

Seroprevalence of Herpes Simplex Virus among Human Immunodeficiency Virus-Positive Patients in Resource-Limited Setting

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Abstract

Introduction: There are two types of herpes simplex virus (HSV): HSV Type 1 (HSV-1) and HSV Type 2 (HSV-2). Viral comorbidity in HIV is on the increase. This study determines the seroprevalence of HSV 1 and 2 among immunodeficient patients in Gwagwalada, Nigeria. **Materials and Methods:** This is a hospital-based descriptive cross-sectional study which spanned 24 months from October 2014 to September 2016. A total of 160 HIV seropositive patients were recruited from venereology clinic. **Results:** The overall prevalence of herpes simplex infection among HIV seropositive patients in this study was 13.8%, the prevalence of herpes simplex Type 1 was 63.6%, while that of herpes simplex Type 2 was 36.4%. The mean age of the patients was 29 ± 13.9 years and the male-to-female ratio was 1:2. There were 52 male (32.5%) and 108 female (67.5%) seropositives. Among the 22 patients with positive HSV result, seven representing 31.8% were males, while 15 (68.2%) were females. The buttock was the predominant site of the body affected by herpes lesions in 7 of the patients representing 31.8%, four of these patients were infected with herpes simplex Type 2, while three representing 21.4% were herpes simplex Type 1. Other body sites are labia/penile (18.1%), oral (22.7%), and nasal (13.6%). In association with CD4 counts, five (35.7%) Herpes simplex Type 1 was isolated from patients with CD4 counts of 200–500 cell/mm and >500 cells/mm, respectively. The seroprevalence of herpes simplex Type 2 among patients with CD4 counts of <200 cell/mm was 62.5%. **Conclusion:** Herpes simplex infections are important viral comorbidity among HIV patients; this was more observed among females. Sexual practice play an important role with the occurrence of HSV-1 in patients with genital rash and predominance of buttock lesion.

Keywords: Gwagwalada, HIV seropositive, HSV-1, HSV-2, immunology, Nigeria

INTRODUCTION

Herpes simplex virus (HSV) Type 1 (HSV-1) and Type 2 (HSV-2) are members of *Herpesviridae* family-DNA viruses. HSV-1/HSV-2 are common human pathogens and might cause severe illness.^[1,2] Following primary infection, the viruses establish lifelong latent infection and are transmitted by close contact, both sexual and nonsexual.^[1,3] In most cases, primary HSV-1 and HSV-2 infections are asymptomatic and self-limited in immunocompetent individuals but can be complicated with fulminant diseases in neonates, young children, and immunocompromized hosts.^[1,2,4]

Traditionally, HSV-1 is considered as a pathogen of oral vesicular lesions occurring above the umbilicus but with

changing sexual behaviors among adolescence and indeed adults. HSV can cause genital ulcers, herpetic whitlow, and corneal blindness.^[4-7] Furthermore, in a study of US college students, the percentage of genital herpes specimens that were attributable to HSV-1 increased from 31% in 1993 to 78% in 2001.^[2,6-8]

Immunologic responses to HSV infections can be by innate and viral-specific anti-HSV.^[9-11] Advance protective

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responses might involve viral specific cytotoxic T-cells and antibody-producing humoral immunity.^[9,12-15] In our world of increasing importance of the prevalence studies to guide vaccine trials and to monitor trends associated with herpes infections,^[7,16-18] there are few data on the seroprevalence of herpes simplex infection in the tropics; therefore, this study determines the seroprevalence of HSV 1 and 2 among immune deficient patients in Gwagwalada, Nigeria.

MATERIALS AND METHODS

Study design

This is a hospital-based descriptive cross-sectional study which spanned 24 months from October 2014 to September 2016.

Study area

This study was carried out at the Microbiology Research Laboratory (MRL), Microbiology and Parasitology Department, University of Abuja Teaching Hospital (UATH) Gwagwalada, (F. C. T). The hospital is located in Gwagwalada whose geographical coordinates are 8° 56' 29" North and 7° 5' 31" East.^[19] Abuja is the administrative capital of Nigeria, hosting the national Parliaments and the Presidency. This is a cosmopolitan city by all standards with several nocturnal recreation areas. It renders services to neighboring states such as Nassarawa and the Northern part of Nigeria with population of close to 30 million people.

Study population

A total of 160 symptomatic patients who met the inclusion criterion were recruited from the venereology clinic with the complaint of vesicular rash in the body. This includes children and adult patients.

Inclusion criteria

- i. HIV seropositive patients (Children and adults) presenting with symptoms of vesicular rash in any part of the body and consented to be part of the study
- ii. All hospital patients that are currently or previously on antiviral presenting with vesicular rash.

Study sample size

The sample size was determined using the following equation as described,^[20] and a total of 160 sample populations were enrolled.

Sampling method and research instrument

The purpose of this work was explained to the patients before their consent to participate was obtained. Interviewer-administered, structured questionnaires were used as the study tool. The questions outlined in the data forms were explained to the patients and to parent or guardian (for those <15 years) and then completed with the required information which included biodemographic data, vesicular site, and laboratory processes such that the eventual result was noted in the data forms and communicated to the physicians and the participants (parent or guardian as the case may be).

Procedure

In the clinic side laboratory, Tzanck test was performed for the entire participant included in the research for the presence of

HSV. This was followed by collection of 4 ml of blood which was taken to MRL for determination of IgG-class antibodies to type-specific HSV glycoprotein G (IgG) using enzyme-linked immunosorbent assay (The fortress diagnostics^R, LA, USA) to determine the prevalence of HSV 1 and 2. The blood was centrifuged to obtain the serum.^[21] The test was performed according to the manufacturer guidelines.

Principle

Specific Herpes simplex antigen is bound on the surface of the microtiter strips. Patient serum was pipetted into the wells of the microtiter plate with the aid of ready to use calibrators. A binding between the class-specific IgG antibodies in the serum and the immobilized herpes simplex antigen takes place. After 1-h incubation at room temperature, the plate is rinsed with diluted wash solution, in order to remove unbound material. Then, ready-to-use antihuman (IgG) peroxidase conjugate is added and incubated for 30 min. After a further washing step, the substrate 3,3',5,5'-Tetramethylbenzidine (TMB) solution is pipetted and incubated for 20 min, inducing the development of a blue dye in the wells. The color development is terminated by the addition of a stop solution which changes the color from blue to yellow. The resulting dye is measured spectrophotometrically at the wavelength of 450 nm, the concentration of the class-specific IgG antibodies is directly proportional to the intensity of the color.^[21]

Statistical analysis

All generated data were analyzed using SPSS version 20.0 using Chi-square contingency table and a degree of freedom of 95%, $P < 0.05$ was reported as statistically significant. The data were statistically represented in terms of mean, percentage, range, and standard deviation. Comparison between different groups will be done using Fisher's exact test, Pearson Chi-square, Student's *t*-test, and test of correlation was performed using the Spearman correlation test.

Ethical approval

The ethical clearance for this study was obtained from the Research Ethics Committee of the UATH.

RESULTS

From the 160 patients, the overall prevalence of herpes simplex infection among HIV seropositive patients in this study was 13.8%, the prevalence of herpes simplex Type 1 was 63.6%, while that of herpes simplex Type 2 was 36.4%.

The mean age of the seropositive patients was 29 ± 13.9 years, and the male-to-female ratio was 1:2. Among HIV seropositive patients recruited, the predominant study population was within the 21–30 and 31–40 age groups accounting for 30.6% and 23.1%, respectively. Age group 21–30 recorded the highest HSV seropositive with 5 (22.7%) which comprises 2 (14.3%) HSV-1 and 3 (37.5%) HSV-2. Among 0–10 and >61 age groups, the prevalence of herpes simplex Type 1 was 21.4% and 28.6%, while the seroprevalence of herpes simplex Type 2 was 0.0% and 0.0%, respectively. This distribution was statically significant ($P < 0.05$) [Table 1].

Table 1: Age and herpes simplex infection in Abuja, Nigeria

Age groups	Frequency (%)	HSV -ve (%)	HSV +ve (%)	HSV -1 (%)	HSV -2 (%)
0-10	9 (5.6)	6 (4.3)	3 (13.6)	3 (21.4)	0 (0.0)
11-20	18 (11.3)	15 (10.9)	3 (13.6)	1 (7.1)	2 (25.0)
21-30	49 (30.6)	44 (31.9)	5 (22.7)	2 (14.3)	3 (37.5)
31-40	37 (23.1)	34 (24.6)	3 (13.6)	1 (7.1)	2 (25.0)
41-50	19 (11.9)	17 (12.3)	2 (9.0)	1 (7.1)	1 (12.5)
51-60	21 (13.1)	19 (13.8)	2 (9.0)	2 (14.3)	0 (0.0)
>61	7 (4.4)	3 (2.2)	4 (18.1)	4 (28.6)	0 (0.0)
Total	160	138	22	14	8

HSV: Herpes simplex virus

There were 52 male (32.5%) and 108 female (67.5%) HIV seropositive patients and the male-to-female ratio was 1:2. Among the 22 patients with positive HSV result, seven representing 31.8% were male, while 15 (68.2%) were female. The prevalence of herpes simplex Type 2 among males in this study was 62.5%, and the seroprevalence of HSV-1 was 14.3%. Among the female, there were 12 (85.7%) patients that were positive for herpes simplex Type 2 out of the 15 patients positive for herpes simplex. In addition, three of the female patients representing 37.5% were positive for herpes simplex Type 1. There was a significant relationship between the virus and gender [odds ratio = 12.462, 95% confidence interval = 2.667–49.992, $P = 0.004$, Table 2].

The buttock was the predominant site of the body affected by herpes lesions in seven of the patients representing 31.8%. Other body sites are labia/penile 4 (18.1%), oral 5 (22.7%), and nasal 3 (13.6%). HSV-1 was predominantly found among patients with oral lesions representing 4 (28.6%), while four patients representing 50.0% were positive for HSV-2 with lesion occurring in the buttocks. The seropositive of HSV, HSV-1, and HSV-2 isolated from the oral, labia, and buttock lesions were statistically significant, with P value of 0.002, 0.03, and 0.001, [Table 3].

In association with CD4 counts of HIV seropositive patients, 69 of these patients representing 43.1% had CD4 counts of <200 cells/mm, while 36 (22.5%) of the patients recruited had CD4 counts of >500 cells/mm. From this distribution, 9 (40.9%) herpes simplex was isolated from patients with CD4 counts of <200 cells/mm. Five (35.7%) herpes simplex Type 1 was isolated from patients with CD4 counts of 200–500 cell/mm and >500 cells/mm, respectively. The seroprevalence of herpes simplex Type 2 among patients with CD4 counts of <200 cell/mm was 62.5%. The differences observed was statistically significant ($P = 0.0001$, Pearson $\chi^2 = 25.217$, $df = 2$, positive Spearman Correlation = 0.624) [Table 4].

DISCUSSION

Infections with HSV-1 and HSV-2 are among the most common human viral infections. HSV-1 is the usual cause of orolabial herpes and HSV-2 of genital herpes. Up to 70% of genital HSV infections are unrecognized; therefore, seroepidemiological studies are critical to understanding the pattern and distribution

of HSV infection within populations. Most people who are infected shed this virus at various times and are therefore potentially infectious. HSV-2 is almost always sexually transmitted and as such has been shown to be a good marker of sexual behavior in populations.^[2,4,17]

The prevalence of herpes simplex infection in Abuja was 13.8%. The overall prevalence rate of HSV was low compared to the results reported in a multicenter study conducted in four cities in Sub-Saharan Africa: 90.0% in Cotonou, Benin Republic; 96.6% in Benin, Nigeria; and 93.9% in Kisumu, Kenya.^[13] Olufunke reported a rate of 61.6% in Lokoja, Nigeria.^[22] Furthermore, similar to the overall seroprevalence of HSV among HIV patients in large-scale community-based studies conducted in Asia and Europe.^[1,2,17,18] This shows that there is a relationship between HSV and HIV infections with herpes simplex Type 2 more evident in our study. This may be due to several mechanisms which include mucosa mucosal inflammation during HSV-2 reactivation allowing free movement of HIV and may also be due to recruitment of macrophages to site of herpes inflammation acting as cofactor in the entry of HIV.

The seroprevalence of HSV-1 infection (63.6%) was higher than that of HSV-2 (36.4%) in this study, and the former is high in most geographic regions across the world and more prevalent than type 2 HIV infection among known high-risk populations.^[4,16,18] The rate of HSV-1 decreased during the sexually active stage of life, but increased infection rate observed during the latter stage of life. The prevalence rate of HSV-2 was low in this, which is consistent with other hospital-based studies with the prevalence rate from 14% to 30%.^[9,11,16,18] A population-wide study with cross-country outlook documented a significant increase in the prevalence rate of HSV-2 which was around 16%.^[17] Nag in Eastern India got an overall seroprevalence of 42.3% for HSV-2 IgG. In Nigeria, the prevalence studies of HSV-2 had shown markedly higher rates. Ojinmah recorded a prevalence rate of 77.8% in Enugu,^[11] and Agabi observed an 87% prevalence rate in Jos^[14] which was among patients attending venereology clinics in Jos. In Sub-Sahara Africa, rates of 87.7% and 84.0% were recorded in Zambia and Yaoundé, Cameroon, respectively.^[13] The varying prevalence rate across the world might be due to changing sexual behaviors among the sexually active

Table 2: Gender and herpes simplex virus in Abuja, Nigeria

Gender	Frequency (%)	HSV (%)	HSV -1 (%)	HSV -2 (%)	P
Male	52 (32.5)	7 (31.8)	2 (14.3)	5 (62.5)	0.004
Female	108 (67.5)	15 (68.2)	12 (85.7)	3 (37.5)	
Total	160	22 (100.0)	14 (100.0)	8 (100.0)	

OR=12.462, 95% CI=2.667-49.992, $P=0.004$. HSV: Herpes simplex virus, CI: Confidence interval, OR: Odds ratio

Table 3: Body sites and herpes simplex virus in Abuja, Nigeria

Sites of herpes	HSV (%)	HSV -1 (%)	HSV -2 (%)	P
Oral orifice	5 (22.7)	4 (28.6)	1 (12.5)	0.002
Nasal orifice	3 (13.6)	3 (21.4)	0 (0.0)	0.712
Nipple	2 (9.1)	2 (14.3)	0 (0.0)	0.711
Labia/penile	4 (18.2)	2 (14.3)	2 (25.0)	0.03
Buttock	7 (31.8)	3 (21.4)	4 (50.0)	0.001
Anal	1 (4.5)	0 (0.0)	1 (12.5)	0.53
Total	22	14	8	

HSV: Herpes simplex virus

Table 4: CD4 count and herpes simplex infection in Abuja

CD4 counts	Frequency (%)	HSV	HSV-1	HSV-2	P
<200	69 (43.1)	9 (40.9)	4 (28.6)	5 (62.5)	0.001
200-500	55 (34.4)	6 (27.2)	5 (35.7)	1 (12.5)	
>500	36 (22.5)	7 (31.8)	5 (35.7)	2 (25.0)	
Total	160	22	14	8	

population and the ease of vertical transmission of HSV-2 from mother to child.

There is a clear relationship between HSV-1 and HSV-2 with gender^[2,4,7,14,16,18,22] with the female gender more associated with the HSV seropositivity accounting for almost 70% of the disease burden, as shown in this study, and this association was statistically significant (0.004). There was lower HSV-2 infection rate among females in this study which was consistent with Nag in Eastern India,^[16] but contrary to findings by Jen in Taiwan,^[3] Ojinmah in Enugu,^[11] Nigeria, and Anejo-Okopi in Jos, Nigeria.^[12] The acquisition of HSV-2 primarily results from sexual contacts.

There might be several factors responsible for the location of lesions in patients with HSV infections. Predominance of HSV-1 in the oronasal mucosa might be due to age-specific appearance of lesion in HIV-positive patients. Predominance of HSV-2 lesion in the Buttock (60%) higher than vulva/penile lesion was observed, and this might be due to preferred sexual practice among the patient. Nongenital route of transmission may account for higher prevalence of HSV-1 with buttocks lesions. Factors such as hygiene and cultural behaviors might be involved, especially during naming ceremony in our environment. Herpes simplex Type 2 was predominantly isolated from patients with reduced CD4 counts (<200 cell/mm) which was consistent with the role of immunity in preventing herpes infections.

Recommendations

1. To undertake a community research in order to have a true seroepidemiology data
2. Handwashing policy should be inculcated at all times in order to reduce the burden of HSV-1 and other infectious agents.

Limitation

The study was hospital based and did not include other cohort populations such as pregnant women and public baby nurseries.

CONCLUSION

The seropositivity of HSV was found to be higher in HIV-positive patients which indicates that the two viruses collaborate in infection of patients. HSV-2 was predominant among males than females and was more evident among patients with reduced CD4 counts.

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Conflicts of interest

There are no conflicts of interest.

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