Clinical spectrum of herpes zoster in HIV-infected versus non-HIV infected patients in Benin City, Nigeria

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Summary

***Background*: Herpes zoster is due to reactivation of the varicella-zoster virus (VZV) at the sensory nerve ganglia. Some reports indicate that there might be differences in the pattern of presentation of herpes zoster in HIV infected patients. The objective of this study therefore, is to compare the clinical spectrum of herpes zoster in HIV-infected versus non-HIV infected patients.**

***Study design*: In this prospective study all patients presenting with clinical features of Herpes zoster had serological test (ELISA) for Human immunodeficiency viral (HIV) antibodies done and confirmed by the Double/Triple test algorithm. They were examined clinically to determine the dermatome(s) involved, the severity of the disease and the presence of any complication. The patients were categorized according to their HIV-status for the purpose of statistical analysis.**

***Results:* Fifty-two out of the seventy-three patients seen during the study period were evaluated: 22 male (42.3%) and 30 female (57.7%) patients. Thirty-six (69.2%) patients were HIV-positive while 16 (30.8%) were HIV-negative. The age distribution of the patients was bimodal; the mean age of patients in the HIV-positive group was 36.1 ± 16.14 years while that of the HIV-negative group was 56.3 ±17.51 years. Multidermatomal involvement, affectation of the Trigeminal nerve dermatome and the presence of systemic symptoms such as fever and weakness correlated significantly with the presence of HIV infection. Mean times to cessation of new vesicle formation, crusting, and resolution of zoster-associated pain were also significantly longer in the HIV-positive patients. There were no statistically significant differences in the incidence of post-herpetic neuralgia, keloids, and bacterial super-infection in both groups.**

***Conclusion:* Herpes zoster was generally more severe in the presence of HIV infection.**

Keywords: ***Herpes zoster, HIV Infection, Nigeria.***

Résumé

Introduction: Herpès Zoster est attribuable à la réactivité de virus varicella-zoster (VZV) dans le ganglion nerveux sensoriel. Il y a des repports qui montrent qu'il pourrait y avoir des différences dans la tendance des présentation des herpès zoster chez des patients atteints de VIH. L'objet de cette étude est donc de comparer le spectre clinique d'herpès zoster dans le virus infecté par VIH chez des patients non VIH infectés.

Plan d'étude: Dans cette étude en perspective, tous les patients qui se sont présentés avec des traits cliniques d'Herpès Zoster avaient une épreuve sérologique (ELISA) pour le virus immunodéficitaire humain (VIH) anticorps fait et confirmé à travers une épreuve algorithm Double/ Triple. On les avait tous examiné cliniquement afin de décider le(s) dermatome(s) impliqué(s), la gravité de cette maladie et la présence des complications possible. Les patients ont été divisés selon leur statut de VIH afin d'avoir une analyse statistique.

Resultats: Quarante deux sur soixante trieze patients vus au cours de cette étude ont été étudiés: 22 du sexe masculin soit 42,3% et 30 du sexe féminin soit 57,7% patients. Trente six soit 69,2% des patients étaient notés d'etre VIH positif tandis que 16 soit 30,8% étaient VIH négatif. La répartition d'âge des patients était bimodale; l'âge moyen des patients dans le groupe de VIH positif était 56,3±17,51 ans. Implication multidermatomale, l'affectation du Trigeminale nerf dermatome et la présence des symptomes systémiques tels que la fièvre et affaiblissement était remarquablement en correlation avec la présence de l'infection de VIH. Temps moyen concernant la cessation de la formation d'un vésicle nouveau, la coûte, et la resolution de la douleur de Zoster liée ont été également remarquablement prolongée chez des patients avec VIH positif. Il n' y avait aucun difference importante dans l'incidence de la neurlgie post-herpetique, kéloides, et bectériel super-infection chez les deux groupes.

Conclusion: Dans l'ensemble, Herpes Zoster est beaucoup plus grave en presence de i'infection de VIH.

Introduction

Herpes zoster or Shingles usually presents as a localized maculopapular eruption accompanied by pain in a dermatomal distribution. These skin lesions evolve over a few days to form true vesicles, pustules, and crusts[1,2,3]. The nature, severity and duration of these lesions vary greatly between individuals but most will resolve in two to four weeks. There is usually a prodrome of dermatomal itching, pain and/or parasthesiae and some patients may experience systemic symptoms such as fever and malaise. Sometimes the lesions may be generalized or involve non contiguous dermatomes. Some patients develop post-herpetic neuralgia after resolution of the acute eruptive

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phase[4,5].

The disease is due to reactivation of the varicella-zoster virus (VZV) at the sensory nerve ganglia[1,2,3]. It gains access to the nervous system through sensory cutaneous nerve endings, migrates centripetally along the nerve fibers to reach the ganglia where latency is established for an indefinite period via incorporation of the viral nucleoprotein within the ganglionic cells[6]. Decrease in cellular immunity to VZV antigens results in active replication of the virus at the sensory nerve ganglia and subsequent migration along nerve fibers to the mucocutaneous surface where the lesions manifest. Reactivation of the virus at more than one ganglion may occur with zoster affecting non-contiguous dermatomes[1-6].

The incidence of Herpes zoster increases with advancing age, the highest incidence being in those aged 50 years and over[1,2]. Herpes zoster occurs at all stages of the human immunodeficiency viral (HIV) infection[7-12] where VZV reactivation is due to HIV-induced immunodepression. Thus herpes zoster is becoming more frequent in the younger age group in whom HIV has the highest prevalence[8-12]. The disease might be the first clinical evidence of immunodeficiency; some reports indicate that there might be differences in the pattern of presentation of herpes zoster in HIV infected patients[7-12].

The objective of this study therefore, is to compare the clinical spectrum of herpes zoster in HIV-infected versus non-HIV infected patients.

Patients and Methods

Patients

All patients presenting with features of Herpes zoster to the Dermatology and Venereology unit of the Department of Medicine, University of Benin Teaching Hospital (UBTH), Benin City, Nigeria, from May 1997 to April 2002 were admitted into the prospective study. The criterion for entry into the study group was the presence of grouped papulovesicular rash distributed in a dermatomal fashion.

Methods

Each patient was interviewed to get details of the clinical history, and socio-demographic data such as gender, age, occupation, and marital status as well as the social and past medical history. They were then examined physically to determine the dermatome(s) involved, the severity of the disease based on the extent and degree of the vesiculation, crusting and pain and the presence of any complication. The patients were followed up weekly for the first month and thereafter on a monthly basis for at least six month or until clinical features resolved if they persist for longer than six months.

All patients admitted into the study had serological test using Enzyme linked immunosorbent assay (ELISA) for Human immunodeficiency viral antibodies done after a pretest counseling using Wellcozyme Kit (Wellcome Laboratory, Dartford England) and Immunocomb HIV 1 & 2 Bispot (PBS Organics, Cedes, France) confirmation was by using the Double/Triple test algorithm[13]. Other ancillary tests done were fasting blood sugar, skin swab of lesions for microbial culture, blood count and blood film examination. Those patients who have Diabetes mellitus or clinical and/or laboratory evidence of malignancies were excluded from the study.

Statistical methods

For the purpose of statistical analysis, the patients were grouped into two categories according to their HIV-status; HIV-positive versus HIV-negative. The data were analyzed using EPI-INFO 2000 version 6, computer statistical Programme. Means, standard deviation and Student's t-test were used for continuous data, while tests of proportion were used for categorical data. Chi-squared (x^2) test (Yates corrected) was applied to determine the level of significance of observed differences, except where an expected cell value is less than 5 and Fisher exact results (2-tailed P-Value) recommended. A P-Value of = 0.05 was considered statistically significant (95% confidence interval).

Results

Epidemiology

Seventy-three patients had Herpes zoster during the five-year study period, of these only fifty-two agreed to HIV screening tests and also completed the follow-up reviews and were therefore evaluated. There were 22 male (42.3%) and 30 female (57.7%) patients, giving a male to female sex ratio of 1 to 1.36. Thirty-six (69.2%) of these patients tested positive to Human immunodeficiency viral antibodies (HIV-positive) while 16 (30.8%) tested negative (HIV-negative). In the HIV-positive group, 15 (41.7%) were males and 21 (58.3%) females while in the HIV-negative group, 7 (43.8%) were males and 9 (56.2%) females, thus there were no gender specific difference in relation to the HIV status (P = 0.8699383).

The age distribution of the patients was bimodal. The mean age of patients in the HIV-positive group was 36.1± 16.14 years; they were responsible for the peak in younger (20 to 29-year) age group, while the mean age for the patients in the HIV-negative group was 56.3 ± 10.51 years (P = 0.0003). and these were responsible for the later peak in the 50 to 59-year age group. Thus in patients below 50 years of age, Herpes zoster was significantly associated with HIV infection (P = 0.0000032). (Table 1)

Clinical features

The Herpes zoster rash affected a single dermatome in 39 (75.0%) patients. Twenty-three patients (63.9%) in the HIV-positive group and all the 16 patients (100%) in the HIV-negative group had a unidermatomal rash whereas multidermatomal involvement was seen in 13 patients (36.1%) in the HIV infected group only (P = 0.0047946). Thus multidermatomal involvement correlated significantly with the presence of HIV infection. Also non-

Table 1 Epidemiology

Variable	HIV Status					
	Positive (%) n = 36	Negative (%) n = 16	Total (%) n = 52	Chi-Squared Value (X^2)	Odds Ratio	P-Value
Age group (Years)						
20 – 29	15(41.7)	0(0.0)	15(28.9)	7.45	-	0.0019765*
30 – 39	9(25.0)	1(6.25)	10(19.2)	1.45	5.00	0.1468013
40 – 49	8 (22.2)	2(12.5)	10(19.2)	0.19	2.00	0.7045074
50 – 59	4(11.1)	8(50.0)	12(23.1)	7.37	0.13	0.0040944*
60 – 69	0(0.0)	4(25.0)	4 (7.7)	6.55	0.00	0.0067227*
≥ 70	0(0.0)	1(6.25)	1 (1.9)	0.18	0.00	0.3076923
Age (Years)						
< 50	32 (88.9)	3(18.8)	35(67.3)	21.68	34.67	0.0000006*
> 50	4(11.1)	13(81.2)	17(32.7)	21.68	0.03	0.0000006*
Gender						
Male	15(41.7)	7(43.8)	22(42.3)	0.03	0.92	0.8699383
Female	21(58.3)	9(56.2)	30(57.7)	0.03	1.09	0.8699383

**Statistically significant*

Table 2 Clinical features

Variable	HIV Status					
	Positive (%) n = 36	Negative (%) n = 16	Total (%) n = 52	Chi-Squared Value (X^2)	Odds Ratio	P-Value
Dermatome						
Trigeminal	14(38.9)	1(6.3)	15(28.8)	4.27	9.55	0.0205028*
Facial	0(0.0)	1(6.3)	1(1.9)	0.18	0.00	0.3076923
Cervical	6(16.7)	3(18.8)	9(17.3)	0.05	0.87	1.0000000
Thoracic	16(44.4)	7(43.8)	23(44.2)	0.07	1.03	0.7979917
Lumbar	2(5.6)	4(25.0)	6(11.5)	2.42	0.18	0.0644377
Sacral	0(0.0)	0(0.0)	0(0.0)	–	–	–
Distribution						
Unidermatomal	23(63.9)	16(100.0)	39(75.0)	5.90	–	0.0047946*
Multidermatomal	13(36.1)	0(0.0)	13(25.0)	5.90	–	0.0047946*
Non-contiguous	2(5.6)	0(0.0)	2(3.8)	0.03	–	1.0000000
Disseminated	0(0.0)	0(0.0	0(0.0)	–	–	–
Recurrence	2(5.6)	0(0.0)	2(3.8)	0.03	–	1.0000000
Complications						
Post-herpetic Neuralgia	8(22.2)	3(18.8)	11(21.2)	0.01	1.24	1.0000000
Keloids	2(5.6)	2(12.5)	4(7.7)	0.09	0.41	0.5780220
Bacterial Super-infection	15(41.7)	7(43.8)	22(42.3)	0.03	0.92	0.8699383
Systemic constitutional symptoms	27(75.0)	7(43.8)	36(69.2)	3.50	3.86	0.0614277

**Statistically significant*

Table 3 Comparison of means for severity and age

Variable	HIV Status		t-statistic	P-Value
	Positive (%) n = 36	Negative (%) n = 16		
Mean time for cessation of New vesicle formation (Hours)	68.3 ± 4.26	47.1 ± 3.52	17.412	<0.0001*
Mean time for healing of crusted lesions (Days)	14.7 ± 5.14	8.2 ±4.83	4.285	<0.0001*
Mean time for Resolution of Zoster-associated pain (Days)	38.3 ± 9.62	27.6 ± 8.14	3.870	0.0003*
Mean age (Years)	36.1 ± 16.14	56.3 ± 19.51	3.904	0.0003*

**Statistically significant*

contiguous dermatomal rash and recurrence of Herpes zoster were seen in two patients (7.4%) each in the HIV-positive group only.

The most frequent sites affected were the thoracic dermatomes in both groups. Sixteen patients (44.4%) in the HIV-positive group and 7 patients (43.8%) in the HIV-negative group had their lesions in the thoracic dermatomes, while 6 (16.7%) and 3 (18.8%) patients in the HIV-positive and HIV-negative groups respectively, had the lesion in the cervical dermatomes. Six patients had the lesions in the lumbar dermatomes; two (5.6%) were HIV-positive and 4 (25.0%) were HIV-negative subjects. Fourteen patients (38.9%) in the HIV-positive group and one (6.3%) in the HIV-negative group had involvement of the trigeminal dermatomes, the difference here was statistically significant (P = 0.0205028). The facial nerve dermatome was involved in only one HIV-negative patient who had the Ramsay-Hunt syndrome. The sacral dermatomes were not involved in any of these patients and no case of disseminated Herpes zoster was recorded. Thus there were no statistically significant differences in the dermatomal distribution of lesions in both groups except in those involving the Trigeminal nerve dermatome.

Systemic constitutional symptoms such as fever and weakness were present in 27 (80.6%) of the HIV-positive patients whereas they occurred in only 7patients (43.8%) in the HIV-negative group (P = 0.0614277).

Post-herpetic neuralgia occurred in 8 (22.2%) and 3 patients (18.8%) the HIV-positive and HIV-negative groups respectively. Bacterial super-infection with *Staphylococcus aureus* occurred in 15 patients (41.7%) in the HIV-positive group and in 7 (43.8%) in the HIV-negative group. Keloids developed in 2 (5.6%) in the HIV-positive group and 2 (12.5%) in the HIV-negative group. (Table 2)

Table 3 shows the Mean time to cessation of new vesicle formation was 68.3 ± 4.26 hours in the HIV-positive group and 47.1± 3.52 hours in the HIV-negative group (P < 0.0001). Crusted lesions took a Mean time of 14.7± 5.14 days in the HIV-positive group and 8.2± 4.83 days in the HIV-negative group to heal (P < 0.0001). The Mean time for resolution of pain in those with post-herpetic neuralgia was 38.3± 9.62 days in the HIV-positive group and 27.6 ± 8.14 days in the HIV-negative group (P = 0.0003). These were all statistically significant.

Discussion

After primary infection, Varicella zoster virus remains latent in nerve ganglia and may reactivate in the form of zoster in 10-20% of immunocompetent people, often in the later decades of life.[14] Reports indicate that the incidence of herpes zoster is greater in HIV-infected patients than that in the general population and can occur at any CD4+ count [7-12]. Buchbinder et al [10] compared the incidence of zoster in HIV-seropositive and seronegative men; the incidence of index cases of zoster was 29.4 cases per 1000 in HIV- positive men and 2.0 cases per 1000 in HIV-negative men. HIV infection was associated with an increased relative risk of herpes zoster in all age groups.[10] Complications of herpes zoster such as post herpetic neuralgia and ocular disorders are also more frequent in immunocompromised patients; those with the most severe and prolonged suppression of cellular immunity are at the greatest risk for herpes zoster, Varicella zoster virus viremia, and its complications.[14,15] We found a similar trend in this study where 69.2% of our patients with Herpes zoster were HIV-positive. Most of the HIV-positive patients with Herpes zoster were in the younger age bracket with a mean age of 36.1 ± 16.14 years, this is in keeping with the peak prevalence of HIV in this age group in the general population. Some authors suggest that the trend of high zoster incidence in younger HIV patients may be

due to their inability to fully develop cell-mediated immunity to Varicella zoster virus before they acquired HIV infection[14]. This study has demonstrated that in patients below 50 years of age, Herpes zoster was significantly associated with HIV infection (P = 0.0000006). The mean age of the HIV-negative subjects was 56.3 ± 19.51 years, this is in keeping with the increasing prevalence of Herpes zoster in the later decades of life in the general population.

Multidermatomal and Trigeminal nerve involvement correlated significantly with the presence of HIV infection in this study (P= 0.0047946 and 0.0205028 respectively). This is in agreement with reports from other regions.[10,12,16,17,18] Recurrence of Herpes zoster was seen only in the HIV-positive patients (5.6%) in this study, some authors have proposed that the increased risk for zoster seen in patients with a previous episode of zoster reflects an inability of HIV-infected adults to boost cell-mediated immunity after exposure to zoster.[14]

The incidence of Post-herpetic neuralgia, keloids and bacterial super-infection with *Staphylococcus aureus* were not significantly different between the HIV-positive and HIV-negative patients. The occurrence of systemic symptoms such as fever and weakness, though higher in the HIV-positive patients was also not statistically significant (P=0.0614277).

Mean times to cessation of new vesicle formation, crusting, and resolution of zoster-associated pain were significantly longer in the HIV-positive patients, thus Herpes zoster was generally more severe in the presence of HIV infection.

Thus multidermatomal presentation, Trigeminal nerve involvement, and young age correlated positively with the presence of HIV infection in patients suffering from Herpes zoster infection in our locality.

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