RELEVANCE OF HUMAN IMMUNODEFICIENCY VIRUS SEROPOSITIVITY AMONG PATIENTS WITH HERPES ZOSTER OPHTHALMICUS AT AWKA, NIGERIA.

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ABSTRACT

Aim: To determine the relevance of human immunodeficiency virus seropositivity among patients with herpes zoster ophthalmicus (HZO) seen at the Chukwuemeka Odumegwu Ojukwu University Teaching Hospital Awka, Nigeria.

Methods: This is a retrospective hospital based study done at the Chukwuemeka Odumegwu Ojukwu University Teaching Hospital Awka. We retrospectively studied folders of patients diagnosed of herpes zoster ophthalmicus (HZO) between January 2014 and December 2019 in the Eye Unit of the institution. Relevant information on demographic data which included age, sex and marital status, as well as the relevant signs and symptoms were extracted for the audit. The results were analysed using descriptive statistics.

Results: Out of the 32 patients with herpes zoster ophthalmicus (HZO), 6(18.8%) were seronegative while 26(81.2%) were seropositive for human immunodeficiency virus (HIV). Of the 32 patients, 11(34.4%) were males and 21 (65.6%) were females, with male to female ratio of 1:1.9. The age range was 25 years to 76 years. Seven (21.9%) patients were aged between 41 and 45 years, median age was 47 years. Nine (28.1%) patients came with early symptoms and signs of HZO consisting of tingling sensation, pains and vesicular eruptions.

The last follow-up visual acuity were 6/6 - 6/18 in 13 (40.6%) individuals, < 6/18 - 3/60 in 9 (28.19%) patients and < 3/60 in 10(31.3%) others.

Conclusion: The association between human immunodeficiency virus (HIV) seropositivity and herpes zoster ophthalmicus (HZO) is authentic. Viral screening and early presentation of all patients with HZO should be encouraged. Not all HZO patients are seropositive for HIV. Some cultural practices which retain women in their parental homes to perpetuate the family lineage should be abolished as this tends to encourage promiscuity with the attendant risk for HIV and HZO.

Keywords: Relevance, Human Immunodeficiency Virus, Seropositivity, Herpes Zoster Ophthalmicus, Nigeria.

INTRODUCTION

The pandemicity of Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) has become a contending global health issue for decades with the attendant financial burden. The HIV belongs to the lentivirus group within the family of retroviridae and subfamily of arthoretrovirinae[1.] On the basis of genetics and antigenicity, HIV is divided into type 1and type 2 (HIV-1and HIV-2).[2,3,4]

The immunodeficiency virus of non-human primates (simian immunodeficiency virus - SIV) is also grouped under the lentivirus genus. Available epidemiologic and phylogenetic information suggests that HIV was introduced into the human population between 1920 to 1940.[2,3,4] HIV-1 evolved from non-human primates immunodeficiency virus from Central African Chimpanzees (SIV CPZ) while HIV-2 came from West African Sooty Mangabeys (SIV SM).[2,3,4]

Genome structure (HIV-1): The HIV genome consists of two identical single stranded RNA molecules that are enclosed within the core of the virus particle.[5] The genome of the HIV provirus, also known as proviral DNA, is generated by the reverse transcription of the viral RNA genome into DNA, degradation of the RNA and integration of the double stranded HIV-DNA into human genome.[5]

Particle structure: The mature HIV particle is round, measures approximately 100nm in diameter with an outer lipid membrane as its envelope. HIV-2 is closely related to SIV-2 of Mangabey monkeys in West Africa (SIV SMM) and is morphologically indistinguishable from HIV-1 but differs from it both in antigenicity and in the genome.[5] The HIV-2 however has a lower pathogenic potential than HIV-1.[5,6]

Infection of human cells: The initial steps of infection of a cell are characterized by complex protein interactions. The surface glycoprotein gp120 of the mature HIV particle binds to the clustered differentiated-4 cells (CD-4 cells) receptors of the host cell. All the CD4-positive cells such as T-helper cells, macrophages, dendritic cells and astrocytes are susceptible to HIV. After attachment to the CD-4 molecule via the CD domain of gp120, a conformational change in CD-4 and gp120 occurs, opening up an additional site for gp120 to enable binding to the co-receptor like chemokine receptor 5 (CCR5) or chemokine receptor 4 (CXCR4 or Fusin) on the cell surface.[7,8] Fusion of the viral and cellular membranes leads to translocation of the viral capsid into the cytoplasm. Series of events will finalize the HIV infection of the cell and establishment of a persistent infection.[9,10] After a long lasting HIV infection, the continuous loss of T-helper lymphocytes results in immunodeficiency. HIV integrated into the host genome of long–lived cells like macrophages, astrocytes or memory T cells can persist in the latent stage for several years (half-life of certain target cells is 7 years). Activation of such cells results in the production of infectious HIV particles.[5]

Infection and Infectious Disease: HIV is able to enter the body via intact mucous membranes, eczematous or injured skin or mucosa and parenteral inoculation. When transmitted by sexual contact, HIV attaches first to dendritic cells like Langerhans cells or macrophages and monocytes. HIV, using CCR-5 (R_5 Viruses) as a co-receptor, is then preferentially replicated.[11] One to two days after infection, HIV can be detected in regional lymphatic tissue.[12.] Within 5 - 6 days, and after 10 - 14 days post infection, HIV can be detected in the regional lymph nodes, and the whole body including the nervous system, respect ively.[12] In the course of the HIV infection, and depending on the CD-4 cell count, at first unspecific symptoms can be observed. These may include short episodes of fever, diarrhea, malaise, fatigue and weight loss. These symptoms are regarded as AIDS-related complex (ARC).[12]

The normal CD-4 count is between 500 - 1200 cells/mm^3 in adults. When immunodeficiency progresses, usually observed when the CD-4 cell numbers are less than 300 cells/mm^3, the immune response is weakened and opportunistic infections and neoplasms develop.[5] HIV infection is therefore considered to cause the breakdown of immune surveillance of malignant cells and some of the normal human commensals, like candida, as a result of suppression of cell mediated immune response.[13,14]

Characteristic features of HIV infection are periods of good health followed by periods of illness which become more frequent and longer lasting in the course of infection.[15,16] Consequent upon the

immune down regulation in HIV/AIDS, the frequently occurring opportunistic pathogens are toxoplasma gondi, cryptosporidium parvum, pneumocystis jirovecti, mycobacterium tuberculosis, atypical mycobacteria, salmonella species, pneumococci, human polyoma virus JC, cytomegalovirus (CMV) and herpes simplex virus (HSV).[5] The typical neoplasia observed in HIV infections are Kaposi Sarcoma which is associated with human herpes virus type 8 (HHV-8), non-Hodgkins lymphoma, eg. Epstein-Bar virus (EBV) associated B-cell lymphoma, carcinoma of the penis, the anus and the cervix which are induced by human papilloma virus (HPV).[5,17,18] There is a strong evidence that HIV is a major risk factor for ocular surface squamous neoplasia (OSSN).[19,20,21,22,23,24]

Epidemiology: Globally, an estimated 35 million people were living with HIV in 2013.[25] Since 1999, the number of new infections has been decreasing continuously and for 2013, 1.9 million newly infected persons was estimated.[25] Africa is the hub of HIV infection. About 25 million people in Africa live with HIV, about 22 million of who dwell in sub-Saharan Africa. Nearly two-third of the reported new infections originate from this region.[5,25]

The countries most affected by HIV, with a high prevalence among 15 - 49 years old, are Swaziland (approximately 27%), Lesotho (approximately 23%) and Botswana (approximately 23%).[25] However, Nigeria is the hub of HIV epidemic in West and Central Africa with an estimated 1.2 - 4.2 million HIV patients.[26] Heterosexual contacts are the main route of infection in Africa. Sex work and sexual violence contribute significantly to the spread of the disease.[25]

Herpes zoster ophthalmicus (HZO) is an acute infection of the Gasserian ganglion of the 5th (trigeminal) cranial nerve by the varicella-zoster virus (VZV).[27,28] It is caused by human herpes virus 3 (HHV-3) which is morphologically identical to herpes simplex virus (HSV) but differs both antigenically and clinically.[27,28,29] The risk factors for HZO include increasing age, malnutrition, decreasing immune-competence which may be due to immune suppression by the human immunodeficiency virus (HIV) infection, malignancy, systemic lupus erythematosus (SLE) and the use of immune suppressive agents.[27,30,31,32,33,34,35]

Consequently, HZO in any healthy looking young adult should alert health workers of the possibility of HIV/AIDS.[32,36] In many patients, opportunistic disease may be the first manifestation of HIV infection.[30] Herpes zoster ophthalmicus has been recognized as a clinical marker of HIV infection and as an ocular manifestation of AIDS.[30,37,38,39,40]

Varicella (chicken pox) and zoster are different conditions caused by the same virus.[28,30,31] Herpes zoster ophthalmicus occurs in 10 -17.5% of patients with herpes zoster.[28,41,42,43] Of the three divisions of the 5th cranial nerve, the ophthalmic branch is involved 20 times more frequently than the other divisions.[31] HIV-positive patients have 15 - 25 times greater prevalence of zoster compared to the general population.[44]

After an attack of chicken pox (primary infection) and its attendant viremia, some viral particles are retained in the dorsal root ganglia perhaps arriving by retrograde spread along the sensory nerve from skin lesions and also by haematologic spread.[28,48] The territory of ophthalmic division of the fifth cranial includes the eyelid, brow, forehead skin and tip of the nose.[29] The nasocilliary branch innervates the skin of the tip of the nose and also the eye ball, cornea and uvea. For this reason, involvement of the tip of the nose or Hutchinson's sign is highly correlated with ophthalmic involvement.[49,50,51]

With the HIV/AIDS pandemic, reports of HZO associated with HIV infections have been on the rise in Nigeria and Africa.[37,45,46,47.]

Herpes zoster ophthalmicus is strongly associated with HIV seropositivity in the older age group and a significant proportion of the patients develop post herpetic neuralgia necessitating long term management.[47]

Clinical Features: The clinical manifestation of herpes zoster is divided into 3 phases, namely the pre-eruptive phase, the acute eruptive stage and the chronic phase [29]. The pre-eruptive stage is characterized by neuropathic-type symptoms often described as burning, tingling or shooting type pain that may initially be mild and typically is limited to a particular dermatome. The acute eruptive phase is defined by the peculiar vesicular rash that is typical of herpes.[29, 43] The skin manifestation of herpes zoster strictly obeys

the midline rule with involvement of one or more branches of the ophthalamic division of the trigeminal nerve, namely supra orbital, lacrimal and nasociliary branches[31, 47]. The virus damages the eye and surrounding structures by secondary perineural and intraneural inflammation of sensory nerves.[52]

MATERIALS AND METHODS

This is a retrospective hospital-based study carried out at the Chukwuemeka Odumegwu Ojukwu University Teaching Hospital Awka, Nigeria. Ethical approval was sought and granted by the Ethical Committee of the hospital with reference number: **COOUTH/CMAC/ETH.C/Vol.1/FN :04/218.** The case notes of patients who presented with clinically diagnosed herpes zoster ophthalmicus (HZO) at the Eye Unit of the hospital from January 2014 to December 2019 were analyzed. The seropositive patients who hadn't received anti-retroviral treatment were sent to the HIV clinic for evaluation and possible commencement of the highly active anti-retroviral therapy (HAART). Relevant information on demographic data such as age, sex, marital status and occupation were extracted for the study. Also recorded were the signs and symptoms at presentation. The retroviral screening test used was Determine test which if positive, a confirmatory test was performed with Unigold or Stat pack method. If screening was negative initially, confirmatory test was not done. The data were analysed using the scientific calculator and presented as frequency tables. Drugs such as oral acyclovir, topical acyclovir, carbamazepine, topical antibiotics, topical anti-inflammatory agents, topical cycloplegic and anti-glaucoma agents were used on the patients as occasion demanded.

RESULTS

Of the 3985 new patients seen at the eye clinic within the study period (January 2014 - December 2019), 32(0.8%) had herpes zoster ophthalmicus (HZO). Eleven (32.4%) were males and 21(65.6%) females, with male to female ratio of 1:1.9

The age range was 25 years - 76 years. Seven patients (21.9%) were between the 41 – 45 years age range (table 1).

Age Range (years)	Males	Females	Total	Percentage
25-30	0	1	1	3.1
31-35	1	2	3	9.4
36-40	1	3	4	12.5
41-45	2	5	7	21.9
46-50	1	3	4	12.5
51-55	2	1	3	9.4
56-60	0	3	3	9.4
61-65	2	1	3	9.4
66-70	1	0	1	3.1
>71	1	2	3	9.4
Total	11	2	32	100

Table 1: Distribution of patients with Herpes Zoster Ophthalmicus (HZO) by age.

The median age was 47 years.

Of the 32 participants with the HZO, 6(18.8%) were HIV seronegative, 26(81.2%) patients were seropositive. Among the 26(81.2%) cases who were HIV seropositive, 8(25.0%) were males, while 18(56.2%) others were females. Of the 6(18.8%) seronegative patients, 3(9.4%) were males; females were also 3(9.4%). Among the 18(56.2%) seropositive women, 8(25%) were married, 5(15.6%) were widows, 3 (9.4%) were single while 2(6.3%) were culturally kept at their respective parents' homes with the intention to reproduce male children who would perpetuate the family lineage. Of the 8 (25%) seropositive men, 4 (12.5%) were married, 2(6.3%) were widowers while 2(6.3%) others were single. The 6(18.8%) HIV seronegative patients (3 males and 3 females) were all married (tables 2, 3 and 4). History of risk factors for HIV such as shared use of unsterilized needles and unscreened blood transfusion were absent among the seropositive group.

Age Range (years)	HIV+VE	HIV-VE	MALE	FEMALE
25-30	1	0	0	1
31-35	3	0	1	2
36-40	2	2	1	3
41-45	6	1	2	5
46-50	4	0	1	3
51-55	3	0	2	1
56-60	2	1	0	3
61-65	3	0	2	1
66-70	0	1	1	0
>71	2	1	1	2
Total	26	6	11	21

Table 2: HIV status of patients with HZO by age and sex.

HIV- Status	Males	Females	Total
HIV-Negative	3	3	6
HIV-Positive	8	18	26
Total	11	21	32

Table 3: Distribution of HIV status by gender

Marital Status	No	HIV-Negative	HIV-Positive	M	F
Married	18	6	12	7	11
Widow	5	0	5	0	5
Widower	2	0	2	2	0
Single	5	0	5	2	3
Culturally unmarried	2	0	2	0	2
Unmarried	0	0	0	0	0
Total	32	6	26	11	21

Table 4: Marital status and HIV status

Some of the patients were civil servants, retirees, petty traders, drivers and artisans by occupation. The major complaints of the patients were burning and tingling sensation 20(62.5%), pains on one side of the face 25(78.1%), vesicular eruptions 32(100%). There were reports of visual disturbances in 18(56.3%) cases, sandy sensation in 15(46.9%), tearing and occasional ocular discharges in 19(59.4%). Some people had more than one symptom. However, only 9(28.1%) patients were able to visit the eye clinic within one week of onset of symptoms and signs. The other 23(71.9%) cases presented with various degrees of ocular involvement, complications and burnt out lesions (table 5).

Complications	No	Percentage
Eyelid and Facial Scar/Conjunctivitis	25	33.3
Kerato-conjunctivitis	15	20.0
Anterior uveitis	10	13.3
Glaucoma	7	9.3
Nocomplications	7	9.3
Post herpetic neuralgia	6	8
Cataract	3	4
Phthisis bulbi	2	2.7
Total	75	100

Table 5. Ophthalmic Complications in Patients with HZO.

WHO Category	Presenting visual Acuity	Last follow up visual acuity at Six months
Normal vision 6/66/18	Affected Eye 7 (21.9%)	Affected Eye 13(40.6%)
< 6/183/60	19(59.4%)	9(28.1%)
< 3/60	6(18.8%)	10(31.3%)
Total	32(100%)	32(100%)

Table 6: Visual acuity (VA) at presentation and at last follow up visit at 6 months

The preponderance of HZO vesicular eruptive lesions were on the left hemi face 18(56.3%) while 14(43.7%) were on the right half of the face. None was bilateral.

The affectation of the ophthalmic division of trigeminal nerve was noted in 31 (96.9%) cases. One (3.1%) patient developed involvement of the ophthalmic and maxillary divisions of trigeminal nerve.

Those who were seronegative for HIV responded better to treatment than the seropositive patients. However, one seronegative case developed severe corneal ulcer, corneal perforation and eventually phthisis bulbi.

Both the presenting and the last recorded visual acuity obtained after six months of follow up are shown in table 6.

The difference between the initial visual acuity at presentation and the visual acuity recorded at six months follow up was not statistically significant, (p-value 0.293975 at $P<0.05$).

Complications recorded ranged from eyelid deformity, facial scar and conjunctivitis (33.3%), to phthisis bulbi in 2(2.7%) cases. Some patients had more than one complication (table 5). Seven (9.3%) individuals had no complications.

DISCUSSION

Human immunodeficiency virus (HIV) infection is one of the causes of immune down regulation in the affected patients. The reduction in cellular immunity can create room for opportunistic infections of which herpes zoster ophthalmicus (HZO) represents the ocular form.[30] The prevalence of HIV seropositivity in this study was 81.2%. Other authors have cited similar high prevalence rate of HIV among HZO patients.[37,40,53,54] This may point to immune down regulation leading to reactivation of latent Varicella in the cranial (Gasserian) nerve. The high association between HIV and HZO has led to the recognition of HZO as a marker for HIV in Africa.[37,38,55] In Nigeria and elsewhere, several studies had reported association between HIV seropositivity with HZO.[37,45,47,54,56,57,58,59,60,61,62] However, Adio et al reported a low HIV seropositivity of 20% among those who presented with HZO at the University of Port Harcourt Teaching Hospital eye clinic in Nigeria.[30] This may be due to the fact that she did not

screen all her subjects for HIV.

There is preponderance of females with HZO in this study which is in consonance with the review by others.[29, 37] Incidentally, this is at variance with the report by Adio et al and Bayu et al who recorded more males than females with HZO in their respective series.[30, 53] Despite the gender disparity in the incidence of HZO in the cited reports, no literature has characterized HZO with sex-predilection.[53] The sex differences in different series could be either due to under reporting or having better access to health care facilities.[63]

Observance of the cultural practice which keeps women in their parents' homes in order to reproduce male children who would perpetuate the family name predisposes those women to having multiple sex partners. Two ladies in this study admitted to having multiple sex partners as a consequence of this customary practice. It predisposed them to acquiring the HIV infection and HZO. The impact of marital status however differs from the observation of others who found the conditions (HIV and HZO) to be almost the same in both the married and the single.[30,40,53] This possibly indicates that other modes of HIV innoculation and immune suppression, besides sexual transmission, could be contributory.[33, 34, 35]

Most often, HIV seropositivity complicated by immune down regulation is one of the causes of HZO. Factors such as late presentation, poor nutrition and not receiving anti-retroviral therapy may lead to immune down regulation which triggers the reactivation of dormant varicella virus thereby leading to HZO. In contrast, early presentation, good nutrition and adherence to anti-retroviral therapy would boost immunity against varicella virus reactivation.

The age range in this study is 25 years - 76 years with the peak age incidence at the 41 years - 50 years age bracket. This is consistent with the findings from another study.[30] Although the age range in our survey is similar to that of Bayu et al, both reports differ in their respective peak age bracket.[53] Herpes zoster ophthalmicus was predominantly observed in the elderly originally, but this pattern changed with the advent of the HIV pandemic.[41,53,65,66] The loss of regulatory control of T-cells which occurs with aging and immunocompromised conditions are believed to contribute to the reactivation of the virus.[57] No occupational vulnerability to HZO was noted in our series, a finding that is shared by others.[30,53,67]

The major complaints of the patients were burning and tingling sensation in 20(62.5%) cases, pains on a hemi face with vesicular eruptions in 25(78.1%), scar in 32(100%) and visual disturbances in 18(56.3%) individuals. This is in accord with the observations elsewhere.[30, 31] A preponderance of HZO classical lesions (crusting vesicular eruptions and scar) were noted on the left half of the face in concordance with the findings by Adio et al and Bayu et al.[30,53] In contrast, Womack et at[68] reported that the dermatomal distribution of HZO lesion was observed with equal frequency on right and left sides of the face.[58] Waife in his study noted that these HZO lesions obey the midline rule with involvement of one or more branches of the ophthalmic division of the trigeminal nerve, namely the supraorbital, lacrimal and nascociliary branches but he was silent on the laterality of HZO lesions.[31] However, no case of bilateral herpes zoster ophthalmicus was documented in the available literature assessed.

The ophthalmic division of trigeminal nerve was affected in 31(96.9%) of our cases. One (3.1%) patient had involvement of the ophthalmic and maxillary divisions. The preponderance of ophthalmic nerve division involvement is not surprising since HZO occurs when the human herpes type 3 reactivation occurs in the first division of the trigeminal nerve.[29] The reactivation may manifest with pains and a periocular cutaneous rash limited to the periorbital region, of which 50% to 72% of cases demonstrate involvement of the eye itself.[43,51,69,70,71]

The involvement of two or more branches of the trigeminal nerve (5%) by HZO was reported elsewhere in immune compromised patients.[72] However, only 1 (3.1%) patient in our series had involvement of two divisions of the trigeminal nerve. Many of our HIV positive patients were referred from the HIV clinic to the Eye Unit and were all on anti-retroviral therapy (ART). As such, they did not show signs of disseminated zoster. Both systemic and topical acyclovir were used to treat these patients. However, the frequency of dosing (at 5 times daily) could have adversely affected their drug compliance. These patients were treated on out-patient basis. A previous study from our centre had reported poor ART compliance with increased frequency of dosing.[73] Valacyclovir and famciclovir which have simpler dosing regimen (3 times daily)

could improve the compliance rate. Unfortunately, these brands were not available in our practice environment during the period under review.

The rate of visual loss following herpes zoster attack in this audit is significantly high (31.3%). This compares to findings by Adio et al (25%).[30] Late presentation and severe immune suppression were likely contributory. Furthermore, oral acyclovir would provide better response and protection against ocular complications and would reduce the severity and incidence of post herpetic pain only when this ART is administered early, within the first 72-hours after the onset of HZO.[32,74,75,76.]

The disease process (HZO) was noted to be more severe and prolonged in HIV seropositive patients in our survey and this correlates well with the findings by Adio-et al. [30] However, one elderly dependent seronegative male patient in our series had severe disease with phthisis bulbi. He came with malnutrition, corneal ulcer and perforation although the history of topical steroid use and traditional medication therapy were not elicited. The loss of regulatory control of T-cell which occurs with aging and immune down regulation had been previously observed.[57]

The complications found in this study are in agreement with the report from other authors[30, 53.] However, Bayu et al observed a higher rate of these complications except for phthisis bulbi, which may be due to the higher HIV seropositivity (95.3%) in their series as against the 81.3% and 20.6% in our audit and that of Adio et al respectively.[30,53] Also Bayu et al had difficulty sourcing the antiviral drug, acyclovir, in contrast with our experience and that of Adio et al. Seven (9.3%) patients in our centre recorded little or no complications similar to the findings by Adio et al.[30] This may be due to the comparable number of seronegative patients in both studies. Incidentally, Bayu et al was silent on complication-free patients in their series.

There is an association between HZO and ocular complications in immune down regulation which HIV seropositivity represents. Majority of our patients presented late which is associated with profound ocular complications and the poor visual outcome observed. All these findings are in agreement with the report of others.[30,53,76] In general, HZO with HIV seropositivity, late presentation and lack of acyclovir do collaborate to cause profound ocular complications.[53,66]

In conclusion, there is a strong association between HZO and HIV seropositivity. Early presentation with adequate ART cover could mitigate the ocular complications of HZO. HIV serosurveillance and early presentation should be encouraged among the patients. The cultural practice of keeping women in their parents' homes for the propagation of the family name should be abolished.

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