SNI

SURGICAL NEUROLOGY INTERNATIONAL

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: **Ali Akhaddar,** M.D., IFAANS Avicenne Military Hospital, Marrakech, Morocco

SNI: Infection

Original Article

Prevalence of human immunodeficiency virus infection in brain glioma patients: Is the virus protective from gliomas?

Luxwell Jokonya, Aaron Musara, Ignatius Ngene Esene[1], Kantenga Dieu Merci Kabulo, Charles Matumba Kabeya, Kazadi Kaluile Ntenga Kalangu

Department of Surgery, University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe, [1]Department of Neurological Surgery, School of Medicine and Public Health, University of Wisconsin, Madison, USA

E-mail: *Luxwell Jokonya - doclux@gmail.com; Aaron Musara - musaraaaron@zol.co.zw; Ignatius Ngene Esene - ignatiusesene@yahoo.co.zw; Kantenga Dieu Merci Kabulo - dmkabulo@gmail.com; Charles Matumba Kabeya - kabeyacm@gmail.com; Kazadi Kaluile Ntenga Kalangu - kazkal2003@hotmail.com
*Corresponding author

Received: 14 November 17 Accepted: 02 April 18 Published: 24 May 18

Abstract

Background: Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is associated with an increased prevalence of some malignancies. However, some observational studies have revealed an ever-decreasing prevalence of HIV in glioma patients. The relationship between HIV and brain gliomas has not been well established.

Methods: A cross-sectional study was carried out in sub-Sahara Africa, a high HIV prevalence setting, to determine the prevalence of HIV among all glioma patients over a 2-year period.

Results: A markedly reduced prevalence of HIV was found in glioma patients (8.3%) in comparison to the general population (14.3%). The presumably "antiglioma effect" of HIV and/or its treatment resulted in a 42% decrease in glioma occurrence in HIV positive patients compared to HIV negative individuals. Age and sex-adjusted prevalence were also lower among glioma patients with the protective effect observed more in younger patients and female sex.

Conclusion: Our results corroborate the protective effect of HIV positivity vis-à-vis gliomas. This "antiglioma effect" could be attributed to either the HIV, its treatment, or both. Future studies focused on this "effect" may help unveil better preventative and possible therapeutic avenues for gliomas.

Key Words: Brain tumors, glioma, human immunodeficiency virus, infections

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/sni.sni_423_17

Quick Response Code:

INTRODUCTION

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) has been associated with an increased prevalence of malignancy. Reduced immunity leading to the decreased surveillance of oncogenic elements and increased incidence of oncogenic opportunistic infections are among some of the reasons for such an increased incidence of malignancy.[2] With the advent of HIV, some cases have been reported

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Jokonya L, Musara A, Esene IN, Kabulo KD, Kabeya CM, Kalangu KK. Prevalence of human immunodeficiency virus infection in brain glioma patients: Is the virus protective from gliomas?. Surg Neurol Int 2018;9:103. http://surgicalneurologyint.com/Prevalence-of-human-immunodeficiency-virus-infection-in-brain-glioma-patients:-Is-the-virus-protective-from-gliomas?/

© 2018 Surgical Neurology International | Published by Wolters Kluwer - Medknow

of HIV and brain glioma comorbidity, leading to the assumption that HIV infection increases the incidence of gliomas, (especially the higher grades) as it does for other tumors.[6] However, observational studies have shown an ever-decreasing rate of comorbidities of HIV and brain gliomas. This has led to speculations that HIV or its treatment may have a protective effect from brain gliomas. In a 20-year study done in Mexico and Brazil, they showed an ever-decreasing incidence of gliomas in HIV patients (only 2 patients in 20 years).[1,11] This led the researchers to hypothesize that gliomas are becoming exceedingly rare in HIV/AIDS patients. Similarly, reports have been published from the other continents.[1] Such studies have not yet been done in Africa: a high HIV prevalence setting. We have done this study in sub-Saharan Africa where the prevalence of HIV is highest in the hope that this helps in elucidating more information. In this study, we set the objective to determine the prevalence of HIV in the glioma population of Zimbabwe in comparison to that of the general population and assess for any associations that may exist.

MATERIALS AND METHODS

A cross-sectional study was carried out in Zimbabwe. All patients who presented to Zimbabwe Hospitals and eventually had a histological diagnosis of a brain glioma between January 1, 2014 and December 31, 2015 were enrolled for the study. Patients whose initial presentation was outside the study period were excluded. Case definition of a brain glioma patient was as per World Health Organization (WHO) grading system 2007. It included all glial cell origin tumors: astrocytomas, ependymomas, oligodendrogliomas, and mixed glial cell tumors.

Liaison was constantly made with all the neurosurgeons in the country during the study such that information about any glioma patient seen was availed. In addition, liaison was also made with all the pathology laboratories in the country so that information on all brain biopsy results in the country were accessed. This allowed access to data on all patients who had brain tumors operated on in the country. The patients were managed as per the prevailing neurosurgical protocol and the study did not interfere with their standard management.

All patients eligible were contacted, and none declined consent. The patient or caregiver was interviewed and imaging and histology done were reviewed. Histological grading was done using the WHO grading system and immunohistochemistry was done for equivocal cases. If the patient did not have a recent (within 3 months) documented HIV test result, he/she was offered HIV counselling and testing. Those who were HIV positive would have cluster of differentiation 4 (CD4) counts done. The data collected were then analyzed.

A confidential data collection form was administered by the researchers. Data were then captured into Epi info™ 7(The Epi info Software, Centers for Disease Control and Prevention "CDC" in Atlanta, Georgia, USA) for analysis. Data were then exported to Stata 13 (StataCorp, Texas, USA) for further analysis.

We analyzed our data making comparison to that of the Zimbabwe Health Survey[13] that screened 2,274,328 individuals for HIV status [Table 1].

RESULTS

A total of 60 patients were suspected of having brain gliomas during the study period. Forty-nine of these had biopsy done but only 48 cases (with a histologically proven glioma and known HIV status) were included in the final analysis. One had an unknown HIV status and was excluded. For the other 11 patients excluded in the subsequent analysis, the diagnosis of glioma was based on imaging studies only. The reasons for lack of biopsy were inoperability in diffuse pontine glioma (4), declined operation (3), demised before operation (2), too ill for operation (1), and lost to follow-up before biopsy (1).

The mean age [±standard deviation (SD)] of the study group (n = 48 patients) was 40.5 ± 23.3 years (min 3 years; max 87 years). Age distribution was bimodal with peaks at around 3 years and another between 40 and 50 years. There were more females, 54.1% (26/48), among the study participants. There was no significant difference in age distribution between males mean age (±SD) [38.6 ± 21.9 years] and females (±SD) [42.1 ± 24.8 years] (P = 0.6156). Eighty-five percent (n = 41) were black, 15% (n = 7) were whites. Urban settlers accounted for 85.4% (n = 41) of the patients, whereas 14.6% (n = 7) were from rural areas. The majority were from Harare (urban).

Table 1: Relationship between HIV serology and glioma occurrence

	Glioma patients	Nonglioma cases*	Total
HIV positive	4	325,229	325,233
HIV negative	44	1,949,099	1,949,143
Total	48	2,274,328	2,274,376

Prevalence of HIV among glioma patients=4/48=8.3% (95% CI: 3.3-19.6) = 8,333 per 100,000 persons
Prevalence of HIV among nonglioma cases (i.e., general population) = 325,229/2,274,376=14.3% (95% CI: 14.25-14.35) = 14,300 per 100,000 persons
Prevalence ratio=8.3/14.3=0.58 (95% CI: 0.33-0.77) [P**=0.3043]
Strength of the association between HIV and glioma=1 - Prevalence ratio=1-0.58=0.42=42%

*Data from Zimbabwe Survey.[13] **Fisher's exact test

Four participants were HIV positive. Three (75%) were males and there was one female (25%). The median age of the four cases was 49.5 years (p25 = 38; p75 = 54) (min = 29, max = 57) [Table 2]. The CD4 counts of these four patients were 289, 81, 240, and 530. Only one patient was not on antiretroviral therapy (CD4 289). The rest were taking the following different regimes: Atazanavir + ritonavir/abacavir/lamivudine; tenofovir, lamivudine, and efavirenz; and stavudine, lamivudine, and nevirapine in respective order to CD4 counts above [Table 3]. Of the four cases with an HIV positive serology, two patients (50%) had a WHO grade 4 (glioblastoma) and the other 2 (50%) had WHO grade 2 tumors (fibrillary astrocytoma). There was no significant association between HIV status and tumor grade at $P = 0.788$ [Table 2].

The prevalence of HIV among glioma patients was 8.3% (95% CI: 3.3; 19.6) and among nonglioma cases was 14.3% (95% CI: 14.25; 14.35). This gave a prevalence ratio of 0.58 (95% CI: 0.33; 0.77). The strength of the association between HIV (exposure) and glioma (disease or outcome) was 42% implying the "antiglioma effect" of HIV and/or its treatment resulted in a 42% decrease in glioma occurrence in HIV positive patients compared to HIV negative individuals [Table 1].[10]

Age and sex-adjusted prevalence revealed lower proportions of HIV seropositivity among glioma patients compared to the general population. The prevalence was lower in younger patients (≤40 years) [1 case (4.6%)] and females [1 case (3.9%)]. Of the four cases with HIV positive serology, one patient not on antiretroviral therapy, one had a protease inhibitor in his regiment, whereas the other two did not have a protease inhibitor in their regiment [Table 3].

DISCUSSION

Our study showed an 8.3% prevalence of HIV in glioma patients versus 14.3% in the general population.[13] With a prevalence ratio of 58%, our results reveal a 42% reduction in glioma occurrence in HIV positive patients compared to HIV negative cases [Table 1]. This is consistent with the results of the worldwide epidemiological analysis[1] that included data from most of the world's continents except Africa. The low prevalence of HIV in glioma patients may be explained either by an "antiglioma effect" of either the HIV itself or its treatment or both, assuming that gliomas themselves are not protective from HIV.

The distribution of gliomas in the country is evidently skewed. Majority of the glioma patients were from urban centers, which corresponds with a lower risk for HIV infection. The heterogeneous distribution of HIV rates is such that urban centers were at 14%, and Harare (where most glioma patients were from) 13% versus 8.3% for glioma patients.[13] These figures show a significant discrepancy of HIV rates between general population versus glioma patients. They also show an inverse relationship between HIV rates and glioma prevalence in different geographical locations within the country. The marginally higher HIV rates in some rural areas (22%) corresponding to lower glioma rates further strengthen the hypothesis of the HIV "antiglioma effect."[9]

Epidermal growth factor has been found in increased amounts and has been shown to stimulate vascular endothelial growth factor (VEGF) production in glioblastoma, and plays a key role in the pathogenesis of glioblastoma.[4,5] Some antiretroviral drugs, particularly protease inhibitors, have been found to decrease the VEGF expression in glioblastoma cells *in vitro* with the resulting antitumoral activity.[11] This may explain the low glioma prevalence in HIV patients on protease inhibitors.

Furthermore, an inverse relationship between acute infections and the subsequent development of some cancers (such as meningiomas, melanomas, and gliomas) has been established. Overall risk reduction increased with frequency of infections, with febrile infections affording the greatest protection. However, chronic infections can be viewed as resulting from a failed immune response and an increasing number has been associated with an increased cancer risk.[7] HIV infection, despite being a chronic infection, has an acute infection stage which is marked by an acute rise of inflammatory markers. It may present with pyrexia as a flu-like illness.[3,12] In addition, HIV infection will predispose to numerous acute infections which will have a cumulative protective effect. This may explain the "antiglioma effect" in HIV infected patients. Nonetheless, infection with HIV is more complex. The chronic phase of HIV is not caused by a lowered immunity, but it actually causes lowered immunity.

It is interesting to note that some glioma cells have an "anti-HIV effect." A study demonstrated that some but

Table 2: Summary of age and sex of HIV positive patients among glioma cases

Age	Sex	Type of glioma	WHO grade of glioma	Type of antiretroviral drug	CD4 count
29	Female	Fibrillary astrocytoma	2	Stavudine, lamivudine, and nevirapine	81
47	Male	Fibrillary astrocytoma	2	Tenofovir, lamivudine, and efavirenz	530
52	Male	Glioblastoma	4	Atazanavir + ritonavir/abacavir/lamivudine	530
57	Male	Glioblastoma	4	Not on antiretroviral	240

Table 3: Age and sex-adjusted HIV prevalence

	n	HIV prevalence *n* (%)	95% CI	*P*
All glioma cases	48	4 (8.3%)	(3.3-19.6)	
Age				
>40	26	3 (11.5%)	(4-29)	0.614*
≤40	22	1 (4.6%)	(0.8-21.8)	
Sex				
Male	23	3 (13.6%)	(4.5-32.1)	0.320*
Female	26	1 (3.9%)	(0.7-18.9)	

*Fisher's exact test

not all glioma cells secrete inhibitory molecules to HIV infection that contribute to lowering HIV infection in the central nervous system *in vivo*.[8] Certainly in HIV and glioma comorbidity, the glioma cells have not been found to have the virus.[6] So, while HIV patients may still have gliomas, it is unlikely that the HIV itself would be responsible.[2] The interaction between glioma cells and HIV is complex. The exact pathophysiological processes causing the "antiglioma effect" in HIV infection remain to be fully elucidated.

The possible presence of undiagnosed cases of gliomas in the general population could be a confounding factor questioning the internal validity of our study and rendering the general population not ideal as a comparison group. However, the low prevalence of gliomas in our setting dilutes the possible confounding effect. Among the glioma patients, the onset of HIV infection is difficult to determine, complicating the establishment of an association between HIV and glioma. However, our study provides evidence from Africa, the only continent where data was lacking on the relationship between HIV/AIDS and glioma prevalence to supplement those of the other continents.[1] Unlike previous studies which were retrolective and retrospective chart reviews, ours was planned with prolective data collection from the entire country.

CONCLUSION

This study, done in a setting of high HIV prevalence, shows a prevalence of HIV in glioma patients that is markedly less than in the general population, notwithstanding that the sample size was small owing to the short duration of the study. Based on the prevailing status quo, it would make sense that any effort made at preventing gliomas would stand a better chance in fighting this menace. Perhaps, a more detailed exploration of how this "antiglioma" effect of HIV works may help unveil better preventative and possible therapeutic technologies.

Funding: No funding was received for this research.

Ethical approval: Authority to perform the study was obtained from the Joint Research and Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Cedeno-Laurent F, Trujillo JR. Gliomas and brain lymphomas in HIV-1/AIDS patients: Reflections from a 20-year follow up in Mexico and Brazil. Microbiol Res (Pavia) 2011;2:11.
2. Chaudhry NS, Ahmad FU, Blieden C, Benveniste RJ. Brainstem anaplastic glioma in patients with AIDS: A case report and review of the literature. BMJ Case Rep 2013;2013:bcr2012008384.
3. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. N Engl J Med 2011;364:1943-54.
4. Gabizon A, Leibovich SJ, Goldman R. Contrasting effects of activated and nonactivated macrophages and macrophages from tumor-bearing mice on tumor growth *in vivo*. J Natl Cancer Inst 1980;65:913-20.
5. Goldman CK, Kim J, Wong WL, King V, Brock T, Gillespie GY. Epidermal growth factor stimulates vascular endothelial growth factor production by human malignant glioma cells: A model of glioblastoma multiforme pathophysiology. Mol Biol Cell 1993;4:121-33.
6. Hall JR, Short SC. Management of glioblastoma multiforme in HIV patients: A case series and review of published studies. Clin Oncol (R Coll Radiol) 2009;21:591-7.
7. Hoption Cann SA, Van Netten JP, Van Netten C. Acute infections as a means of cancer prevention: Opposing effects to chronic infections? Cancer Detect Prev 2006;30:83-93.
8. Hoque SA, Tanaka A, Islam S, Ahsan GU, Jinno-Oue A, Hoshino H. Suppression of HIV-1 infectivity by human glioma cells. AIDS Res Hum Retroviruses 2016;32:480-8.
9. Kerina D, Babill SP. HIV/AIDS: The Zimbabwean situation and trends. Am J Clin Med Res 2013;1:15-22.
10. Newcombe RG. Two-sided confidence intervals for the single proportion: Comparison of seven methods. Stat Med 1998;17:857-72.
11. Pore N, Gupta AK, Cerniglia GJ, Maity A. HIV protease inhibitors decrease VEGF/HIF-1alpha expression and angiogenesis in glioblastoma cells. Neoplasia 2006;8:889-95.
12. Stevanovic M, Sharpe F. Acute infections. In: Wolfe S, Pederson W, Hotchkiss R, Kozin S, Cohen M, editors. Green's Operative Hand Surgery. Elsevier Inc.: New York; 2010. pp 41-84.
13. Zimbabwe NAC, Zimbabwe, Care M of H and C. Zimbabwe National HIV and AIDS Strategic Plan (ZNASP) 2015–2018. Commitment Towards Fast Tracking 90.90.90. Targets by 2020 and Ending AIDS by 2030. Available from: https://searchworks.stanford.edu/view/11748462. [Last accessed on 2017 Aug 20].