

Frequency of Cryptococcal Meningitis in HIV-1 Infected Patients in North Central Nigeria

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Abstract

Background: Cryptococcal meningitis (CM) is the most common severe life threatening fungal infection in AIDS patients. It is an important cause of morbidity and mortality. There is paucity of data on the prevalence of CM in Nigeria.

We aimed to determine the frequency of CM, the clinical presentation and immunological profile.

Methods: A cross sectional study was carried out at the Jos University Teaching Hospital (JUTH), A total of 100 HIV-1 infected patients suspected of having meningitis or meningoencephalitis were subjected to cerebrospinal fluid (CSF) analysis (including Indian ink preparation and fungal culture by conventional methods) and CD4 count was determined using flow cytometry (count bit Y-R 1004 Partec Muster Germany).

Results: The frequency of CM was 36% in our cohort. The commonest clinical presentation included headache (100.0%), neck stiffness (77.8%), fever (72.0%), vomiting (55.6%), personality changes (55.6%), photophobia (27.8%) and convulsions (27.8%). The mean duration of symptoms was 24 ± 22 days with a median of 17 days. The mean CD4 count was 89 ± 60 cells/mm³ with a median of 82 cells/mm³.

Conclusion: The high prevalence of CM and the associated severe immunosuppression underscores the importance of early diagnosis of HIV infection which may reduce the incidence of CM. There is the urgent need for access to Amphotericin B and fluconazole in resource constrained settings in addition to a wide access to HAART.

Key words: Cryptococcal meningitis, HIV, North central Nigeria

Date Accepted for Publication: 5th July 2010

NigerJMed 2010; 395 - 399

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Introduction

Cryptococcal meningitis in Acquired Immune deficiency Syndrome (AIDS) is an important infection described as AIDS defining because it's presence is highly suggestive of an underlying severe immune deficiency. It is caused by

Cryptococcus neoformans which is an encapsulated yeast-like fungus. It is an important cause of morbidity and mortality in patients with AIDS and is widely considered as the most common life-threatening AIDS related fungal infection^{1,2,3}.

Worldwide, 33.2million people are infected with HIV, out of which 22.5million (68%) live in Africa. In Nigeria there are an estimated 2.9million adults and children living with HIV /AIDS⁴. Cryptococcal infection in AIDS is always associated with profound immunodeficiency with CD4 T cells count almost invariably less than 100cells/ml⁵. Most HIV/AIDS patients in Sub-Saharan Africa present with severe immunosuppression which is largely due to poor access to care and treatment. In Nigeria only 15% of persons with HIV/AIDS who need antiretroviral therapy are currently on treatment.⁴

In the USA approximately 7-15% of patients with AIDS develop cryptococcal infection⁶. In 1993 the US Center for Disease Control and Prevention (CDC) reported that 6% of 274,150 patients with AIDS developed cryptococcal diseases. Furthermore, patients with AIDS associated cryptococcal infection now account for 80-90% of all patients with cryptococcal diseases⁶.

Sub-Saharan Africa carries the largest burden of Cryptococcal diseases with 15-30% of all patients with AIDS in this sub region developing cryptococcal diseases⁷. However higher figures have been observed in some countries with a high prevalence of HIV/AIDS. In a report by Mossa et al, 88% of AIDS patients in Zimbabwe had Cryptococcal infection as their AIDS defining illness while in South Africa, 84% of patients with AIDS have Cryptococcal infection as their AIDS defining illness⁸. The prevalence of Cryptococcal infection in Nigeria is unknown due to lack of accessible data.

Sub-acute meningitis or meningo-encephalitis has been reported as manifestation of Cryptococcal infection in 70-90% of AIDS patients, making it the most common manifestation of Cryptococcal infection in AIDS patients^{1,9,10}. Most of these patients (75%) present with

fever, malaise and headache, and are generally symptomatic for 2-4 weeks before presentation¹¹.

Overt meningeal symptoms and signs such as neck stiffness or photophobia are uncommon and are observed in only about 25% of patients¹² Consequently all patients suspected of having Cryptococcal infection must be evaluated for meningeal involvement. Nausea and vomiting occur in about 40% of patients and about 30% of patients have symptoms compatible with encephalopathy, such as lethargy, altered mentation, personality changes and memory loss. Focal neurologic signs or seizures are unusual and occur in about 10% of these patients¹².

Cryptococcoma (large cryptococcal granuloma within the brain) is rare in AIDS patients. Abnormalities in brain imaging such as computed tomography scans or magnetic resonance imaging are seen in up to 20% of patients.

Because of the limited health resources in our environment and consequent lack of diagnostic facilities, there are few studies on the frequency and clinical presentation of Cryptococcal meningitis in AIDS patients in Nigeria. This study was aimed at evaluating the frequency and describing the clinical presentation of cryptococcal meningitis in HIV infected patients in Jos University Teaching Hospital.

Materials and Methods.

A cross sectional study was carried out at the Jos University Teaching Hospital (JUTH), which is a tertiary referral centre and one of the foremost site of the free Antiretroviral treatment programme of the Nigerian government and PEPFAR Harvard. A total of 100 confirmed HIV-1 infected patients suspected of having meningitis or meningoencephalitis were subjected to cerebrospinal fluid (CSF) analysis (including Indian ink preparation and fungal culture by conventional methods) and CD4 count was determined using flow cytometry (count bit Y-R 1004 Partec Muster Germany).

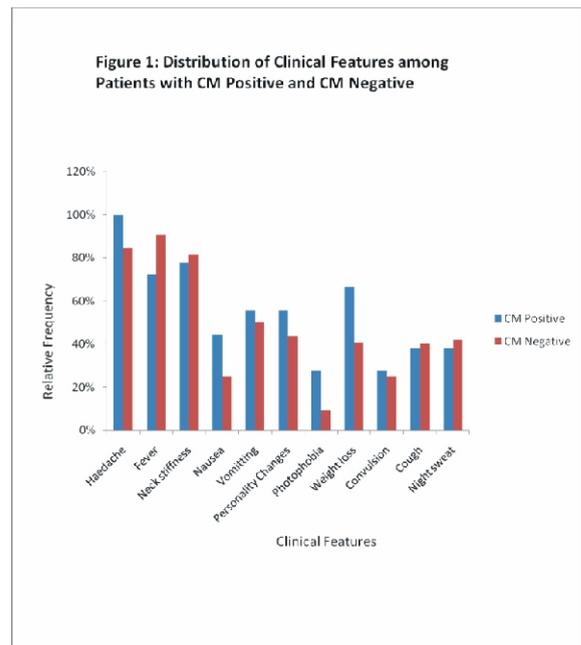
Results

One hundred HIV-1 infected patients with features of meningitis or meningoencephalitis were studied. There were 34 males and 66 females. The frequency of CM was 36% in our cohort. The mean age of the patients with Cryptococcal meningitis was 35.61±7.89 years; it ranged between 21.00 to 51.00years. The largest population of the patients is in the age group 31-40years (44%). The commonest clinical presentation included headache

(100.0%), neck stiffness (77.8%), fever (72.0%), vomiting (55.6%), personality changes (55.6%), photophobia (27.8%) and convulsions (27.8%). The mean duration of symptoms was 24 ±22 days with a median of 17 days. Persistent headache of more than fourteen days was reported in 61% of patients with CM. The mean CD4 count was 89±60 cells/mm³ with a median of 82 cells/mm³.

| Variable | CM Positive N= 36 Number (%) | CM Negative N=64 Number (%) | All Subject N=100 |
|-----------------------|------------------------------------|-----------------------------------|----------------------|
| Sex | | | |
| Male | 12 (33.3) | 22 (34.4) | 34 |
| Female | 24 (66.7) | 42 (65.6) | 66 |
| Age Group | | | |
| 21-30 | 12(33.3) | 22(34.4) | 34 |
| 31-40 | 16(44.4) | 28(43.8) | 44 |
| 41-50 | 6(16.7) | 12(18.8) | 18 |
| 51-60 | 2(5.6) | 2(3.1) | 04 |
| Occupation | | | |
| Civil Servant | 6 (16.7) | 22 (33.4) | 28 |
| Self Employed | 20 (55.6) | 26 (40.6) | 46 |
| Student | 6 (16.6) | 8 (12.5) | 14 |
| Unemployed | 4(11.1) | 8 (12.5) | 12 |
| Marital Status | | | |
| Divorced | 0 (00.0) | 4 (6.3) | 04 |
| Married | 18 (50.0) | 30 (46.9) | 48 |
| Single | 12 (33.3) | 18 (28.1) | 30 |
| Widowed | 6 (16.7) | 12 (18.7) | 18 |

CLINICAL FEATURES OF THE PATIENTS



CM Cryptococcal Meningitis

DISCUSSION

Cryptococcal meningitis is the most common life threatening fungal infection in patients with AIDS. The frequency of cryptococcal meningitis has been on the increase since the discovery of HIV but there's been a halt of this trend with the introduction of Highly Active Antiretroviral Therapy (HAART). However in countries where patients have a poor access to HAART, the Frequency of Cryptococcal meningitis is still high.

The study showed a frequency of 36% for Cryptococcal meningitis among HIV/AIDS patients in JUTH presenting with meningitic features. Similar results were observed by Bekondi et al, in a hospital study in Bangui, where they reported a frequency of 39.1% and Cryptococcal meningitis was noted as the commonest cause of meningitis in HIV infected patients with meningitic symptoms¹³. In another study in Zimbabwe, Halim et al found that 45% of patients with meningitic features had Cryptococcal meningitis and it was also the most common form of meningitis¹⁴. In Bamako, Mali, a frequency of 30.9% was reported by Oumar AA et al¹⁵

This high frequency of Cryptococcal meningitis may be due to the fact that most of our patients in JUTH sought medical attention at advanced stage of the disease because a large proportion of them were not on HAART or had failed antiretroviral therapy.

In countries with a fairly wider access to antiretroviral drugs and a better care seeking attitude, there have been reports of lower frequency. In South Africa, Bergeman et al reported a frequency of 13%¹⁶. Another study by Jowi and co-workers in a hospital in Nairobi found Cryptococcal meningitis in 22% of HIV/AIDS patients with neurological complications¹⁷. Other studies done in South America showed frequencies between 20.3 - 29.4%^{18,19,20}.

The age at presentation of patients with cryptococcal meningitis was at a median age of 35.5 years and two thirds of the patients were females. Similar findings was observed in the age presentation of patients, by Melaku et al in a study in Ethiopia with a median age of 35 years, however, a male predominance was noted (65.6%)⁵⁸. Millogo and colleagues also found a median age of 34.25 years in Burkina Faso, and a male preponderance (66%)²¹. Similar findings were also found in studies conducted in Malawi and Argentina^{22,19}.

The median age of the patients fell within the age bracket of 15 and 49 which is the age bracket worst affected by HIV infection worldwide⁴. The higher female preponderance in the present study could be explained

by the higher number of female patients presenting for care in our hospital. Unpublished audit in our clinic data shows that females make up 66.5% of the total number of persons with HIV/AIDS attending our clinic. This is probably due to the better health seeking behavior of women in this geo-political zone. Other factors like stigmatization have been reported as a major constraint for men. However there may be some other socio-cultural influences which may be elucidated in further studies.

The major clinical features reported by patients in this study were headache (100%), neck stiffness (77.8%), fever (72.0%), weight loss (66.7%) and personality changes (55.6%), vomiting (55.6%), nausea (44.4%).

These findings are comparable with the findings in Malawi by Maher et al of headache (97%), neck stiffness (74%), fever (61%) and altered consciousness (58%).²² This frequency of symptoms were also similar in a study in Ethiopia by Melaku et al with headache (99%), fever (97.1%) vomiting (93.1%) and alteration in mentation (39.1%) as the major symptoms²³. In South Africa, Argentina, Spain and India similar symptoms profile was also found.^{24,25,26,27}

These high frequencies of symptoms show that most of our patients present with acute or subacute meningitis. It is also important to note that the low CD4 cell count of the patients could predispose them to other opportunistic infections that could modify their presentation.

However some other studies have reported a lower frequency of symptoms. In Bamako, a lower frequency of symptoms in patients with cryptococcal meningitis was observed, with disorders of consciousness in 23.6%, fever in 11.8% and signs of meningism in 64% of the patients. Chuck et al also found a low frequency of meningeal signs and symptoms (25%), vomiting (40%) and encephalopathy (30%)¹¹. These findings are more in keeping with a chronic presentation of CM.

The median duration of meningitic symptoms was 17 days. There was no significant difference from those without cryptococcal meningitis. (P=0.5800). This finding is in consonance with a study in Malawi²². Chuck et al also documented in a review of CM a duration of 2-4weeks¹¹. However the time from onset to diagnosis ranged from days to months because cryptococcal meningitis can present as an acute, sub-acute or chronic presentation with waxing and waning symptoms²⁸.

Logistic regression showed that clinical features were not good predictors of the presence or absence of cryptococcal meningitis. Only fever and weight loss had a significant probability value of 0.003 and 0.031 respectively. However these two clinical features could be attributable to many other opportunistic infections and HIV disease itself. Therefore it could be misleading to use it as a sole predictor of Cryptococcal meningitis in isolation without considering other clinical features. Studies in Tanzania also showed that clinical features are insensitive for establishing the diagnosis or prognosis of cryptococcal meningitis¹⁸.

It is also important to note that fever and weight loss were symptoms reported by the patients which could be misleading depending on the patient's perception of the symptom.

Headache was the most prominent feature in patients with CM (100%), this finding was also reported in studies in Malawi and South Africa^{22,24}. Persistent headache of more than fourteen days was reported in 61% of patients with CM. In Burkina Faso, a higher percentage (75%) had persistent headache with CM²¹. In CM several factors which include raised intracranial pressure, meningo-encephalitis and systemic cytokine release could contribute in the pathogenesis of headache.

In patients without CM, 41% had persistent headache. Patients with CM are more likely to have persistent

headache than patients without CM ($X^2=3.87$, $p=0.049$). In all 2% of patients had persistent headache with negative cultures, a cerebrospinal fluid cell count of less than 5cells/ml and without meningeal signs. This may group may constitute what is referred to as HIV headache. The pathophysiological mechanism is largely unknown but it is thought to be due to systemic cytokine release because it may sometimes herald the onset of systemic infection such as Pneumocystis pneumonia^{29,30}.

This study found a median CD4 T cell count of 82 cells/mm³ in patients with Cryptococcal meningitis. There was no significant difference from the patients without Cryptococcal meningitis. ($P=0.86$). Crowe and colleagues⁵ also showed that CM is always associated with profound immunodeficiency with CD4 T cell count almost invariably less than 100 cells/mm³. A Study in Botswana by Bisson et al has shown an even lower median CD4 count of 41 cells/mm³³¹. In Kenya a median CD4 T cell count of 17cells/mm³ was found. Knudsen et al in Denmark found a median CD4 count of 18cells/mm³³². But the similar CD4 T cell count in patients without Cryptococcal meningitis may probably mean that our patients with HIV infection still present mainly at an advanced stage of AIDS. Those without cryptococcal meningitis may purely be a matter of non-exposure to *C. neoformans* if the quality of their CD4 T cell is equal. These may be a subject of further research.

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