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CASE REPORT

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Cryptococcal meningitis among perinatally HIV-infected adolescents: Case series on presentation and management challenges

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Abstract

Diagnosis and management of cryptococcal meningitis in HIV-infected adolescents is challenging in poor resource settings. A high index of suspicion based on clinical presentation is critical for early identification and treatment. This report sought to describe the clinical presentation and outcomes of HIV-associated cryptococcal meningitis in adolescents.

KEYWORDS

adolescents, antiretroviral therapy, Cryptococcal meningitis, HIV, opportunistic infections

1 | INTRODUCTION

Globally, there is an estimated 220,000 cases of human immunodeficiency virus (HIV) associated cryptococcal meningitis (HIV-CM) each year. This accounts for 10%–20% of HIV-related deaths in persons living with HIV (PLHIV) with a mortality rate of 70% in sub-Saharan Africa.[1,2] The expanded and improved access to pediatric HIV treatment has resulted in increased survival of perinatally infected children.[3] This has contributed to the growing population of adolescents living with HIV (ALHIV) in addition to the population of AYA infected later in life mainly through sexual transmission.[4] There is an estimated 83% of ALHIV in sub-Saharan Africa.[5]

These ALHIV face issues such as perceived stigma, poor handling of disclosure, lack of health system that is responsive to their peculiar needs and lack of close clinical follow-up. These culminate in poor adherence to antiretroviral therapy (ART) which puts them also at a high risk of developing HIV-associated opportunistic infections including HIV-CM like the adults.[6] The prevalence of cryptococcus among PLHIV diagnosed with meningitis was 2.4% in Ghana[7] which is low compared to findings from other studies elsewhere,[2,8,9] mortality associated with HIV-CM is high.

Diagnosis and management of HIV-CM are usually done at the tertiary facility level in our setting where such patients are referred to for specialized care. However, rapid diagnosis of HIV-CM in adolescents and young adults is often missed by healthcare workers (HCWs) at the community and primary care levels due to a low index of suspicion for opportunistic infections such as HIV-CM. Focus is mainly on the routine management of malaria, pneumonia enteric fever for any febrile illness presented by ALHIV. In this era of task-sharing, different cadres of health professionals other than doctors provide HIV care

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at various ART clinics. Most of these HCWs lack the capacity to suspect and investigate opportunistic infections such as HIV-CM as differential diagnosis. This leads to delayed diagnosis and therefore increase in mortality among this population. Lack of point-of-care tests for HIV-CM rapid diagnosis is another contributory factor to delayed diagnosis and early treatment. Prompt treatment initiation, early identification, and management of treatment-related side effects and intensive follow-up care of patients are keys to survival.[10,11] HIV-CM characteristics have been well documented in adults living with HIV, but little information is available on HIV-CM in ALHIV. Documenting the presenting characteristics of HIV-CM in ALHIV is important in increasing awareness about the existence of HIV-CM among ALHIV. This will be key in educating and aiding healthcare workers especially those in the primary and secondary levels of health care in the early identification of such patients for early management (where appropriate) or referral. It will also help them to have a high index of suspicion of CM when providing services for ALHIV. This study reports on CM characteristics and management outcomes in four ALHIV managed at the HIV Unit of the Korle Bu Teaching hospital in Accra, Ghana.

2 | CASE PRESENTATIONS

A retrospective single-center hospital-based chart review was conducted at the HIV unit of the Korle-Bu Teaching hospital (KBTH) in Accra, Ghana. The admissions and discharge records from 2015 to 2019 were reviewed to identify ALHIV with laboratory confirmed CM and admitted. Adolescent was defined as any patient aged 10–19 as defined by the World Health Organization (WHO).[12] Four ALHIV who all had HIV-type 1 were identified, and their clinical files reviewed. The HIV Unit adopts the guidelines of IDSA in the management of HIV-CM.

2.1 | Case 1

An 18-year-old male patient on ART (Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), and ritonavir boosted Lopinavir (LPV/r)) for 8 years, weight 25 kg, Cluster of differentiation cells (CD4) of 14, HIV viral load of 18,682 copies/ml at time of admission. He was referred from a primary facility and presented with a 2-week history of persistent global headaches with neck stiffness, photophobia, blurred vision, vomiting, and an episode of loss of consciousness. Physical examination was generally unremarkable except for clubbing of finger and toenails.

Cerebrospinal fluid (CSF) analysis revealed numerous cryptococcal antigens (CrAg) using latex agglutination test and positive India ink test. Pre-treatment and monitoring tests such as magnesium, calcium, complete blood count, renal and liver function tests were essentially normal. Patient had one therapeutic LP to relieve persistent headaches. Patient received 12 days of IV deoxycholate amphotericin B and oral fluconazole and not 14 days due to electrolyte imbalance challenges. Patient experienced hyponatremia of 130 mmol/L (treatment day 4), hypomagnesemia of 0.63 mmol/L (treatment day 4), and hypokalemia of 2.1 mmol/L (treatment day 7) all of which were corrected. Patient also experienced chills, rigors, and diarrhea anytime amphotericin was given and were managed with analgesics and adequate hydration. He was discharged on day 20 of admission and continued oral fluconazole 400 mg/day for 8 weeks, thereafter, 200 mg daily as maintenance therapy. Patient is currently alive, stable, and retained in care.

2.2 | Case 2

A 19-year-old female patient on ART (Zidovudine (AZT), 3TC and Efavirenz (EFV)) for 11 years, an attendant at the clinic, weight of 39 kg and had a CD4 of 47. She presented with a week's history of severe frontal headaches and a day's history of photophobia and intermittent vomiting. She was non-compliant on ART as evidenced from the history. Her CD4 levels 14 months prior to current admission were 415.

Physical examination and ophthalmology assessment were unremarkable except she had pruritic papular dermatitis (PPD). A pro bono head computed tomography (CT) scan and CSF analysis were done on day 8 of admission as caregivers had financial challenges. Head CT scan was unremarkable. CSF was positive for both CrAg (1:2560) and India ink test. Patient received only oral Fluconazole 800 mg as caregivers could not raise funds to purchase amphotericin. Patient was discharged on day 14 (after 5 days of taking fluconazole and no complaints) and scheduled for review in 1 week.

Patient defaulted clinic reviews and was re-admitted 5 months postdischarge with persistent generalized headaches with neck stiffness, photophobia, focal seizures of left lower limb, persistent vomiting and an episode of loss of consciousness and CD4 of 5. She had bilateral optic disc swelling and optical neuritis on fundoscopy (suggestive of raised intracranial pressure (ICP)). Two therapeutic LPs 5 days apart with 12 mLs of CSF drained each time were performed to relieve persistent headaches. Oral fluconazole 800 mg daily was restarted on day 1 of admission but amphotericin B was started on day 10 of the second admission due to lack of funds. Patient experienced spikes in temperature anytime amphotericin was set up and was

managed with analgesics. Pre-treatment laboratories were essentially normal. Amphotericin was discontinued on day 5 due to severe hypokalemia (2.0 mmol/L) and worsening urea (9.8 mmol/L) and creatinine (166.1 μmol/L) all detected on day 5 of amphotericin treatment and efforts at correcting electrolytes initiated. Caregivers had no funds to do subsequent monitoring laboratory tests. Patient did not improve and died 6 days after amphotericin was discontinued.

2.3 | Case 3

A 19-year-old female patient, with weight 36 kg, and on ART (AZT, 3TC, LPV/r) for 11 years. She was referred and presented with a 10-day history of persistent global headaches with neck pain and stiffness, intermittent generalized tonic–clonic seizures, photophobia, blurred vision, vomiting, and diplopia. Patient was non-compliant on ART as documented in the history due to size of pills. An accompanying head CT scan report indicated a differential diagnosis of cerebral toxoplasmosis and tuberculous meningitis (TBM). Patient was initially managed for both conditions though these diagnoses were not confirmed. However, condition worsened despite initial treatment. Ophthalmology assessment revealed left lateral rectus palsy, atrophy of optic nerve and bilateral optic disc swelling suggestive of raised ICP. A diagnostic LP was done on day 7 of admission, and CSF analysis results obtained 4 days later revealed positive India ink test, fungal elements (yeasts), and positive CrAg (1:80). Oral fluconazole 800 mg daily was started on day 11 of admission. Patient had 4 therapeutic LPs 3 days apart on days 9, 12, 15, and 17 of admission with 12 mLs each time to relieve headaches. Amphotericin was started on day 19 of admission due to its scarcity. Patient received 2 days of amphotericin and died on day 21 of admission.

2.4 | Case 4

A 17-year-old female patient, on ART (TDF, 3TC and EFV) for 7 years, with weight 43 kg, CD4 of 1 and an attendant at the clinic. She presented with a 7-day history of severe occipital headaches with neck pain and stiffness, photophobia, seizures, and vomiting. She was non-compliant on her antiretroviral drugs from the obtained clinical history. Physical examination was generally unremarkable except for PPD. Ophthalmology assessment revealed bilateral optic disc swelling.

A diagnostic LP was done on admission day 4 with delay due to financial challenges on the part of patient's caregivers. CSF analysis revealed positive India ink test. CSF CrAg was not done as patient's caregivers could not pay for it. Pro bono amphotericin at was initiated on day 9 of admission. Patient received 14 days of amphotericin and fluconazole without any complications. One therapeutic LP with 12 mLs CSF drained was conducted on day four of admission. Patient was discharged on day 26 and scheduled for postdischarge reviews. Patient defaulted reviews and was re-admitted 2 months postdischarge but died on day three of re-admission with a diagnosis of CM.

3 | DISCUSSION

We described the presenting features, management, and outcomes of HIV-CM among ALHIV in a tertiary hospital in southern Ghana.

Our study reports four cases over a period of 4 years suggestive of a low prevalence. However, this apparent low prevalence is likely due to missed diagnosis or low index of suspicion by healthcare workers (HCWs) which is common in HIV care.[13,14] These are because of issues with lack of capacity for laboratory and clinical diagnosis of CM diagnosis in Ghana. Ghana implements the WHO recommended task-sharing policy to address shortage of HCWs and increase access to HIV care.[15] According to this policy, other cadre of HCWs aside doctors are trained to conduct HIV test, counsel, clinically evaluate PLHIV, initiate ART treatment, and do appropriate referral.[15] However, diagnosis and management of co-morbidities or co-infections especially in HIV-positive children and adolescents are challenging due to lack of clinical capacity and confidence to do so among the other cadre of HCWs. This leads to low index of suspicion of co-infections, thus missed diagnoses and poorer outcomes in ALHIV. With the increasing population of HIV-positive children surviving into adolescence, but lack of clinical capacity for their management, missed diagnosis such as CM is likely to occur. This contributes to the supposed low CM prevalence being seen among ALHIV.

The common presenting symptoms in our patients were persistent global or frontal headaches, neck stiffness with or without pain, photophobia, blurred vision, vomiting, seizures, and loss of consciousness. Similarities of these presenting symptoms to symptoms of malaria and enteric fever result in HCWs leaning towards the latter diagnoses as they are common in our settings. Thus, ALHIV are treated as such and discharged home without a differential diagnosis of possible CNS OI such as CM to warrant investigation. This study highlights key symptoms, signs in low resource settings that is necessary in aiding all cadre of HCWs to have a high index of suspicion to

facilitate early CM diagnosis among ALHIV and prompt referral. Even for ALHIV with suspected CM, delay in diagnosis confirmation and treatment initiation was noted among two of our patients due to lack of funds from caregivers. Advocacy for rapid point-of-care test is necessary to also aid prompt diagnosis of CM.

Three out of our four patients died. This high mortality is similar to findings from other studies among adult PLHIV diagnosed with CM.[6,8,16] Mortality among our ALHIV may be due to the late diagnosis, late start of treatment and also inadequate CNS clearance of cryptococcus by amphotericin and fluconazole employed at our facility compared to the standard recommended therapy of amphotericin and flucytosine.[10,17] CSF fungal burden and rate of clearance of the cryptococcal infection predicts acute mortality in HIV-CM.[17] Successful management of CM requires prompt and effective clearance of cryptococcus from the CNS which is achieved with induction therapy combination of amphotericin and flucytosine.[10] Flucytosine is widely unavailable especially in less developed countries including Ghana.[10,11] Early diagnosis and treatment is key to reduce risk of the associated high mortality.

All our patients had optic disc swelling suggestive of elevated ICP which is an indication of late presentation or diagnosis. This is similar to findings reported from other studies where patients were also reported to have bilateral disc edema.[18,19] This increase in ICP is associated with severe headaches which our patients experienced.[10,18,19] Aggressive management of elevated ICP is a key and involves conducting serial therapeutic LPs as done for the ALHIV.[11,19] Therapeutic high volume CSF drainage of 100 mLs over 2 weeks has been reported to relieve headaches from increased ICP and also contribute to CRAG clearance from the CSF.[17] However, our patients had at least one therapeutic low volume CSF drainage due to inability to monitor CSF pressure. The facility lacks a manometer and only relies on those purchased by patients' caregivers to measure ICP. Getting items needed for LP is on a cash and carry basis, and it is not covered by the national health insurance. Safer approaches for monitoring of elevated ICP and drainage of CSF in a resource limited setting are needed.

Although amphotericin-based therapy is the mainstay treatment for CM, occurrence of related side effects as well as cost of monitoring is challenging in poor resource settings as evidenced from our findings.[10,11] Some of our patients experienced electrolyte imbalances postamphotericin initiation which is similar to reports in other studies indicating electrolyte wasting begins 5 days postinitiation of amphotericin.[11,20]

All our patients were non-compliant on ART which is similar to medication adherence issues reported among ALHIV.[21,22] Effective medication adherence support is vital to preventing opportunistic infections including CM.[23] Due to the varying factors attributed to medication adherence among adolescents, service providers need to thoroughly engage adolescents on adherence issues in order to provide adolescent centered care.[24,25]

Two of our patients defaulted postdischarge clinic reviews and thus discontinuing treatment. This is uncommon as challenges in retention among ALHIV have been documented in studies.[25–29] Our facility had no follow-up mechanism in place to ensure retention in care to follow-up on patients.

4 | CONCLUSION

All our patients presented with persistent global or frontal headaches, neck stiffness with or without pain, photophobia, blurred vision, vomiting, seizures, and loss of consciousness. Though these symptoms are not exclusive to HIV-CM, it warrants a high level of suspicion and therefore investigations to rule it out as a CNS OI.

AUTHOR CONTRIBUTIONS

PP and VJG were involved in the design, planning, data collection, analysis, writing, draft, and final review of the manuscript. IA, BOA, KPB, OO, EA, FL, and AA were involved in the data collection, writing and draft and final review of the manuscript.

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DATA AVAILABILITY STATEMENT

No data are available.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

ETHICS

Ethical approval was obtained from the Institutional Review Board of KBTH (KBTH-IRB/00093/2020).

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy. For patients who died, ethical approval and consent were sought from the hospital to review and extract their clinical data as relatives could not be engaged due to unavailability of contact information.

An informed written consent was obtained from the surviving patient.

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