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THE PREVALENCE, CLINICAL FEATURES, RISK FACTORS AND OUTCOME ASSOCIATED WITH CRYPTOCOCCAL MENINGITIS IN HIV POSITIVE PATIENTS IN KENYA

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Abstract

Objectives—To determine the prevalence, clinical features, risk factors and outcomes associated with cryptococcal meningitis (CM) in human immunodeficiency virus (HIV) positive patients at two referral hospitals in Nairobi, Kenya.

Design—Prospective, observational study.

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Setting—Kenyatta National Hospital (KNH) and Mbagathi District Hospital (MDH), Nairobi, Kenya

Subjects—Three hundred and forty HIV patients presenting with suspected CM.

Results—Of three hundred and forty suspected CM patients, 111 (33%) were diagnosed with CM by CrAg. Among CM patients, in-hospital mortality was 36% (38/106), median age was 35 years (range, 19–60 years) and median CD4 count was 41 cells/μL (n=89, range 2–720 cells/μL). Common clinical manifestations among CM patients included headache 103 (93%), neck stiffness 76 (69%) and weight loss 53 (48%). Factors independently associated with CM were male sex, headache, blurred vision and previous antifungal drug use. Night sweats and current use of anti-retroviral therapy were associated with reduced risk for CM.

Conclusions—There is a high prevalence of CM and CM-associated mortality in HIV patients at KNH and MDH despite treatment with antifungal and anti-retroviral drugs. This study demonstrates the need to address the existing inadequacies of CM patient outcomes in Kenya.

INTRODUCTION

The human immunodeficiency virus (HIV) epidemic continues to be a major challenge in Kenya. There are 1.4 million people infected with HIV in Kenya and the prevalence of HIV among adults aged 15–49 years is currently estimated at 7.8% (1, 2). As a consequence of this epidemic, the opportunistic infection cryptococcal meningitis (CM) has become a leading cause of morbidity and mortality. Recent estimates from observational studies in Africa report mortality in CM patients ranging from 17% to 100% (3–8). Moreover, Africa has the highest burden of CM, with countries such as Rwanda, Democratic Republic of Congo, South Africa, Uganda, Kenya and Zimbabwe reporting double digit figures (4, 5, 9–12). CM is becoming a more important cause of meningitis in HIV patients compared to bacterial and viral meningitis (5).

There are few studies on CM among HIV patients in Kenya (4,15,16). Problems with management of CM in hospitals in Kenya, as in many resource constrained settings, are compounded by over crowding, lack of essential equipment such as lumbar puncture (LP) needles, shortage of trained health providers and difficulties in obtaining antifungal therapies (5, 6). Amphotericin B (AMB) is the drug of choice for treatment of CM (13, 14). Current guidelines for treatment of AIDS-associated CM for sub-Saharan Africa recommend 1 mg/kg/d AMB for two weeks as induction therapy or, if unavailable, FLC 800 mg for four weeks (14). However, the widespread use of AMB in Kenya has been limited by nephrotoxicity and cost (15).

The aim of this study was to define the burden, clinical features, risk factors and outcome associated with CM in HIV positive patients presenting with suspected meningitis at two referral hospitals in Kenya. We sought to conduct this study because of the need to understand the epidemiology of CM, an important tool in planning for the management of the disease (12).

MATERIALS AND METHODS

Study design

We conducted a prospective, observational study in HIV patients with suspected CM at KNH and MDH in Nairobi, Kenya. Patients were recruited from the admitting wards between August 2008 and February 2009.

Study settings and Participants

KNH is a large referral and teaching hospital in Kenya with 1,800 bed capacity. It serves as the primary hospital for the four million residents of the capital city of Nairobi. MDH is a 169-bed public hospital that serves as the Tuberculosis Referral Centre for Nairobi. Study participants were recruited from both hospitals. The following inclusion criteria were used: (i) patient is an adult male or female aged 17 years and older; (ii) patient's underlying immunosuppression is HIV infection; (iii) patient is suspected to have CM based on physician's diagnosis using clinical symptoms. Suspected CM was defined as: (i) signs of meningeal irritation such as photophobia, neck rigidity, vomiting, and headaches; (ii) fever with altered mental state; (iii) unexplained change in mental state, or headache (5). Patients who had one or more of these symptoms were suspected to have CM. This definition was used by the admitting physicians at the two hospitals as the basis for recommending a lumbar puncture for confirmatory laboratory testing for CM. The exclusion criteria were: (i) Children; (ii) pregnant mothers; (iii) HIV negative patients even if their diagnosis indicated suspected CM.

Ethical approval and permission for this study were obtained from the UAB Institutional Review Board and the Kenyatta National Hospital and University of Nairobi Research and Ethics Committee.

Patient data collection

A structured questionnaire was administered to each enrolled patient. Data including demographic characteristics, duration of illness, symptoms and signs on admission, prior use of antifungal drugs (defined as antifungal drug consisting of AMB, FLC and clotrimazole, used any time prior to the current admission), anti-retroviral therapy (ART) status, FLC treatment and clinical status of HIV infection were collected. Patient medical records were also used retrospectively to obtain information such as date of HIV diagnosis, CD4 counts, HIV viral load, previous illnesses and treatments. We also recorded information on CM management including; antifungal drugs used, therapeuticlumbar puncture (LP), fundoscopy, computed tomography (CT) scan, creatinine measurements and monitoring, and opening pressure measurements.

In-hospital mortality was obtained from the admission registry and confirmed using patient clinical records. At the time of discharge, patients were referred to the KNH Comprehensive Care Center (CCC) where they were started on oral FLC. Patients were followed monthly for three months after discharge to assess treatment outcomes.

Laboratory tests

Laboratory determination of cryptococcal infection was done at the University of Nairobi microbiology laboratory using CSF. Lumbar puncture (LP) was performed as part of the standard management of suspected CM cases. All suspected CM patients had the LP performed before initiation of antifungal treatment. Five milliliters of CSF was obtained and stored at 2°C – 8°C in sterile 10 ml glass vials. CSF samples were tested using the Cryptococcal Antigen (CrAg) Latex agglutination test (Latex-Crypto test, Immuno-Mycologics, Norman, Oklahoma USA). Patients whose CSF tested positive for CrAg were considered to have CM. CSF was cultured on Sabouraud's dextrose agar (SDA) to obtain cryptococcus isolates. To rule out contamination the presence of Cryptococcus species was confirmed by a positive urease test and the ability to grow at 37°C. The isolates were then transferred into SDA slants and stored at room temperature or aliquoted in glycerin and milk solution and stored at −80 °C. Isolates were shipped by air to the division of laboratory machine, department of pathology at the University of Alabama at Birmingham for antifungal susceptibility testing and confirmation of identification. Antifungal susceptibility

testing was performed by broth micro dilution method as outlined in the Clinical and Laboratory Standards Institute (CLSI) document M27-A3 (17) using FLC and AMB. Interpretive criteria for FLC (susceptible, MIC [minimum inhibitory concentration] ≤8 μg/ml, susceptible dose dependent, MIC 16–32 μg/ ml and resistant, MIC ≥64 μg /ml) and AMB (resistant, MIC ≥2) was based on the study by Nguyen and Yu (18).

Clinical management of CM patients

The daily rate of patient admission was approximately 30–40 at KNH and 10–15 at MDH. All consenting new patients admitted in the wards were tested for HIV as part of the standard of care irrespective of their previous HIV diagnosis. All patients received voluntary counselling and testing at the hospitals before and after HIV testing. All ART naïve patients were referred to start ART. The treatment protocol for CM differed in the two hospitals. At KNH, patients with CM were treated with AMB (50 mg or 35 mg) for 14 days and then given FLC (400 mg or 200 mg) orally for eight weeks followed by FLC 200 mg until CD4 counts were >200 cell/μL. At MDH, AMB (only available to patients who could afford it) was escalated in dose: 12.5 mg on the first day, 25 mg on the second day and 35 mg for each of the next 12 days. FLC 800 mg was then given daily for two weeks, followed by maintenance treatment with FLC400 mg. Information on therapeutic LP and measurement of opening pressure was not available as these procedures were not done routinely.

Data analysis

Categorical variables are represented as frequencies and percentages, and continuous variables as medians (range). The comparisons were performed using Chi-square test for categorical data and student's t-test for continuous data. Correlation analyses were performed to detect multicollinearity between independent variables. A multivariable logistic regression analyses using a significance level of <0.05 was used to determine risk factors associated with CM. Variables that were statistically significant at $p<0.05$ on the bivariate model and those known to be associated with CM in HIV patients based on previous studies were entered into the multivariable model using the stepwise method. Odds ratios (OR) and 95% confidence intervals (CI) were generated as measures of association for all variables entered into the model. Observations with more than 10% missing values were excluded from the analysis. Data analysis was conducted using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Patient demographic characteristics

Of the 340 HIV positive patients with suspected CM who were enrolled into the study, 111 (33%) had laboratory confirmed CM. Most patients were young males with secondary education or vocational training and were hospitalised for the first time with clinical suspicion of CM (Table 1). Positive CSF detection of *Cryptococcus* species in CM positive patients by CrAg and culture were 111/111 (100%) and 86/111 (77%) respectively.

Clinical features

Common clinical manifestations among patients with CM were; headache, neck stiffness and weight loss(Table 1). CM-related clinical features that were significantly more common among CM patients compared to the CM negative patients were headache($p<0.001$)and blurred vision($p<0.001$). Prior use of antifungal drugs was significantly higher in CM patients compared to patients without CM ($p<0.001$). Tuberculosis infection was the most common concurrent morbidity among CM positive patients.

Laboratory Findings

The median CD4 lymphocyte counts for confirmed CM cases whose CD4 test results were available was 41 cells/μL (n=89, range 2–720 cells/μL). There was a significant difference in CD4 counts between patients with CM compared to those without (p<0.001). The median viral load among CM cases was 376,000 RNA copies / ML (n=55, range <40–6,000,000 RNA copies/ML). There was significant difference in viral load counts between CM positive patients and CM negative patients (p=0.01) (Table 1). Interestingly we found that all (67) *C. gatti* isolates from these patients were susceptible to both FLC (median MIC = 4.0, range 0.25–16.0 μg/ml) and AMB (median MIC = 1.0, range 0.5–1.0 μg/ml).

Risk factors for CM

Our multivariable logistic regression results show that male sex (OR=2.3, CI 1.3–3.9, p=0.003), headache (OR= 3.7, CI 1.6–8.6, p=0.002), blurred vision(OR=2.3, CI1.3–4.3, p=0.007)and prior antifungal drug use (OR=5.9, CI 3.3–10.3, p<0.0001) were independently associated with increased risk of having CM. Night sweats (OR= 0.4, CI 0.2–0.8, p=0.005) and being on anti-retroviral therapy at the time of admission (OR= 0.5, CI 0.2–1.0, p=0.04) were associated with reduced risk for CM.

Patient Outcomes

In-hospital mortality among CM patients was 36% (Table 1). In-hospital mortality was not significantly higher in CM cases when compared to non-CM cases. Most of the CM patients 52/68 (76%) were lost to follow-up after discharge from hospital. The remaining 16 CM patients who were followed at the CCC were all alive after three months of follow up.

DISCUSSION

Our results provide a rare description of the epidemiology of CM in HIV patients presenting with suspected CM at public hospitals in Kenya. We are reporting a CM prevalence of 33% and in-hospital mortality of 36% in HIV patients presenting with suspected CM at KNH and MDH. These results show the need to address the existing gaps in the management of this disease in Kenya.

The CM prevalence in this study was higher than what is reported in a similar study by Jowi *et al* (4). We suspect these results over-estimated the true prevalence of CM in the general population. The study population consisted of patients who presented with signs of meningitis. These patients were more likely to have CM compared to the general hospital population. Higher CM prevalence in this study may also be attributed to the characteristics of patients admitted to KNH and MDH. Majority of the patients in this study live in the surrounding low income neighbourhoods and slums, typical characteristics of patients presenting with CM in Africa (3, 11).

Clinical presentation of CM patients in this study was similar to those reported in other studies (3, 5). Majority of our patients presented with headaches, neck stiffness and weight loss. Headache, blurred vision and a history of antifungal drug use predicted CM in this study. These predictors can be useful for early disease detection and timely management of CM in resource constrained settings like Kenya (3, 5). Night sweats and current use of ART were associated with reduced risk for CM. Based on these results; increasing access to ART to HIV patients can reduce the incidence of CM.

Mortality was high in our cohort despite the use of either FLC or AMB therapy, both of which were highly efficacious against all our isolates. We suspect that late presentation of patients contributed greatly to high CM-associated mortality in our study (3). Late

presentation is evidenced by our finding that a large proportion (48%) of the CM patients showed signs of weight loss on admission and had a high level of immunosuppression. These patients had low CD4 counts and high viral loads at presentation. Renal toxicity associated with AMB may also have contributed to poor patient outcomes. A study by Ochieng *et al* reported a high incidence of nephrotoxicity among CM patients receiving AMB at KNH (15).

High CM-associated mortality rate in this study warrants an evaluation of the current CM management guidelines at the two hospitals. Despite its toxicity, AMB should continue to be the drug of choice for treatment of CM in Kenya. AMB clears cryptococcal infections more rapidly than FLC (19–21). AMB was not universally available to patients in this study due to cost. The average cost of a two week dose of AMB in Kenya is approximately $88 or Kshs 500/50 mg vial of AMB. At MDH patients waited for their families to procure AMB before treatment was initiated. Thus, treatment with AMB was either delayed, given partially or never administered. Efforts to improve access to AMB in public hospitals in Kenya will be useful.

There were a number of limitations in this study. It is difficult to generalise our finding to the wider national population. However, our study sites are referral hospitals that admit patients from different regions of the country; thus reflecting the national situation. Patient follow-up was difficult. We did not confirm what diagnosis the CM negative patients in this study had. Our efforts concentrated on quantifying the prevalence of CM among these patients. We suspect that some of the patients may have had bacterial or viral meningitis. It will be interesting to determine the prevalence of other causes of meningitis among HIV patients in future studies. Most patients did not respond to our phone calls after they were discharged. We could not confirm mortality attributable to CM since our study did not include diagnostic tests that would confirm the presence of other opportunistic infections. Nevertheless, the study confirms the continued high prevalence of CM among HIV patients with suspected CM, and provides new information on excessively high in-hospital mortality of these patients despite the administration of FLC and AMB. It also identifies steps that can be taken to improve management and outcome of CM patients.

In conclusion, the study reports a high prevalence of CM and CM-associated mortality among immunosuppressed HIV/AIDS patients at public hospitals in Kenya. Even with the FLC donation programme greater treatment success is hampered by the inadequate capacity to manage CM and late presentation of patients with advanced CM. Developing a standard national guideline for CM management, improving access to AMB and expanding of laboratory capacity for diagnosing CM in public hospitals can help improve outcomes.

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Table 1

Characteristics of HIV positive patients with suspected CM at KNH and MDH, August 2008 – February 2009.

Characteristic	Total N=340 (%)	CM Positive n=111(%)	CM Negative n=229 (%)	P Value
Sex				
Male	162 (47.5)	64 (57.7)	98 (43.0)	0.01
Female	178 (52.5)	47 (42.3)	131 (57.0)	
Age (in years)				
Median (Range)	35 (17–65)	35 (19–60)	35 (17–65)	1.0
Education				
Primary	168 (49.1)	52 (46.0)	116 (51.1)	0.39
Secondary/Vocational	172 (50.9)	59 (54.0)	113 (48.9)	
On Antiretroviral drugs				
Yes	104 (30.6)	33 (29.7)	71 (31.0)	0.81
No	236 (69.4)	78 (70.3)	158 (69.0)	
Prior use of antifungal drugs				
Yes	101 (29.7)	48 (43.2)	38 (16.6)	<0.01
No	239 (70.3)	63 (56.8)	191 (83.4)	
First time hospitalization *				
Yes	319 (93.8)	99 (89.2)	220 (96.1)	0.01
No	21 (6.2)	12 (10.8)	9 (3.9)	
Clinical outcomes				
Discharged alive	221 (65.0)	68/106 (64.0)	139/211 (66.0)	<0.78
In-hospital mortality	119 (35.0)	38/106 (36.0)	72/211 (34.0)	
CD4 cell count (cells/μL)				
<100	153/269 (57.0)	66/88 (75.0)	87/181 (48.1)	<0.01
100–200	46/269 (17.0)	11/88 (12.5)	35/181 (19.3)	
>200	70/269 (26.0)	41 (2–720)	104 (1–1089)	<0.01
CD4 cell count (cells/μL)				
Median (Range)	72 (1–1089)	41 (2–720)	104 (1–1089)	<0.01
Viral load (RNA levels, Copies/ML)				
<100,000	82/177 (46.3)	18/55 (32.7)	64/122 (53.0)	0.01
>100,000	95/177 (53.7)	37/55 (67.3)	57/122 (47.0)	
Viral load (RNA levels, Copies/ML)				
Median (Range)	164,000 (<40–10 million)	376,000 (<40–6 million)	49,000 (<40–10 million)	<0.01
Concurrent morbidity				
Tuberculosis	111/191 (74.5)	45/56 (80.4)	66/93 (71.0)	0.32
Malaria	17/191 (11.4)	4/56 (7.1)	13/93 (14.0)	
Pneumonia	10/191 (6.7)	2/56 (3.6)	8/93 (8.6)	
Other +	11/191 (7.4)	5/56 (8.9)	6/93 (6.5)	
Time to Discharge				
Median Days (Range)	14 (0–90)	19 (0–90)	11 (1–50)	<0.01
Time to Death				

Characteristic	Total N=340 (%)	CM Positive n=111(%)	CM Negative n=229 (%)	P Value
Median Days (Range)	8 (2–73)	8 (2–73)	8 (2–33)	1.0
Signs and symptoms at presentation				
Headache	274 (80.6)	103 (92.8)	171 (74.7)	<0.0001
Coughs	161 (47.4)	42 (38.0)	119 (52.0)	0.01
Night sweats	121 (35.6)	25 (22.5)	96 (41.9)	0.0005
Blurred vision	74 (21.8)	39 (35.1)	35 (15.3)	<0.0001
Neck stiffness	211 (62.1)	76 (68.5)	135 (59.0)	0.09
Altered mental status	178 (52.4)	50 (45.1)	128 (55.9)	0.06

Values in bold are statistically significant at $p<0.05$

Chi square was used for categorical data and student t-test for continuous variables.

CM = Cryptococcal meningitis

KNH = Kenyatta National Hospital

MDH = Mbagathi District Hospital

Denominators included to show missing values

[*] First time hospitalisation for suspected CM

[+] Other concurrent morbidities were herpes, diabetes, hypertension and osteoarthritis.