration of rupture of membranes have also been increased risk of transmission (Corey and Wald, 2009; Marquez *et al*, 2011).

In the current study, out of 14 patients undergo blood transfusion, eight patients showed seropositive HSV-2 followed blood transfusion. Due to neutropism, herpes simplex viruses (HSV) types 1 and 2 are considered to be of minor relevance. However, several reports gave evidence that a HSV DNAemia might occur and HSV could therefore be transmissible by blood products (Juhl *et al*, 2010).

One limitation of this study is that we don't have data for those seropositive patients before blood transfusion processes, so this result did not support the evidence which suggest that HSV-2 may be transmitted from blood donor.

Another possible explanation for those children infected with HSV after blood transfusion in current study is that individuals with an illness that causes anemia, such as chronic debilitated disease will often be required blood transfusion and such conditions lead to weaken the immune system make them under highest risk for acquiring HSV infection.

Results of current study revealed that mode of neonate feeding mode had non-significant influence in terms of antibody response for HSV-2. This result quite accords with study of Elena Anzivino *et al* (2009).

In this study, seven children were treated with immune suppressor drug for different reasons, 4 of whom (57.14%) developed anti-HSV-2 IgG antibodies. On the other hand, 5 (71.43%) of immunocompromised children developed IgM antibodies. These findings are consistent with several clinical studies, which improved that, reactivation of latent HSV is the most common viral infection in patients during the profound neutropenia that occurs during remission induction in patients with lymphoma and acute leukemia as a consequence of the radiotherapy and chemotherapy used for conditioning and the degree of immunosuppression is an important factor in determining the resistant to HSV infection (Ljungman, 2002; Ferrari *et al*, 2005; Mostad *et al*, 2000).

In this study, out of 100 involved children, 58 (58%) children were symptomatic the clinical manifestations are diverse between jaundice to eye lesion with significant

association of jaundice with anti-HSV-2 IgM. The clinical manifestations of HSV-2 infection are a direct reflection for the site and extent of viral replication (Whitley and Gnann, 2002). Intrauterine congenital infection is usually associated with eye, oral or neurological manifestations with high mortality rate (Sauerbrei and Wutzler, 2007). On the other hand, an infant or a child infected intrapartum or postnatally develops either localized skin, eye and/or mouth lesions or has disseminated HSV-2 infection with an involvement of multiple organs like liver, lung, brain, eye, skin and/or mouth. The mortality rate in the last case is very high (Arvin *et al*, 2006). The majority of children positive for jaundice and anti-HSV-2 IgM were infants (data not presented) and the significance association between jaundice and anti-HSV-2 IgM may be unreal. Rather those infants had developed physiological jaundice related to blood group incompatibility between their parents.

Moreover, in a considerable proportion of infected children, the clinical symptoms associated with herpes infection are a broad and non-specific. They may go unrecognized or may be attributed to another disease process. In most cases, the initial symptoms of HSV infection present within the first four weeks of life. Occasionally, disease presents for the first time between four and six weeks after birth the absence of skin lesions does not negate the possibility of an HSV diagnosis (Howard *et al*, 2003; Nahmias *et al*, 1971; Kohl, 2002).

The variations in the frequency of symptomatic and asymptomatic HSV infection may raise a question of why some children develop symptomatic disease whereas others remain symptom free. Factors such age, genetics, immune response, route of transmission, and differences in the virulence of the viral strain are probably all related to the clinical outcome either singly or in combination

From this study, we concluded that there is high prevalence of HSV infection in Iraqi children under five, when compared with the rate of most neighboring developing countries. Immune suppression for different reasons play the crucial role.

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