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Research Article

Prevalence of cryptococcal meningitis among HIV patients attending Central University Hospital of Kigali

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Abstract

Background: Cryptococcal meningitis (CM) is a severe fungal infection caused primarily by *Cryptococcus neoformans* and less commonly by *Cryptococcus gattii*. It poses a significant threat to individuals with compromised immune systems, particularly those living with Human Immunodeficiency Virus (HIV). Despite advancements in antiretroviral therapy (ART), CM remains a leading cause of mortality among HIV-infected individuals, especially in low- and middle-income countries.

Aim: This study was done to determine the prevalence of *Cryptococcus* among HIV-infected patients attending at Central University Hospital of Kigali, Rwanda and the level at which a patient's CD4 count is significantly associated with cryptococcal meningitis.

Methodology: A retrospective study was conducted at Central University Hospital of Kigali, Rwanda. This study included 60 HIV-infected patients whose serum and CSF samples were examined for *Cryptococcus* by one of or all 4 tests (CSF culture, CSF CrAg, serum CrAg and Indian Ink) and their results were recorded.

Results: Among the 60 HIV-infected patients enrolled, 8 (13%) were positive for cryptococcal meningitis. Among these 8 patients the CD4 count ranged from 2-200 cells/ul, and 31.82% (7 of 8) was among patients with CD4 count ≤100 c/ul and 6.25% (1 of 8) was among patients with CD4 count levels between 101 c/ul and 200c/ul. Based on the study results, CD4 count levels lower or equal to 100 cells/ul was highly associated with cryptococcal meningitis as the P-value=0.001 and Odd ratio=0.058.

Conclusion: Based on the study results there was a significant association between cryptococcal meningitis and lower CD4 count levels. HIV-infected patients with CD4 counts ≤100 cells had the highest prevalence. Therefore, the level of CD4 count below or equal to 100 cells/ul is highly associated with positive cryptococcal meningitis. However, there were cases of positive CM among HIV patients with CD4 count ≥100 cells/ul.

Keywords: Cryptococcal meningitis, CD4 count, HIV,

INTRODUCTION

Cryptococcal meningitis (CM) is a severe fungal infection caused primarily by *Cryptococcus neoformans* and less commonly by *Cryptococcus gattii*. It poses a significant threat to individuals with compromised immune systems, particularly those living with Human Immunodeficiency Virus (HIV). Despite advancements in antiretroviral therapy (ART), CM remains a leading cause of mortality among HIV-infected individuals, especially in low- and middle-income countries. Cryptococcal meningitis is a major public health concern among HIV-infected populations. Globally, it is estimated to cause approximately 15% of AIDS-related deaths, with a significant burden in sub-Saharan Africa, where the incidence of CM is highest[1]. In this region, around 135,000 deaths annually are attributed to CM, accounting for 73% of global cases[2]. The high prevalence in sub-Saharan Africa is primarily due to limited access to ART, delayed diagnosis, and inadequate healthcare infrastructure[3].

Southeast Asia and Latin America also report significant incidences of CM, though to a lesser extent than sub-Saharan Africa[2]. In high-income countries, the incidence has decreased substantially due to the widespread use of ART and effective prophylactic measures. However, sporadic cases continue to emerge, particularly among individuals who are either unaware

of their HIV status or non-adherent to ART[4]. The emergence of antifungal resistance and diagnostic delays further complicate the management of CM in both resource-rich and resource-limited settings[5].

The clinical presentation of cryptococcal meningitis can vary widely, typically developing over several weeks, which complicates early diagnosis. Common signs and symptoms include Headache, Fever, Neck Stiffness, Photophobia, Altered Mental Status, Nausea and Vomiting, Seizures[6,7,8]. The non-specific nature of these symptoms often leads to misdiagnosis or delayed diagnosis, emphasizing the need for heightened clinical suspicion in HIV-infected patients, especially those with low CD4 counts.

The management of cryptococcal meningitis involves a combination of antifungal therapy, control of intracranial pressure, and optimization of the patient's immune status. The treatment regimen is typically divided into three phases: induction, consolidation, and maintenance[6,9,8]. Management of intracranial pressure is crucial, as elevated pressure is associated with poor outcomes. Therapeutic lumbar punctures to drain CSF can provide symptomatic relief and are often necessary to control pressure[10].

Cryptococcal meningitis remains a significant opportunistic infection among HIV patients, particularly in regions with limited healthcare resources and ART access. Early recognition of symptoms and prompt initiation of appropriate antifungal therapy are crucial for improving patient outcomes. Enhancing access to ART and diagnostic tools, coupled with effective antifungal treatment protocols, is essential to reduce the burden of this life-threatening infection. Continued research into new therapeutic options and strategies to combat antifungal resistance is also imperative to address this global health challenge. Therefore, the aim of this study is to evaluate the prevalence of cryptococcal meningitis among HIV patients attending Central University hospital of Kigali, Rwanda.

METHODOLOGY

Study area

The study was conducted at Central University Hospital of Kigali, Rwanda.

Study design

This study was a retrospective and was conducted in the laboratory department of Central University Hospital of Kigali, Rwanda. The study record review was done on records of 60 HIV infected patients who attended Central University Hospital of Kigali, Rwanda regardless of their ART status and who were tested for cryptococcal meningitis regardless to test method used (either CSF CrAg, CSF culture, Indian Ink or Serum CrAg), in the hospital with their C Rwanda, D4 count measurements. Taking this background, those HIV patients who visited the hospital from 2022 April to April 2023 and their data had been registered, CD4 count and cryptococcal meningitis results were included for analysis. Data was retrieved directly from laboratory registration logbook and hospital system (open clinic) using data extraction sheet in July 2023.

Study population

All HIV-infected patients (adults and young of all age groups and gender) attended Central University Hospital of Kigali, Rwanda from 2022 April to April 2023 who are suspected to have *Cryptococcus*.

Sample size

The present study considered 60 HIV patients who attended Central University Hospital of Kigali, Rwanda during the study period.

Data collection

Data of one year from April 2022 to April 2023 on HIV patients tested for *Cryptococcus* were retrieved and recollected from the registration book of Central University Hospital of Kigali, Rwanda in laboratory where logbook and system (open clinic system) were used to count the cases of HIV patients tested for *Cryptococcus* and their CD4 count levels, in order to determine prevalence of cryptococcal meningitis.

Statistical analysis

In this study, data collected was analyzed using Microsoft Excel and SPSS version 22. Descriptive statistics and chi-square test was used to determine association between CD4 count level and positivity of cryptococcal meningitis. Tables, graphs and charts were used to summarize and display the data in excel. These data were also used for comparative analysis of data according cryptococcal meningitis and CD4 count level.

RESULTS

Prevalence of *Cryptococcus* among HIV-infected patients (n=60)

In table 1 and figure 1 below shows positive and negative of cryptococcal meningitis from this current study, the prevalence of cryptococcal meningitis among HIV infected patients attending Central University hospital of Kigali, Rwanda was determined.

Table 1: Prevalence of cryptococcal meningitis among HIV-infected patients enrolled.

CM Test results	Frequency	Percent
Negative	52	87
Positive	8	13
Total	60	100

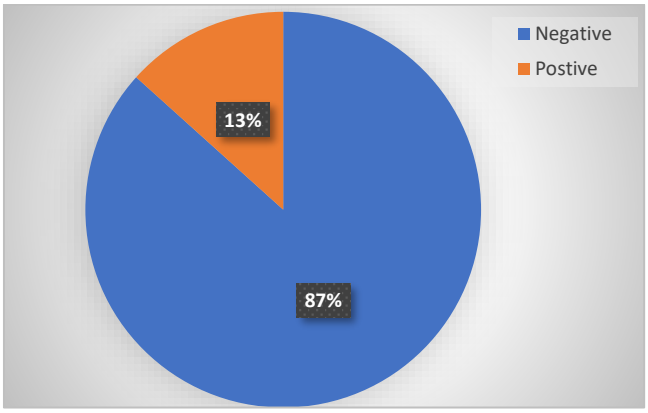

Figure 1: Prevalence of cryptococcal meningitis among HIV-infected patients enrolled.

Within 60 HIV-infected patients tested for *Cryptococcus*, 8 of 60 (13%) tested positive as prevalence of cryptococcal meningitis and 52 of 60 (87%) tested negative for CM. These findings add to the mounting evidence for the public health importance for cryptococcal meningitis among HIV-infected patients in Rwanda, particularly Central University Hospital of Kigali, Rwanda. These results are in the similar way as the overall prevalence of cryptococcal meningitis of 12.2% (55 of 450) in Congo, 13% in South Africa (45 of 336) and 12.9% (17 of 131) in Bangkok[3], 11.2 (75 of 672) in Cameroon was reported[11]. This reaffirms that in some Sub-Saharan African (SSA) countries there is high positivity rates of cryptococcal infection.

The prevalence report of this study is relatively higher than prevalence rates of other countries; a retrospective data has shown a total prevalence of 4.3% (28/645) CM in South Africa (Jarvis *et al*. 2021), of 333 HIV-infected adults enrolled in their study, 15 (4.4%) had confirmed cryptococcal meningitis in Tanzania[12] , and among 369 HIV patients enrolled, 31 (8.4%) has been reported as prevalence of CM in Ethiopia, the difference here is because patients with late-stage human immunodeficiency virus (HIV) initiating antiretroviral therapy (ART) may reduce cryptococcal meningitis infection. In addition, 13% prevalence of this study is lower than prevalence of cryptococcal infection of (18.0%) 59 of 327 cases[3], in Cambodia.

In contrast with this current study, a study done in Centre of Excellence HIV clinic located at Mulago National Referral Hospital in Uganda, reported only Five patients out of 798 which low prevalence (0.6%) of CM among HIV-infected patients. This is due to two equally possible phenomena namely; HAART improves the body's immunity making it less susceptible to opportunistic infections such as *Cryptococcus* or this particular population could simply have a low prevalence of CrAg[13].

By comparing the results of this study which found the prevalence of 13%, and the study done in Kigali, Rwanda[14] which showed the prevalence of 19%, the prevalence of CM in Rwanda is decreasing. However, we can't conclude this for the reason that these studies were done on the same place/location (Kigali).

CD4 count levels and cryptococcal meningitis

Table below represents how prevalence of cryptococcal meningitis declined with increasing CD4 count levels.

Table 2: Prevalence of CM by CD4 count levels among HIV-infected patients attending Central University Hospital of Kigali, Rwanda

CD4 count(cells/ul)	Negative		Positive		Total			
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	P-value	Odd ratio
≤100	15	68.18%	7	31.82%	22	100%	0.001	0.058
101-200	15	93.75%	1	6.25%	16	100%		
≥200	22	100%	0	0.00%	22	100%		

Table 2 shows the distribution of cryptococcal meningitis among patients enrolled in this study, CM was highly varying according to CD4 count levels; from 31.82% (7 of 22) among patients with CD4 count ≤100 c/ul to 6.25% (1 of 16) among patients with CD4 count levels between 101 c/ul and 200c/ul, and to 0% (0 of 22) among patients with CD4 count greater than 200c/ul. HIV-infected patients with CD4 count ≤100 cells/ul had the highest prevalence which were closely followed by patients with CD4 count between 100-200 cells/ul.

The findings of this study agree with the prevalence of CM in patients with CD4 cell counts < 100 cells/ul and between 100 and 199 cell/ul were 11.7% (83/708) and 4.3% (7/164), respectively reported[15]. Thus, the prevalence of CM declined with increasing CD4 count levels. These can be explained by the fact that low CD4 counts predispose HIV-infected patients to opportunistic infections for instance cryptococcal infections because of weak and dysfunctional immune system. In resource-limited settings, screening of patients with a CD4 count less than 100 cells/ul for *Cryptococcus* may even be more clinically relevant as CD4 tests become more available [16].

Findings of this present study are comparable to the results of a study done in Uganda which indicated that patients with CD4 counts ≤100 cells/ul were more likely to have CM (78%) compared to patients with CD4 counts >100 cells/ul. These findings are also comparable to another study done by Nakale in 2016 in Namibia which found the prevalence 9.38% (36 of 386) with the CD4 count ranged from 2-301 cells/ul, of those 36 positive CM cases, 26 (72.22%) had CD4 counts below 100cells/ul, 9 (25.00%) with CD4 counts between 101-200 cells/ul and 1 (2.78%) with CD4 counts >200 cells/ul, this suggested that it is due to a large number of patients who are already on ART, where these patients could have developed the infection at lower CD4 counts prior to ART initiation and remained antigenic as their CD4 count improved on ART.

There was a significant association between the CD4 count levels and the cryptococcal meningitis positivity as the P. value =0.001 and odd ratio of 0.058, this means that it is 0.058 times more likely to have CM for those with CD4 levels ≤100c/ul than those with CD4 levels of ≥100c/ul and this implying that significantly all HIV-infected patients who tested positive for *Cryptococcus* had lower levels of CD4 count levels. The association between the two variables could be explained by the fact that low CD4 counts predispose HIV-infected patients to cryptococcal infections because of the weak and dysfunctional immune system[16].

CONCLUSION

Overall, 13% of all HIV-infected patients enrolled into this study tested positive for cryptococcal meningitis. This result indicates a low prevalence of CM among HIV-infected patients attending Central University Hospital of Kigali, Rwanda. Despite increased access and use of ART among HIV patients, the burden of cryptococcal infections among them is still there.

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Conflicts of Interest

Authors declare no conflict of interests

Ethical consideration

The permission to conduct the research was granted by both Central University Hospital of Kigali, Rwanda and INES Ruhengeri ethical committees. The principal of confidentiality and respect of patient's privacy was the rules as the research was carried out in health secrete laboratory identifications were used as unique identifiers corresponding to the hospital information system.

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REFERENCES

1. Rajasingham, R., et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. The Lancet Infectious Diseases; 2017;17(8):873-881. https://doi.org/10.1016/S1473-3099(17)30243-8 PMid:28483415

2. Tenforde, M. W., et al. Mortality from HIV-associated cryptococcal meningitis in Africa: a systematic review and meta-analysis. The Lancet Infectious Diseases;2020;20(8):955-963.

3. Meya, D. B., & Muzoora, C. Overview of the management of cryptococcal meningitis in sub-Saharan Africa. Therapeutic Advances in Infectious Disease;2020;7:2049936120916014.

4. Boulware, D. R., et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. The New England Journal of Medicine;2020;382(26):2497-2508.

5. Rothe, C., et al. Emergence of antifungal resistance in Cryptococcus species: current challenges and future directions. Mycoses;2021;64(11):1312-1322.

6. Molloy, S. F., et al. A randomized controlled trial of high-dose fluconazole for treatment of cryptococcal meningitis in HIV-infected adults in Africa. Clinical Infectious Diseases;2020;71(5):1258-1265.

7. Jarvis, J. N., & Harrison, T. S. HIV-associated cryptococcal meningitis. AIDS;2021;35(4):435-441.

8. Sloan, D. J., et al. Treatment of HIV-associated cryptococcal meningitis: Current approaches and future directions. Current Opinion in Infectious Diseases;2021;34(4):333-340.

9. Obeagu EI, Obeagu GU, Transfusion Therapy in HIV: Risk Mitigation and Benefits for Improved Patient Outcomes. Asian Journal of Dental and Health Sciences, 2024;4(1):32-37 https://doi.org/10.22270/ajdhs.v4i1.62

10. van der Horst, C., et al. Management of intracranial pressure in HIV-associated cryptococcal meningitis. Clinical Infectious Diseases;2020;71(2):279-286.

11. Luma, H. N., Temfack, E., Halle, M. P., Tchaleu, B. C. N., Mapoure, Y. N., & Koulla Shiro, S. Cryptococcal meningoencephalitis in human immunodeficiency virus/acquired immunodeficiency syndrome in douala, cameroon: a cross sectional study. North American Journal of Medical Sciences;2013;5(8):486-491. https://doi.org/10.4103/1947-2714.117318 PMid:24083225 PMCid:PMC3784927

12. Wajanga, B. M., Kalluvya, S., Downs, J. A., Johnson, W. D., Fitzgerald, D. W., & Peck, R. N. Universal screening of Tanzanian HIV-infected adult inpatients with the serum cryptococcal antigen to improve diagnosis and reduce mortality: an operational study. Journal of the International AIDS society;2011;14(1):1-7. https://doi.org/10.1186/1758-2652-14-48 PMid:21988905 PMCid:PMC3197468

13. Mukiza, N., Nakalega, R., Nakanjako, L., Ndikuno, C., Kataike, H., Mirembe, D., ... & Nakku-Joloba, E. Diagnostic accuracy of HIV Viral Load as a marker for Cryptococcal Antigenemia screening at a tertiary hospital in Uganda. 2022. https://doi.org/10.21203/rs.3.rs-1614907/v1

14. Bogaerts, J., Rouvroy, D., Taelman, H., Kagame, A., Aziz, M. A., Swinne, D., & Verhaegen, J. AIDS-associated cryptococcal meningitis in Rwanda (1983-1992): epidemiologic and diagnostic features. Journal of infection;1999;39(1). https://doi.org/10.1016/S0163-4453(99)90099-3 PMid:10468126

15. Xu, M., Peng, Z., Xu, C., Chen, Y., Cheng, J., Chi, Y., & Hu, Z. Underlying cryptococcal diseases and the correlation with serum cryptococcal antigen titers in hospitalized HIV-infected patients screened positive for cryptococcal antigenemia.Frontiers in cellular and infection microbiology;2020;10:170. https://doi.org/10.3389/fcimb.2020.00170 PMid:32391288 PMCid:PMC7192964

16. Nakale, T. Prevalence of cryptococcus among HIV infected patients attending the Intermediate hospital Oshakati, Namibia (Doctoral dissertation, University of Namibia). 2016