Published in final edited form as:

Pediatr Infect Dis J. 2016 September ; 35(9): 979–980. doi:10.1097/INF.0000000000001212.

Cryptococcal Meningitis Presenting as a Complication in HIV-Infected Children: A Case Series from Sub-Saharan Africa

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Abstract

Cryptococcal meningitis is a leading infectious disease worldwide as a result of the high burden of HIV and AIDS, although its cumulative incidence is very low in children compared with adults. Very few studies involving the disease in children have been reported including sub-Saharan Africa, with the highest prevalence of HIV infected children in the world. We summarize 5 cases of children diagnosed with cryptococcal meningitis at a tertiary hospital in Harare, Zimbabwe between the 1st of October 2013 and the 30th of September 2014.

Keywords

Children; Cryptococcal meningitis; *Cryptococcus*; HIV

Introduction

Cryptococcal meningitis (CM) is a devastating fungal opportunistic disease found worldwide, especially in sub-Saharan Africa countries which have the highest burden of HIV and AIDS (1,2). It is caused by pathogenic yeast species of the *Cryptococcus* genus with the most commonly isolated species being *C. neoformans* and *C. gattii*. Cryptococcal meningitis is primarily a disease of immunocompromised adults although it has been reported in studies conducted in children living in sub-Saharan Africa (2–4).

In observational studies conducted in South Africa, North and South America, cryptococcosis in children was reported in 2–2.6% of all cryptococcosis cases (3,5). In

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Conflict of Interest: The authors declare no conflict of interest

contrast to the large number of studies that have been conducted in the adult population with HIV and CM coinfection, very few studies have been dedicated to the presentation, progression and management of CM in the children due to the small sample sizes (3).

It is not known how the immunologic status contributes to the development and manifestation of CM in this group of children. Most of the available information on CM in this population is through case reports, case series and retrospective reviews (6). However, although CM is perceived to be common, accurate information on the disease burden in HIV infected children in resource-limited settings including Zimbabwe is scarce. Here we summarize a case series of five patients between the ages of 12 and 16 years diagnosed and treated for CM at a central hospital in Harare, Zimbabwe.

Methods

We conducted a retrospective review of laboratory records of all children presenting with cryptococcal meningitis at a tertiary referral hospital (Parirenyatwa Group of Hospitals) between the 1st of October 2013 and the 30th of September 2014. Patients were identified from hospital laboratory records and medical records. A case was defined as an HIV infected child below the age of 18 years with a positive *Cryptococcus* culture and a positive India ink staining. Common presenting symptoms included headache and vomiting, while others presented with photophobia, seizures and respiratory symptoms. All the cases were managed with standard amphotericin B deoxycholate at a maintenance dose of 1-1.5mg/kg/day and fluconazole at a dose of 300 -800 mg/day. None of the patients received flucytosine, as it is not readily available in Zimbabwe and in most parts of Africa.

Results

Demographic characteristics of the patient case series

Five male patients, median age of 12 (12-16) years, 4 of whom were known to be HIV infected at hospitalization, had a positive India ink staining and positive *Cryptococcus* culture on CSF analysis. All the patients were severely immunosuppressed on hospitalization as indicated by a CD4⁺ count below 20 cells/mm³ in four (80%) of them and 152 cells/mm³ in the other one. Table 1 summarizes the demographics and clinical characteristics at the time of hospitalization.

Presentation and diagnosis—Most of the cases (cases 2, 3, 4 and 5) presented with neurological features namely; headache, vomiting, proptosis, visual loss and seizures. Case 1 presented with respiratory symptoms, which were managed as pneumonia. Five days later, he developed signs of meningeal irritation.

Cryptococcal meningitis was diagnosed through CSF India ink staining and culture in all 5 cases. Four out of 5 isolates were identified as *C. neoformans* with a single isolate of *C. gattii* using creatinine dextrose bromothymol blue thymine (CDBT) media and confirmed using L-canavanine glycine bromothymol blue (CGB) medium (7).

Discussion

Cryptococcal meningitis is a fungal infection with a worldwide distribution as a result of the high burden of HIV and AIDS, though its cumulative incidence is very low in children compared with adults. A retrospective study that was conducted in children in Zimbabwe between 1995 and 2000, before the use of ART, looked at the clinical features and course of illness, but did not relate the clinical outcomes to the *Cryptococcus* species infecting the patient (4). We identified 5 children, 12-16 years of age with HIV and CM coinfection at a tertiary teaching hospital in Harare, Zimbabwe between the period of October 2013 and October 2014.

Of the 5 patients, one patient (case 3) was diagnosed with HIV on admission whereas 4 patients were diagnosed HIV infected before their hospitalization, with age at diagnosis ranging from 8-15 years. All the patients except case 2 had severe immunosuppression, as evidenced by their low CD4⁺ counts. The presence of CM in case 2, in spite of the relatively high CD4⁺ count, could be explained by the fact that *C. gattii* infects and causes disease regardless of immune status (3). Three of the patients (cases 1, 4 and 5) were on second line ART, cases 1 and 4 had first line ART treatment failure and case 5 had a chronic history of defaulting treatment. Case 1 had “unmasking” inflammatory reconstitution disease (IRD) since he presented with CM five months after being initiated on ART and this was due to the immunopathological response to antigens from *C. neoformans* as well as the advanced immunosuppression.

Treatment of CM in children is based on research done in adults where combination therapy with amphotericin B and flucytosine for 2 weeks (induction therapy) followed by fluconazole for a minimum of 8 weeks (consolidation therapy) is used (8,9). The World Health Organization (WHO) guidelines for the treatment and management of CM in children, recommends amphotericin B (0.7-1mg/kg/day) plus flucytosine (100mg/day) or amphotericin B (0.7-1mg/kg/day) plus fluconazole (12mg/kg/day up to 800mg) or fluconazole monotherapy (12mg/kg/day up to 1200mg) if amphotericin B is not available (10). In our patients, dosages for amphotericin and fluconazole were extrapolated using the patient's weight as recommended by the WHO guidelines but the difference in the fluconazole plasma half-life between children and adults (20:30 hours) was not considered (11). Hence there is need for local guidelines for the management of CM in children as most of the patients were probably being under-dosed.

In this case series of children, *C. neoformans* was found in 4 (80%) patients, whilst *C. gattii* was isolated in one patient (case 2). *Cryptococcus* species identification is rarely done in most microbiology laboratories because of the complexity of the biotyping methods and the cost of the reagents. The clinical presentation of the patient infected with *C. gattii* was different from the other 4 patients (cases 1, 3, 4 and 5) that were infected with *C. neoformans*.

In-line with the current WHO guidelines on the use of antiretroviral drugs for treating and preventing HIV-infection, we therefore, recommend early cryptococcal antigen screening before ART initiation in order to reduce cases of cryptococcal meningitis in HIV-infected

children. Clinicians should consider cryptococcal meningitis as a potential cause of meningitis in HIV-infected children particularly those that are severely immunocompromised. It is essential for hospitals in sub-Saharan Africa to carry out annual surveys to determine more accurately the incidence and burden of cryptococcal meningitis in children.

Acknowledgments

We would like also to thank all the clinicians from both the medical and pediatric wards (A4, A5, C5 and C6) of PGH responsible for the management of the patients, medical laboratory scientists from the Microbiology Public health laboratory unit for assisting with the diagnosis.

Sources of Support: This work was supported by Grant number 2U2RTW007367 from the Fogarty International Centre, National Institutes of Health (NIH, USA) through the International Clinical, Operational and Health Services and Training Award (ICOHRTA)

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Summary of the 5 HIV-Infected patients' clinical, laboratory characteristics and outcomes from Cryptococcal Meningitis

Table 1

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	16	12	12	12	14
Age at HIV diagnosis (years)	15	9	12	8	8
Duration of ART (months)	10 (2 nd line ART)	24	0	36 (2 nd line ART)	60 (2 nd line ART)
Signs of meningitis on admission	No history of meningitis	Yes	Yes	Yes	Yes
Co-morbid infections	Pneumonia	None	pseudomembranous candidiasis, tinea corporis, gingivitis	None	None
Baseline CD4 ⁺ cells/mm ³ upon hospitalization	4	152	12	11	14
<i>Cryptococcus species</i>	<i>C. neoformans sensu stricto</i>	<i>C. gatii sensu lato</i>	<i>C. neoformans sensu stricto</i>	<i>C. neoformans sensu stricto</i>	<i>C. neoformans sensu stricto</i>
Outcome	Discharged	Discharged	Died	Discharged	Discharged

ART – Antiretroviral therapy, HIV – Human immunodeficiency virus