Comparison of Prevalence of Kaposi's Sarcoma in $HHV8^+$ and $HHV8^-$ HIV Infected Patients in South-South Nigeria

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Received: October 26, 2010 Accepted: November 9, 2010 doi:10.5539/gjhs.v3n1p231

Abstract

This study was carried out to see if there are any differences between the prevalence of Kaposi's sarcoma in HIV infected patients with antibody to Human Herpes Virus 8 (HHV8) or not.

Methods: The sera of 180 subjects were evaluated for HIV and HHV8 using double ELISA (Genscreen Ultra HIV Ag-Ab ELISA and JN HIV 1/2 ELISA Kit) for HIV screening and advanced Biotechnology Incorporated ELISA for HHV8 IgG antibody detection respectively. Those HIV infected patients that had skin lesions suspected to be Kaposi's sarcoma were biopsied for histological diagnosis.

Results: A total of 180 subjects were recorded for this study. The ratio of male: female was 1:1.02. In all, 100 subjects tested positive to HIV screening and 87 (87%) patients tested positive to HHV8 antibody. Of the 87 patients that were positive to HHV8 antibodies 32 (36.7%) were histologically confirmed to have Kaposi's sarcoma.

Conclusion: We found a high rate of prevalence of Kaposi's sarcoma KS among HIV infected patients with HHV8 antibodies.

Keywords: Kaposi's sarcoma, HHV-8 antibodies, HIV infections

1. Introduction

It has been established that there is a reciprocal interaction between HIV and HHV8 infection (Covey Casper, 2006). The level of interaction is largely determined by the route of transmission; the risk factors involved and, type of cells infected (Viejo Borbolla A, 2003; Gallo R., 1998).

Studies have shown that HIV1 tat protein, HIV induced immunosuppression and HIV cytokines (Interleukins (IL)-1, Interleukins (IL)-6, Interferon (INF)-┌ and oncostatin M) individually or collectively induce or promote HHV-8 lytic replication (Chatlyne LG, 1998; Huang L, 2001). HHV-8 on the other hand has been shown to promote transcend othelial spread of HIV, promotion of infection of new HIV target cells and induction of HIV replication (Beaten J, 2002).

The greatest danger of HHV-8 in HIV infection is its potentiated ability to induce malignancies especially Kaposi's sarcoma. Studies have shown that approximately one third of individuals previously infected with HHV-8 develop Kaposi's sarcoma within 5-10 years of infection with HIV and that high HHV-8 antibodies' titres were associated with faster progression to Kaposi's sarcoma (Gao SJ, 1996). HIV infection is associated with defects in both the humoral and cellular arm of immune system (Michael Lederman, 2006). It is also known to cause Cytokine dysregulation and to polarize the CD^4 T- Cell immune response and the level of immunosuppression as reflected in the CD_4 cell count is an important determinants of the disease progression to Kaposi's sarcoma (Onyemelukwe GC, 2002; Habib AK, 1998); some studies showed that Kaposi's sarcoma has been seen in some patients without significant immunosuppression (Habib AK, 1998).

The role of HIV-1 in the aetiopathogenesis of HHV-8 infection may therefore be independent of its immunosuppressive ability. It can promote transmission of HHV-8 by increasing mucosal shedding of the virus, reactivating lytic replication through the effects of HIV-1 tat protein and cytokines (IL-1 oncostatin M, IL-6 and interferon ┌) in inducing a switch from latent to lytic infection and also facilitate rapid progression of HHV-8

infection to Kaposi's sarcoma (Caselli E, 2001). The positive relationship that exists between HIV and HHV-8 infection may explain the high prevalence of Kaposi's sarcoma in HIV infected patients.

2. Materials/Methods

This study was carried out in the Dermatology/ Venereology Unit of the University of Benin Teaching Hospital. The unit takes care of HIV infected patients and other related sexually transmitted infections.

2.1 Sample Size

The sample size was determined using the Fisher's formula (Oyejide C.O., 2006) below:

$$N = \frac{Z^2 Pq}{d^2}$$

N = Minimum sample size

Z= Normal standard deviation 95% confidence interval (Z = 1.96)

P = Prevalence of the disease

q= 1 – Prevalence

d= Margin of error (0.05)

From the reviewed literature, Dedicoat *et al* put HHV - 8 seroprevalence rate at 2 – 100% depending on geographical region of the population study in Africa while reviewing the distribution of Kaposi's sarcoma herpes virus (Dedicoat M, 2003). Also in Nigeria, a study of HHV – 8 among adult population in Lagos with and without STD revealed an overall prevalence of 26.5%. However, the national HIV infection prevalence as at 2006 is put at 4.4% and for Edo State its prevalence ranges from 4.3% to 7.2%. (FMH, 2005) using 7% prevalence, the sample size was 100 and control will also be 100 using Fisher's formula as indicated above.

A total of 180 subjects were recruited for the study and their sera were tested after a pre-test counselling. HIV screening and confirmation was done based on two positive results of screening test using two different methods namely: dip stick immunocoomb and conventional enzyme linked immunosorbent assay (ELISA) according to standard and manufacturer's instructions. Their sera were further tested for HHV-8 IgG antibodies using whole extract virus lysate from Advanced Biotechnology Incorporated, U.S.A. An elliptical incisional skin biopsy was done for every skin lesion suspected to be Kaposi's sarcoma in HIV infected patients. This was preserved in formalin and dehydrated with 10% alcohol. It was later cut with microtome into slides after fixing with wax and stained with haematoxylin/ eosin. Each of the slides was viewed under light microscope at different magnifications ranging from X40 to X100 to confirm Kaposi's sarcoma histologically.

2.2 Study Design

All consecutive HIV-infected patients with age range from Fifteen (15) years and above were recruited into the study after an oral and written informed consent had been obtained. The subject group excluded: Patients who were HIV negative, Patients' with immunocompromising diseases such as diabetes mellitus, lymphomas, chronic renal disease Patients on drugs such as: steroids or cytotoxic drugs, those who have had organ transplant and presently on immunosuppressant drugs, Pregnant women, and non – counselling patients.

Age and sex matched controls were pooled from apparently healthy patients' relatives who were attending the out patients clinic of the University of Benin Teaching Hospital. They were assessed to be HIV negative.

Healthy hospital staff (workers) ranging from doctors, nurses, security men, ward clerks and administrators who were assessed to be HIV negative were also included.

3. Results

A total of 180 subjects recruited for the study were made up of 100 HIV infected patients (male: female = 49:51) with a mean age of 39.43 ± 10.11 and an age range from 15- 64 years, and 80 HIV negative controls (male: female= 1:1) with a mean age of 39.50 ± 10.63 and age range from 15- 64 years. There was age and sex match for both the HIV patients and the controls ($P>0.05$). (See table 3:

Out of 100 subjects that tested positive to HIV screening, 87 (87%) of them had antibodies to HHV-8 and 13 (13%) of them were HHV-8 negative. Out of the 80 control group 39 of them were positive of HHv-8 antibodies and 41 were negative of HHV-8 antibodies. There was statistically significant association between HIV and HHV-8 at $p \leq 0.0001$. Thirty two (32) of the HIV positive patients had Kaposi's sarcoma and all the HIV patients with Kaposi's sarcoma tested positive to HHV-8 antibodies.

The mean age for those who were HIV positive and had Kaposi's sarcoma, HIV positive without Kaposi's sarcoma, HHV-$8^+$and HHV8^- were 36.94± 9.993, 40.6±10.026, 39.53±10.374, 38±8.467 respectively (Table 2).

There was statistically significant association between HHV-8 and Kaposi's sarcoma in HIV infected persons at $p \leq 0.008$ (Table 1c). We can deduce from table 1c that Relative Risk ratio of 0.80 at 95% CI (0.46 – 1.42) indicates that females with HHV-8 antibodies were more predisposed in acquiring Kaposi's sarcoma. Of the 87 patients that were positive to HHV-8 antibodies 32 (36.78%) were histologically confirmed to have Kaposi's sarcoma. The result in table 4 shows that 59.4%, 21.9%, 18.7% were at patch, plaque and nodular stages respectively.The demographic and sexual behaviour of the patients were highlighted in table 2.

4. Discussion

Studies have shown that lytic viral replication of HHV-8 predispose to development of Kaposi's sarcoma (KS) and among HIV infected patients lytic HHV-8 replication may also promote HIV disease progression (Engels EA, 2003; Caselli E, 2005; Suchankova A, 2003). Reports from Brazil and Cuba (Kouri V, 2004) showed that HHV-8 seroprevalence in patients with AIDS-associated Kaposi's sarcoma to be 79.5% and 77.8% respectively (Keller R, 2001; Kouri V, 2004). This rate was lower than those reported in Tanzania (Wamburu G, 2006), Central African Republic (Duprez R, 2003) and Zambia (He J, 1998) were rates 96.4%, 94% and 92.3% respectively recorded in AIDS-associated Kaposi's sarcoma. The results of HHV-8 antibodies obtained in our study among HIV infected Kaposi's sarcoma was 32 (100%) and this was in keeping with the above quoted study gotten from other African countries. However, when compared with HIV infected patients with no antibodies to HHV-8, it was obvious that HHV-8 might have played a significant role in the prevalence of Kaposi's sarcoma in HIV infected patients.

Early reports from Nigeria indicated that Kaposi's sarcoma was extensively seen in men (Out AA., 1990), but in our study we found both sexes having HIV/AIDS associated KS with more female predominance. It was found from our study that females had more antibodies to HHV-8 than males which is at variance from previous studies in Nigeria (Out AA, 1990). It was also observed that sex might not have played any role in the prevalence of Kaposi's sarcoma among HIV infected patients despite their positive antibody to HHV-8 since there was no statistical relationship between them. There was no statistical association between education and acquisition of HHV-8 antibodies and Education (p=0.920) and this did not influence the prevalence of KS when compared with HIV-infected; HHV-8^- patients.

Previous studies had supported the likelihood of having decreased tendency of acquiring HHV-8 and HIV with higher education and this indirectly translate to decreased prevalence or incidence of KS.

Previous studies had supported positive correlations between HHV-8 and Kaposi's sarcoma among those who had STIs and multiple sexual partners. However, in this study, in spite of the high percentage of multiple sexual partner and sexually transmitted infections among those with HIV/Kaposi's sarcoma, there was no obvious statistical association between the prevalence of KS in HIV infected patients with HHV-8 antibodies as compared with those with no antibodies to HHV-8.

5. Conclusions

We therefore posit from this study that Kaposi's sarcoma is more prevalent in patients that have HIV infection and positive antibodies to HHV-8. It is therefore important for a wide spread awareness campaign to be mounted among HIV patients and at the same time educate them on the role and effect of HHV-8 in acquiring Kaposi's sarcoma.

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Table 1a. RELATIONSHIP BETWEEN KAPOSI'S SARCOMA AND HHV-8$^-$ ANTIBODIES AMONG HIV INFECTED PATIENTS (Distribution according to sex)

Sex	HIV with KS	HIV without KS	Total
Male	0 (0)	9 (69.2%)	9
Female	0 (0)	4 (30.8%)	4
Total	0 (0)	13 (100)	13 (13%)

Table 1b. RELATIONSHIP BETWEEN KAPOSI'S SARCOMA AND HHV-8$^+$ ANTIBODIES AMONG HIV INFECTED PATIENTS (Distribution according to sex)

Sex	HIV with KS	HIV without KS	Total	Prevalence
Male	13 (32.5%)	27 (67.5%)	40	32.5%
Female	19 (40.4%)	28 (50.9%)	47	40.4%
Total	32 (36.78)	55 (63.22)	87	36.8%

Relative Risk ratio 0.80 (0.46<RR<1.42)

Table 1c. RELATIONSHIP BETWEEN KAPOSI'S SARCOMA AND HHV-8 ANTIBODIES AMONG HIV INFECTED PATIENTS

	HHV-8$^+$	HHV-8$^-$	Total	X^2	d.f	P-value	Prevalence
HIV With Kaposi	32	0	32	7.032	1	0.008*	100%
HIV Without Kaposi	55	13	68				80.9%
Total	87	13	100				87%

Fisher's Exact 2- tailed P-value

* Difference not statistically significant

** Difference is statistically significant

Table 2. Demographic Data and Sexual Characteristics of Patients

	HIV/KS$^+$ N=32	**HIV/KS$^-$ N=68**	**HHV-8$^+$ N=87**	**HHV-8$^-$ N=13**
Age (mean) in years ± SD	36.94± 9.993	40.6±10.026	39.53±10. 374	38±8.467
Gender: N (%):				
Male	13 (40.6)	36 (52.9)	40 (46.0)	9 (69.2)
Female	19 (59.4)	32 (47.1)	47 (54.0)	4 (30.8)
Educational Status N (%):				
Primary	9 (28.1)	23 (33.8)	25 (28.7)	5 (38.4)
Secondary	18 (56.2)	22 (32.4)	39 (44.8)	3 (23.2)
Tertiary	5 (15.6)	23 (33.8)	23 (26.4)	5 (38.4)
Marital Status N (%):				
Single	9 (28.1)	14 (20.6)	21 (24.1)	2 (15.4)
Married	18 (56.2)	36 (52.9)	47 (54.0)	7 (53.8)
Widowed	5 (15.6)	8 (11.8)	11 (12.6)	2 (15.4)
Divorced	0 (0)	10 (14.7)	8 (9.2)	2 (15.4)
Sexual Orientation N (%):				
One sexual partner:				
No	29 (90.6)	55 (80.9)	73 (83.9)	11 (84.6)
Yes	3 (9.4)	13 (19.1)	14 (16.1)	2 (15.4)
Multiple sexual partner:				
No	3 (9.4)	14 (20.6)	15 (17.2)	2 (15.4)
Yes	29 (90.6)	54 (79.4)	72 (82.8)	11 (84.6)
Oral intercourse:				
No	23 (71.9)	58 (85.3)	69 (79.3)	12 (92.3)
Yes	9 (28.1)	10 (14.7)	18 (20.7)	1 (7.7)
Anal intercourse:				
No	29 (90.6)	65 (95.6)	81 (93.1)	13 (100)
Yes	3 (9.4)	3 (4.4)	6 (6.9)	0 (0)
Kissing:				
Yes	32 (100)	61 (89.7)	81 (93.1)	12 (92.3)
No	0 (0)	7 (10.3)	6 (6.9)	1 (7.7)

Table 3. Demographic Distribution of HIV Infected Patients and the Control Group in Terms of Age and Sex

	HIV+ (%)	HIV – (%)	Total X^2	P –Value
SUBJECT: Sex				
Male	49 (49)	-	0.04	0.980*
Female	51 (51)	-		
Total	100			
CONTROL:				
male	-	40 (50)	0.000	1.000*
Female	-	40 (50)		
Total	100	80	180	
AGE (YEARS)	t- test value		t- test P-value	
SUBJECT			CONTROL	
MEAN AGE	39.43		39.50	
RANGE	15-64		15-64	>0.05*
* Difference not statistically significant				
** Difference is statistically significant				

Table 4. Frequency Distribution of Histological Staging of HIV Associated Kaposi'S Sarcoma

HISTOLOGICAL STAGE/ TYPE	FREQUENCY	%
EARLY - PATCH	19	59.4
LATE - PLAQUE	7	21.9
LATE - NODULAR	6	18.7
TOTAL	32	100

ISSN 1916-9736 E-ISSN 1916-9744