



Research Article

Sero-prevalence of Herpes Simplex Virus Type-2 Among Patients Presenting with Fever at a Nigerian University Health Services

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Abstract

Fever is a common clinical sign of infection with Herpes simplex virus type 2 (HSV-2) that cause recurrent genital blisters in human. This study determined the seroprevalence of HSV-2 among patients presenting with fever at the University Health Services (UHS), Ahmadu Bello University (ABU), Main Campus, Zaria. A total of 92 blood samples collected from consenting patients were analyzed for HSV-2 antibody using ELISA. Prior to sample collection, questionnaires were used to obtain socio-demographic and clinical data from the patients. A sero-prevalence of 54.3% (50/92) was obtained among the patients. All the patients (100%:3/3) between age group 43-47 years old had antibodies to the virus while only one patient older than 53 had antibodies to the virus ($p=0.729$). Higher prevalence of HSV-2 was recorded among male (67.7%: 21/31) than in female patients (47.5%: 27/61) ($p=0.066$) and among single (63.9%: 23/36) than in married patients (48.2%: 27/56) ($P=0.141$). In relation to occupational status, the highest prevalence was observed among the employed (68.2%:15/22) compared to the self-employed (55.1%: 27/49). There was no significant relationship between the risk factors studied and HSV-2 infection. However, seroprevalence of HSV-2 was higher among those who claimed not to be involved in sexual activities (58.3%: 32/62), higher among those who did not use protection (52.8%: 28/53) and highest among those who claimed to be with only one partner (51.6%: 32/62). More than half of the patients were infected with HSV-2, thus further and larger studies to determine the risk factors associated with acquiring the virus is needed. Creating awareness on the mode of transmission and consequences of infection with the virus is also important.

Key Words: Sero-prevalence, HSV-2, Fever, University, Zaria, Nigeria

INTRODUCTION

Herpes simplex viruses are DNA viruses belonging to the family Herpesviridae that present as grouped vesicles on an erythematous base (McGregor and Huang, 2021). Herpes simplex viruses more commonly known as herpes are categorized into two types: herpes simplex virus type 1 (HSV-1) or oral herpes and herpes simplex virus type 2 (HSV-2) or genital herpes. These viruses are alpha-herpes viruses which share approximately 50% nucleotide sequence homology (Nahnias *et al.*, 1990, Ashley and Wald, 1999). Classically, HSV-2 is characterized by anogenital infection, whereas HSV-1 is associated with orolabial infections. Most commonly, HSV-1 causes sores around the mouth and lips (sometimes called fever blisters or cold sores) and can cause genital herpes, but most cases of genital herpes are caused by HSV-2. Genital lesions induced by these two herpetic viruses transmitted by intimate contact with someone who is shedding the virus are clinically indistinguishable (Davies, 2004).

Herpes simplex virus type 2 is one of the most common causes of genital ulceration in both developed and developing countries (Aurelian, 1999, Wald, 2002, Biswas *et al.*, 2011) and has globally become an increasing common sexually transmitted infection (Nahnias and Keyserling 1996, Brugha *et al.*, 1997, Xu *et al.*, 2006, Xu *et al.*, 2010, Straface *et al.*, 2012). Genital herpes is a lifelong incurable infection that causes medical, psychological and social concerns (Đaković Rode *et al.*, 2008). Primary genital HSV-2 infection may be associated with small, painful lesions affecting the genitals and surrounding areas (Bridges, 2012) as well as generalized symptoms such as fever, muscle aches, and malaise (McGregor and Huang, 2021). Herpes simplex virus type 2 generally causes meningitis (Davies *et al.*, 2004) and the infection is responsible for significant neurological morbidity. Aseptic meningitis occurs in 36% of women with primary HSV-2 genital infection and 13% of men (Corey *et al.*, 1983). Herpes simplex virus type 2 may cause eye lesions, disseminated infections, or foetal malformations (Straface *et al.*, 2012).

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Prevalence of HSV-2 antibodies have been found to be significantly associated with carcinoma of the cervix, especially the squamous cell and women with premalignant and malignant carcinoma of the cervix were shown to have serologic evidence of infection with HSV-2 type (Adelusi *et al.*, 1977). Recurrent infection occurs in a person with preexisting antibodies against the virus (Gupta *et al.*, 2007).

Global research evidence have shown a link between the HIV epidemic and HSV-2 infection (Corey and Handsfiel, 2000, Buvé *et al.*, 2001, Đaković Rode, 2008, Xu *et al.*, 2010). In Africa, Asia and the Americas, the impact of genital HSV infection has increased the risk of HIV acquisition with seroprevalence in people co-infected with HIV being up to 77% for HSV-2 (McGregor and Huang, 2021). There is a synergistic interaction between HSV-2 and HIV (Wald *et al.*, 1997, Chen *et al.*, 2000, Wald *et al.*, 2002) and HSV-2 increases risk of HIV acquisition and transmission while HIV increases clinical and subclinical HSV-2 reactivation

The burden of HSV-2 infection varies from region to region and in different populations (Weiss, 2004, Dakovik-Rode *et al.*, 2008) and so are the associated factors. Globally, about 535.5 million people were infected with HSV-2 with an overall prevalence of 16.2% in 2003 (Looker *et al.*, 2008). Highest prevalence of HSV-2 has been found in some parts of Africa, America and the lowest in Asia (Jennings *et al.*, 2008). In the United States, one in four sexually active adults has HSV-2 infection. Comparably, high HSV-2 rates have been observed in sub-Saharan Africa where HIV prevalence is the highest. Acquisition rates of HSV-2 among South African teenagers are estimated to be 10-20% per year after sexual debut, and 20% of HIV seronegative and 80% of HIV seropositive teenagers are HSV-2 seropositive (Chen *et al.*, 2000, Buvé *et al.*, 2001). Seroprevalence of HSV-2 is >40% among antenatal attendees in Africa and ranges from 60-95% among female sex workers in sub-Saharan Africa (Corey *et al.*, 2004).

Prevalence of HSV-2 has been found to vary by individual-level characteristics with the risk of acquisition being influenced by factors such as gender, age, sexual activity level, marital status, socioeconomic status, education (Biswas *et al.*, 2011), race and ethnicity (Schillinger *et al.*, 2008, Xu *et al.*, 2010). Antibodies to HSV-2 are found more frequently at older age (Cusini and Ghislanzoni, 2001, Cowan *et al.*, 2003, Đaković Rode, 2008, Mir *et al.*, 2010, Mawak *et al.*, 2012, Sudfeld *et al.*, 2013), in females (Suligoj *et al.*, 2000, Smith and Robinson, 2002, Đaković Rode *et al.*, 2008, Looker *et al.*, 2008, Brazzale *et al.*, 2010), in populations with risky sexual behavior and multiple partners (Wald, 2005, Mir *et al.*, 2010, Xu *et al.*, 2010, Biswas *et al.*, 2011, Sudfeld *et al.*, 2013) and in HIV-infected patients (Suligoj, *et al.*, 2002, Wald, 2002, Weiss, 2004, Đaković Rode, 2008).

Importantly, up to 70 percent of genital HSV infections are unrecognized by both patients and clinicians (Corey and Handsfiel, 2000, Russell *et al.*, 2001, Andréoletti *et al.* 2005, Schillinger *et al.*, 2008, Mir *et al.*, 2010, Xu *et al.*, 2010, Grove and O'Connell, 2021), an aspect of HSV-2 infection that raises a major public health challenge. Asymptomatic infection plays a major role in maintaining the virus circulation in society and many cases of genital herpes are transmitted by persons who are unaware that they are infected.

Because HSV-2 causes a lifelong infection with unpredictable reactivation and transmission, detecting antibodies to HSV

plays an important role in identifying carriers of this infection. It is also a good marker of sexual behavior in the population (WHO and UNAIDS, 2001, Smith and Robinson 2002) and is critical in understanding the pattern and distribution of HSV-2 infection within the population.

Prevalence of HSV-2 is on the increase in Nigeria (Agabi *et al.*, 2010), a sub-Saharan Africa country located in a region where HIV and HSV-2 seroprevalence are high. In addition, fever is a common clinical sign of infection with HSV-2 and majority of patients present with this sign in health facilities. There are however a few published reports on HSV-2 in Nigeria conducted among patients attending Sexually Transmitted Infections Clinic in Jos (Agabi *et al.*, 2010) and among females in Enugu (Ojinmah *et al.*, 2012). A seropevalence of 59% has earlier been reported among female sexual workers in Lagos (Dada *et al.*, 1998) and even 2.02% among children above 14years in Ibadan (Adelusi, 1977). However, there is little or no information on the seroprevalence in Zaria. This study was therefore conducted to determine the seroprevalence of HSV-2 infections among patients presenting with fever at the UHS of ABU Zaria, assess the frequency of unrecognized infection and identify some of the predisposing factors to the infection.

MATERIALS AND METHODS

Study Design and Study Area: The study was hospital based, cross sectional and involved consecutive collection of blood samples from every other patient presenting with fever at the University Health Services (UHS), Main Campus, A.B.U., Zaria. The UHS is located within ABU Main Campus, Samaru, and Sabon-Gari Local Government Area of Kaduna, Nigeria. The UHS was set up to provide health services to the staff and students of ABU and people living around the University (Samaru community). Service such as antenatal service, laboratory service, HIV counseling and testing, ophthalmic service and outpatient service, amongst others are rendered at the UHS.

Study Population: The study population included 92 individuals from all works of life, of all ages and gender who presented with fever at the UHS between April and August 2013. Fever was defined as an increase in body temperature above the normal of 37°C.

Data Collection: After obtaining ethical approval from the Ethics Committee of the UHS and informed consent from participants, a self-designed semi-structured questionnaire was used to obtain data on socio-demography and risk factors of infection from each consenting participant.

Sample Collection and Processing: About 3-4ml venous blood sample was collected in EDTA bottles by a Laboratory Technologist from each of the participant enrolled in the study. The sera were separated out by centrifugation at 2500 revolution per min for five minutes and stored at -20°C until analyzed.

Sample Analysis: The serum samples were analyzed using Enzyme linked immunosorbent assay (ELISA) kits (Diagnostic Automation/Cortez Diagnostics Inc. USA) according to the manufacturers' instruction. The Enzyme

Immunoassay used in this study detects IgG class specific antibodies against HSV-2 in human serum or plasma.

Principles of the Test; Purified HSV antigen is coated on the surface of micro wells, diluted serum is added to wells and the HSV-2 IgG specific antibody, if present binds to the antigen. All unbound materials are washed away. After adding enzyme conjugate, it binds to the antibody-antigen complex. Excess enzyme conjugate is washed off and TMB chromogenic substrate is added. The enzyme conjugate catalytic reaction is stopped at a specific time. The intensity of the color generated is proportional to the amount of IgG specific time. The results are read by a micro well reader in a parallel manner with calibrator and controls.

Assay Procedure: Exactly 100ul of 1:40 dilutions of the negative control, positive control, calibrator and each serum sample were added to the appropriate wells in a 96 coated strips plate and mixed well. A well was left empty as the reagent blank. The plate was incubated for 30 minutes at room temperature and washed repeated three times. After washing, 100ul of enzyme conjugate was dispensed into each well and incubated for 15 minutes at room temperature. The plate was again washed three times; 100ul of TMB chromogenic substrate was dispensed into each well and incubated for 15 minutes at room temperature. Finally, 100uL of 2M HCl was added to each well to stop the reaction and the optical density (O.D) were read within 5 minutes at 450nm after adding stop solution using an ELISA plate reader (GF-M3000 B. Bran Scientific and Instrument Company England).

Calculation and Interpretation of Results: To obtain the cut off O.D value, the O.D of the calibrator was multiplied by the value of the Factor (f) printed on label of calibrator (f) vial = 0.5. The IgG index was calculated by dividing the O.D values of each sample by the obtained value of cut off. Any HSV-2 IgG index of 0.90 or less were considered sero-negative for IgG antibody to HSV-2, any HSV-2 IgG index between 0.91-0.99 were considered equivocal and samples were retested and any HSV-2 IgG index of 1.00 or greater were considered seropositive.

DATA ANALYSIS: Data were subjected to statistical analysis using software SPSS version 16.0 (SPSS Inc, Chicago, USA). Multivariate regression analysis was performed at 95% confidence interval. P values ≤ 0.05 were considered statistically significant.

RESULTS

Of the 92 serum samples of patients presenting with fever analyzed for HSV-2 IgG, 50 were positive giving a seroprevalence of 54.3%. Majority (86%: 79/92) of the patients seen at the UHS during the study period were between ages 18-37 years old while the most frequent age group was 23-27 years old (31.5%: 29/92). HSV-2 IgG were detected in all age groups except age ≤53 where only one patient was seen and all the three patients seen in age group 43-47 years old were seropositive. The difference observed in the sero-prevalence of HSV-2 IgG according to age was not statistically significant ($\chi^2 = 4.433$, $df = 7$, $P = 0.729$) (Table1).

The result was analyzed according to socio-demographic factors as shown on Table 2. Even though the percentage (66.3%: 61/92) of female patients presenting with fever enrolled in the study was almost twice (33.7%: 31/92) that of the male patients, HSV-2 IgG was detected with a higher rate among male (67.7%: 21/31) compared to female patients (47.5%: 29/61). Although the observed difference in the seroprevalence was not statistically significant ($\chi^2 = 3.381$, $df = 1$ $p=0.066$), the male patients were 2.3 times more likely to be infected with HSV-2 than female patients (odds ratio [OD] = 2.317, 95% C.I. = 0.937-5.730).

Table 1: Seroprevalence of HSV-2 in relation to age among patients presenting with fever at the UHS of ABU, Main Campus, Zaria, Nigeria

Age group (years)	Total	Positive (%)	Negative (%)
18 – 22	22	13(59.1)	9(40.9)
23 – 27	29	15(51.7)	14(48.3)
28 – 32	21	11(52.4)	10(47.6)
33- 37	7	3(42.9)	4(57.1)
38 – 42	7	4(57.1)	3(42.9)
43 – 47	3	3(100.0)	0(0)
48 – 52	2	1(50.0)	1(50.0)
≥ 53	1	0(0)	1(100.0)
Total	92	50(54.3)	42(45.7)

($\chi^2 = 4.433$, $df = 7$ $P = 0.729$)

Table 2: Seroprevalence of HSV-2 in relation to Socio-demography of patients presenting with fever at the UHS of ABU, Main Campus, Zaria, Nigeria

Variable	Total	Positive (%)	P-value
Gender			
Male	31	21(67.7)	
Female	61	29(47.5)	0.066
Marital status			
Married	56	27(48.2)	
Single	36	23(63.2)	0.141
Occupation			
Employed	22	15(68.2)	
Unemployed	67	33(49.3)	
Self employed	3	2(66.7)	0.275

Most (60.1%: 56/92) of the patients visiting the UHS during the study and hence enrolled in the study were married. However, analysis of the result showed majority (63.9%: 23/36) of the HSV-2 IgG seropositive patients to be single while 48.2% (27/56) were married with no statistically significance difference in the seroprevalence obtained ($\chi^2 = 2.710$, $df = 1$, $p = 0.141$). Seroprevalence of HSV-2 IgG was highest among the employed (68.2%:15/22) and lowest among the self-employed (55.1% (27/49) with no statistically significant difference ($\chi^2 = 2.581$, $df = 2$, $P = 0.275$).

Analysis of the result according to knowledge of HSV-2 showed that 91.3% (84/92) of the patients had no knowledge of the virus and only 8.7% (8/92) ever heard of genital herpes. About 75.0 % (6/8) of the patients that had knowledge of the virus and more than half of those that were not aware (52.4%: 44/84) were seropositive to HSV-2 ($\chi^2 = 1.506$, $df = 1$, $P = 0.220$). Three of the eight patients who had knowledge of HSV-2 heard about the virus from visiting the

hospital and one heard from lecture in the school ($\chi^2 = 1.778$, $df = 3$, $P = 0.620$). Further analysis of the result showed that HSV-2 IgG antibodies was detected with no significance difference ($\chi^2 = 0.024$, $df = 1$, $P = 0.877$) among those who were aware of their HSV-2 status (57.1%: 4/7) and those who were not (54.1%: 46/85) (Table 3).

Result of the analysis according to possible risk factors that might predispose to the infection is shown on Table 4. None of the risk factors studied was significantly ($P > 0.05$) associated with HSV-2 in this study. However, more (60%: 18/30) of those not involved in sexual activity had antibodies to HSV-2 while 51.6% (32/62) seropositive patients were sexually active ($\chi^2 = 0.573$, $df = 1$, $p = 0.449$). About 52.4% (32/61) of patients with single partner were seropositive while the only patient with multiple partner was seropositive ($\chi^2 = 1.240$, $df = 2$, $p = 0.538$). Further analysis showed that 28 (53.8%) of the 53 patients who did not use protection had antibodies to HSV-2 while 5 (50%) out of the 10 who used protection were also seropositive ($\chi^2 = 0.339$, $df = 2$, $P = 0.844$).

Table 3:
Seroprevalence of HSV-2 according to knowledge and Status of patients presenting with fever at the UHS of ABU, Main Campus, Zaria, Nigeria

Variable	Total	Positive (%)	P- value
Knowledge			
Yes	8	6(75.0)	
No	84	44(52.4)	0.220
Source of knowledge			
Hospital	3	2(66.7)	
Media	2	1(50.0)	
Lectures	2	2(100.0)	
School	1	1(100.0)	0.620
HSV-2 status			
Yes	7	4(57.1)	
No	85	46(54.1)	0.877

Table 4:
Seroprevalence of HSV-2 in relation to risk factors among patients presenting with fever at the UHS of ABU, Main Campus, Zaria, Nigeria

Variable	Total	Positive (%)	p-value
Sexual activity			
Yes	62	32(51.6)	0.449
No	30	18(60.0)	
Partner(s)			
1	61	32(52.4)	0.538
>1	1	1(100.0)	
Protection use			
Yes	10	5(50.0)	0.844
No	52	28(53.8)	

DISCUSSION

The present study showed more than half (54.3%: 50/92) of the patients presenting with fever to be seropositive to HSV-2. The sero-prevalence obtained is almost similar to the result of previous studies conducted in Nigeria where seroprevalence of 59% (Dada et al., 1998) and 47.3% (Kalu et al., 2014) were reported. The sero-prevalence is however lower than the 87% and 77.8% recorded in studies in Jos and Enugu, Nigeria (Agabi et al., 2010) and higher than the 16.5% report in the United States (Xu et al., 2006). Infection with HSV-2 in over

half of these patients appears to be silent and unnoticed among the study population with many of the positive patients not aware of the disease. Since infection with HSV-2 has been shown to facilitate HIV transmission (Anuradha et al., 2008) and increase the risk of HIV acquisition, these infected patients are at greater risk of HIV infection. Herpes Simplex Virus type 2 is known to establish lifelong infection that recur more often hence these infected patients serve as reservoir of HSV-2. Moreover detecting antibodies to HSV is often used to identify carriers of HSV-2. In addition, if any of these patients happen to be infected with HIV, recurrence of HSV-2 will be very common in the individual hence recurrent fever. Genital herpes is a lifelong incurable infection that causes medical, psychological and social concerns and these patients might be undergoing some of these concerns.

The seroprevalence of HSV-2 was highest in patients within age group 43-47 years old, which somewhat agree with the finding of a study conducted in Jos where the highest prevalence was found among participant within age group 51-60 years (Agabi et al., 2010). Studies in Nigeria (Adelusi et al., 1977, Ojinmah et al., 2012) and other countries (Cusini and Ghislanzoni, 2001, Đaković Rode et al., 2008, Arama et al., 2010, Mir et al., 2010, Mawak et al., 2012, Sudfeld et al., 2013) have demonstrated an association between HSV-2 prevalence and older age. Cowan et al. (2003) in a study conducted in Brazil, Estonia, India, Morocco and Sri Lanka showed HSV- seroprevalence to increase significantly with age.

The seroprevalence was higher in male than in female patients despite the difference in sample size. The result agrees with a previous report in Nigeria (Agabi et al., 2010). This observation may be because the male patients enrolled in the study were more susceptible to the virus or due to high level of sexual activity or having multiple sexual partners. However, some studies have reported HSV-2 to be more frequent in women than men (Suligoi et al., 2000, Smith and Robinson, 2002, Đaković Rode et al., 2008, Looker et al., 2008, Arama et al., 2010, Brazzale et al., 2010).

The seroprevalence was observed to be higher among the single patients compared to the married which agree with previous report in the United States (Weiss et al., 2004). This observation is in line with previous reports in Kenya (Mehta et al., 2008) and Nigeria (Agabi et al., 2010) and might probably be due to active sexual life, multiple sex partners and contact with commercial sex partners.

Patients who agreed not to be sexually active had higher HSV-2 seropositivity than those who said they were sexually active and the only patient who had more than one partner was infected. This finding agrees with previous report in Nigeria (Agabi et al., 2010) and in Kenya (Mehta et al., 2008). Studies have shown multiple sexual partners to be statistically associated with HSV-2 seropositivity (Wald et al., 2005, Mir et al., 2010, Xu et al., 2010, Biswas et al., 2011, Sudfeld et al., 2013). This goes to confirm the sexual mode of transmission of the virus.

In relation to the use of protection, patients who do not use protection had higher seroprevalence compared to those who do which is not in agreement with previous report (Agabi et al., 2010). This observation might be due the small sample size used for the study.

In conclusion, Herpes Simplex Virus type 2 antibodies was detected in 54.3% of the patients presenting with fever with no visible signs and symptom of the infection. This implies that

these patients had been infected with the virus and had developed antibodies hence are latent carrier of the virus. The virus was not significantly associated with the socio-demographic and predisposing risk factors studied. The results highlight the potential public health impact of HSV-2 in Nigeria where anti-HSV-2 testing is not generally performed in all populations, especially considering the risk of neonatal transmission and the attendant complications at birth.

In view of the high seroprevalence of HSV-2 obtained in this study, there is need for public enlightenment on genital herpes, its mode of transmission and public health significance. Patients presenting with recurrent fever should be screened for HSV-2 antibodies and further studies with larger sample size is recommended. Since the HSV-2 infection is life-long and has no known cure, primary prevention remains the mainstay of its control.

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