



RESEARCH ARTICLE

THE CHALLENGES IN THE MANAGEMENT OF CRYPTOCOCCAL MENINGITIS IN RESOURCE POOR SETTINGS: CASE REPORT

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ABSTRACT

Background: Human immune-deficiency virus (HIV) infection continues to be an important risk factor for the development of central nervous system opportunistic infections (OI) especially cryptococcal meningitis which is an AIDS defining illness. Cryptococcal meningitis is an important contributing factor to morbidity and mortality in HIV infected individuals. It is a life threatening disease with a 100% case fatality in the absence of an appropriate treatment regimen. In high income countries, advances in diagnosis and anti-retroviral (ARV) options, availability of recommended antifungals and monitoring has reduced markedly the mortality and morbidity associated with cryptococcal meningitis when compared to morbidity and mortality indices in low income countries. In this case, a 40year old newly diagnosed retroviral disease patient presented with a two weeks history of recurrent headache, projectile vomiting and neck stiffness. She had an associated history of blurring of vision, gradual weakness of the right upper and lower limbs. She was afebrile, not pale or icteric. She had marked neck stiffness. The power on the left upper and lower limbs was 4/5 and 3/5 on the right upper and lower limbs. Her baseline CD4 was 34cells/mm³. Serum Cryptococcal antigen (CrAg) screening and baseline viral load were not done. The cerebrospinal fluid (CSF) Indian ink staining showed yeast cells of cryptococcal neoformans >30cells per high power field. The CSF chemistry and hematology were normal. She was managed as a case of cryptococcal meningitis. She was admitted and commenced on intravenous fluconazole 1.2g daily, tablets cotrimoxazole 960mg daily. She however became progressively restless, lapsed into coma and died on the fifth day on admission. The challenges of managing cryptococcal meningitis in resource poor settings are a cascade of events ranging from late patient presentation, challenges with early diagnosis using modern test kits, cost and availability of recommended anti-fungal as well as monitoring of side-effects. Others are government policies where health sector funding is low and lack of health insurance schemes targeted at lowering cost of care for the low income earners and the disadvantaged in the society.

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INTRODUCTION

The human immuno-deficiency virus (HIV) infection pandemic continues to be the most important risk factor for the development of central nervous system (CNS) cryptococcosis which is an important contributor to morbidity and mortality in these patients. (Lakshmi et al., 2007; Kambugu et al., 2008) Recent epidemiological shifts and an

explosion of the HIV pandemic have resulted in the emergence of cryptococcal meningitis as a major public health problem. (Jarvis et al., 2010; Park et al., 2009) It is the leading cause of community acquired meningitis in Sub-Saharan Africa and South-East Asia. (Park et al., 2009; Perfect et al., 2010; Liechty et al., 2007) Estimates from Sub-Saharan Africa and South-East Asia in the year 2009 suggested that cryptococcal meningitis affects 957,000 people every year with an annual mortality equaling or exceeding that from tuberculosis. (Park et al., 2009; Perfect et al., 2010) Cryptococcal meningitis is a life threatening disease with a 100% mortality rate in the absence

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of approved anti-fungal therapy especially in resource poor settings. (Mwaba *et al.*, 2001) In-hospital acute mortality from cryptococcal meningitis continues to remain high ranging between 30-50% even with anti-fungal therapy. (Kambugu *et al.*, 2008; Perfect *et al.*, 2010; Sorrell and Chen, 2010)

Case presentation

In this case, a 40-year old newly diagnosed retroviral disease patient presented with a two weeks history of recurrent headache, projectile vomiting and neck stiffness. She had no prior history of convulsions or loss of consciousness. She had a history of blurring of vision and gradual weakness of the right upper and lower limbs. She had no history of urinary or faecal incontinence. She had no history of cough, night sweats or contact with a patient with tuberculosis. She had no history of diarrhea, abdominal swelling or pain but she had a history of progressive weight loss prior to onset of the symptoms. She was married with three children in a monogamous setting. The husband is HIV negative. She was a cleaner in a government owned health facility. She had no history of alcohol intake or cigarette smoking. Physical examination showed a young lady, ill-looking, afebrile, anicteric, not pale. She had no oral thrush. She was conscious and alert. She was oriented with severe neck stiffness. Brudzinski's and kernig signs were positive. The power on the left upper and lower limbs was 4/5 while on the right upper and lower limbs 3/5. Her baseline CD4 was 34 cells/mm³. Serum Cryptococcal antigen (CrAg) screening and baseline viral load were not done because the national guideline recommends a viral load six months after ART initiation. The cerebrospinal fluid (CSF) Indian ink staining showed yeast cells of cryptococcal neoformans >30 cells per high power field. The CSF chemistry and hematology were normal. The lumbar puncture opening pressure and intraocular pressures were not measured because there are no facilities for such procedures. She was managed as a case of cryptococcal meningitis. She was admitted and commenced intravenous Fluconazole 1.2g daily, tablets Cotrimoxazole 960mg daily. She however became progressively restless and lapsed into coma and died on the fifth day on admission.

DISCUSSION

Infection with HIV is widespread and a challenge in resource poor countries. (Lakshmi *et al.*, 2007; Kambugu *et al.*, 2008) Various studies conducted in different parts of the world on the prevalence of cryptococcal meningitis in HIV patients reported a range of 2.09 to 68.6%. (Micol *et al.*, 2007; French *et al.*, 2002) The prevalence of cryptococcal meningitis in an Indian cohort study reported a prevalence of 46%. (Thakur *et al.*, 2008) The most common signs and symptoms of cryptococcal meningitis include headache, fever, abnormal behavior, seizure, vomiting and double vision. (Thakur *et al.*, 2008; Adeyemi and Ross, 2014) Others are weakness of the limbs, complete stroke, incontinence, irreversible blindness, deafness and coma. (Lakshmi *et al.*, 2007; Kambugu *et al.*, 2008; Thakur *et al.*, 2008; Adeyemi and Ross, 2014; Carlson *et al.*, 2014) The index patient presented with a history of recurrent headache, vomiting and neck stiffness. She also had a history of blurring of vision and weakness of the limbs. There are several modalities available for the diagnosis of cryptococcal meningitis in HIV infected persons. (Boulware *et al.*, 2014) Diagnosis of cryptococcal meningitis based on microscopy and culture of the antigen. The use of India ink staining remains a common diagnostic tool for identifying

Cryptococcus in CSF, yet the sensitivity is <86%. (Boulware *et al.*, 2014; Kisenge *et al.*, 2007) Although readily available, the use of India ink as the sole means of diagnosis results in misdiagnosis in 1 of every 11 patients presenting with meningitis as reported by a study from Uganda. (Boulware *et al.*, 2014) India ink analysis is insensitive for low fungal burden, which can be common in patients presenting early after symptom onset or those already on ART. (Boulware *et al.*, 2014; Mahsa *et al.*, 2015) The index patient had Indian ink staining that showed cryptococcal neoformans in CSF. Culture is considered the gold standard for the diagnosis of cryptococcal meningitis, but it has several disadvantages. (Boulware *et al.*, 2014; Mahsa *et al.*, 2015; Boulware, 2012) Fungal culture requires laboratory infrastructure, electricity and trained Technicians. Culture can take up to 7 days to grow and the culture plates need to be incubated for up-to 10 days to ensure reliable quantitative count. Culture can also produce false negative results when the fungal burden is low but diagnostic yield can be improved with higher CSF volume. (Boulware *et al.*, 2014; Mahsa *et al.*, 2015; Boulware, 2012) The managing hospital which is a secondary health care facility located in the state capital and responsible for providing health care to patients among whom are HIV patients had no capacity for culturing cryptococcal neoformans. The absence of equipment to culture cryptococcal neoformans is a common finding in most secondary and tertiary care facilities in developing countries Nigeria inclusive.

The detection of cryptococcal antigen (CrAg) in CSF, serum or plasma has become an essential diagnostic tool and should be performed on CSF for all patients with HIV and suspected meningitis or any central nervous system (CNS) symptoms. (Mahsa *et al.*, 2015; Boulware, 2012; Temstet *et al.*, 1992) CSF testing should occur regardless of other CSF parameters. (Mahsa *et al.*, 2015; Boulware, 2012; Temstet *et al.*, 1992) In resource limited settings, the recent development of CrAg lateral flow assay (LFA) has revolutionized cryptococcal meningitis diagnosis. (Mahsa *et al.*, 2015; Boulware, 2012; Temstet *et al.*, 1992) The CrAg LFA is a point of care test that rapidly detects cryptococcal antibodies against *C. neoformans*. It is inexpensive; doesn't need cold chain, has slightly better sensitivity than latex agglutination or enzyme immune-assay, more sensitive at detecting lower CSF antigen levels and takes only 10 minutes to obtain results. In a reported study in Uganda and South Africa, the specificity and sensitivity of CrAg LFA was reported as 99.1% and 99.3% respectively in CSF while the sensitivity in blood was $\geq 99\%$ when positive in CSF. (Boulware *et al.*, 2014; Jarvis *et al.*, 2011; Lourens *et al.*, 2014) Even though CrAg LFA is recommended as point of care test kit, its unavailability in most health care facilities located in resource poor settings makes it difficult to manage patients such as the 40-year old woman who is presented in the case report. In a recent study in Uganda, there was perfect agreement between finger-stick whole blood, serum and plasma CrAg suggesting that testing from finger-stick whole blood is a viable option for detecting antigen CrAg particularly in settings where phlebotomy is not available or in patients with difficult venous access. (Williams *et al.*, 2014) The CrAg LFA has also been evaluated in both urine and saliva but not sufficient to recommend routine screening using these fluids. (Magambo *et al.*, 2014; Kwizera *et al.*, 2014)

In addition to these primary modalities available for diagnosing cryptococcal meningitis, the use of 1-3- β -D Glucan and PCR

are supportive. (Rhein *et al.*, 2014; Rhein *et al.*, 2014) The management of cryptococcal meningitis is done in three phases: induction, consolidation and maintenance therapy. The goal of induction therapy is the rapid sterilization of the CSF. (Mahsa *et al.*, 2015; Bicanic *et al.*, 2009) Current guidelines recommend a two weeks course of high dose amphotericin-B intravenously in combination with flucytosine as first line therapy for the treatment of cryptococcal meningitis. (Perfect *et al.*, 2010) This recommendation is the outcome of studies comparing the efficacy of three different induction agents consisting of a combination of high dose amphotericin-B and flucytosine, high dose amphotericin-B and fluconazole and high dose amphotericin-B monotherapy. Combination therapy with amphotericin B and flucytosine was associated with a <40% lower hazard of mortality at 10weeks. (Mahsa *et al.*, 2015; Day *et al.*, 2013) This regimen remains widely unavailable in most parts of the world especially where the burden of disease is highest, where this medication regimen is available, it is costly and monitoring side effects is a challenge. (Mahsa *et al.*, 2015; Bicanic *et al.*, 2009; Perfect *et al.*, 2010; Day *et al.*, 2013; Rajasingham *et al.*, 2012) For the index patient, high dose intravenous fluconazole was the only option available at the facility where she presented and this may have negatively impacted the outcome of the case management.

The consolidation phase of therapy currently consists of fluconazole 400-800mg every day for a duration of at least 8weeks. (Perfect *et al.*, 2010) Most guidelines recommend starting consolidation therapy after 2weeks of induction therapy, although the start of consolidation therapy is expected to be individualized based on patient response to induction therapy. (Kambugu *et al.*, 2008; Mahsa *et al.*, 2015; Perfect *et al.*, 2010) Guidelines support the use of longer duration of high dose fluconazole throughout the consolidation phase if suboptimal induction therapy is considered; mainly monotherapy with fluconazole or when CSF sterility has not been achieved. (Perfect *et al.*, 2010) The index patient died on the fifth day of admission despite high dose fluconazole. After successful induction and consolidation therapy, it is recommended that culture negative patients should continue oral fluconazole 200mg daily as maintenance therapy. (Perfect *et al.*, 2010) Secondary prophylaxis can be safely discontinued in patients on ART and with undetectable HIV RNA levels for greater than three months, who attain CD4 cell counts of ≥ 100 cells/ μ L. (Perfect *et al.*, 2010) When HIV viral load testing is unavailable, the WHO recommends continuation of maintenance therapy for one year and discontinuation of the therapy when CD4 counts are >200 cells/ μ L. (WHO 2011) Fluconazole maintenance therapy is to be reinstated in patients demonstrating immunologic failure, ART interruptions, or a fall in CD4 counts to below 100cells/ μ L. (Perfect *et al.*, 2010) The index patient had a baseline CD4 of 34cells/ μ L with no HIV RNA done. Another component of cryptococcal meningitis management is the management of raised intracranial pressure. Elevated intracranial pressure (ICP) is defined as CSF pressure ≥ 25 cmH₂O and is a common complication of cryptococcal meningitis. (Loyse *et al.*, 2010) Elevated ICP is most often characterized by headaches, vomiting, papilledema, reduction of visual acuity, blindness, cranial nerve palsy, confusion, altered mental status and coma. (Lakshmi *et al.*, 2007; Kambugu *et al.*, 2008; Thakur *et al.*, 2008; Adeyemi and Ross, 2014; Carlson *et al.*, 2014) The index patient presented with a complaint of recurrent headache, vomiting, blurring of vision and altered mental status. Management of raised ICP should consist of baseline lumbar

puncture and daily therapeutic tap if ICP ≥ 25 cmH₂O using a manometer to monitor the pressure. (Mahsa *et al.*, 2015; Perfect *et al.*, 2010; Lourens *et al.*, 2014) These high-income country guidelines are not very realistic in resource limited settings and hence typically ignored. (Perfect *et al.*, 2010; Day *et al.*, 2013; Rajasingham *et al.*, 2012; WHO 2011) In resource limited settings where manometers are not available, IV tubing or non-invasive methods such as handheld tonometer or ultrasound to measure intraocular pressure can be used as a surrogate for measuring ICP. (Meda *et al.*, 2014; Nabeta *et al.*, 2014) Other methods of decreasing ICP include; the use of ventriculo-peritoneal shunts, acetazolamide, mannitol or corticosteroids. (Mahsa *et al.*, 2015; (Meda *et al.*, 2014; Nabeta *et al.*, 2014) The index patient did not have the benefit of such procedures because the equipment were not readily available. The timing of ART initiation is an important consideration for persons with cryptococcal meningitis because with advanced immune-suppression, people are at high risk of IRIS and eventual death. (Zolopa *et al.*, 2009) ART initiation should however be balanced against the risk for development of paradoxical immune reconstitution inflammatory syndrome (IRIS) (Mahsa *et al.*, 2015; Zolopa *et al.*, 2009) The reported incidence of paradoxical IRIS is highly variable ranging between 8-49%, presenting as soon as 4days and up to 6years after ART initiation. Paradoxical IRIS carries a mortality rate of 0-36%. (Mahsa *et al.*, 2015; Haddow *et al.*, 2010; Longley *et al.*, 2013; Katchanov *et al.*, 2015) Better microbiologic therapy and achieving CSF sterility is a key principle at reducing the risk of IRIS. (Chang *et al.*, 2013) The index patient died before initiation of ART.

Conclusion

Cryptococcal meningitis remains a prevalent opportunistic infection with high morbidity and mortality especially in resource limited settings. Where laboratory infrastructures are not available, the diagnosis of cryptococcal meningitis with CrAg LFA can help detect disease early and rapidly. The high income countries need to consider support for diagnosis and management of cryptococcal meningitis in resource limited countries. This will help to reduce global contribution to morbidity and mortality from resource limited countries as a result of AIDS defining illnesses.

Consent

Written informed consent was obtained from the patient's husband and daughter who knew of her HIV status.

Competing interest

The Authors do not have a competing interest to declare.

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