PEDIATRIC ONCALL
CHILD HEALTH CARE

ORIGINAL ARTICLE

NEUROMENINGEAL CRYPTOCOCCOSIS IN CHILDREN: CLINICAL AND PROGNOSTIC ASPECTS IN A PEDIATRIC HOSPITAL IN YAOUNDÉ - CAMEROON

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ABSTRACT

Aim: To determine the clinical, paraclinical, and prognostic profile of pediatric neuromeningeal cryptococcosis.

Methods and Material: This descriptive, retrospective study was conducted in children under 15 years of age hospitalized from March 1st, 2010 to March 31st, 2018 for neuromeningeal cryptococcosis in the infectious diseases department of the Mother and Child Center of the Chantal Biya Foundation in Yaounde. Diagnosis of neuromeningeal cryptococcosis was confirmed by direct examination of the cerebrospinal fluid (CSF) and subsequent staining with India ink and/or culture on Sabouraud medium. Hospital records were assessed for clinical features and laboratory parameters. The univariate logistic regression model was used to identify factors associated with prognosis. The significance level of the comparisons was p <0.05.

Results: Total 331 children were hospitalized for infectious meningitis with 12 (3.6%) being confirmed cases of neuromeningeal cryptococcosis. All 12 patients were HIV infected. The mean age at presentation was 11 years with a range of 1-15 years. Clinical manifestations were headache (75%), fever (66.7%), nausea or vomiting (58.3%), convulsions (58.3%), and on clinical examination signs of meningeal irritation (83.5%). All patients had received fluconazole monotherapy. Intra-hospital mortality was 58.3%. Marginally increased cells in the CSF (p=0.04), hypoglycorrhachia (p=0.04), high HIV viral load (p=0.03), and deterioration of consciousness during treatment (p=0.001) were associated with this high mortality.

Conclusion: Neuromeningeal cryptococcosis is a severe opportunistic mycosis in HIV-infected children. In our study, it is associated with a high mortality rate, hence the need for early diagnosis and appropriate treatment to improve the prognosis is needed.

Introduction

Cryptococcosis is a systemic fungus with a subacute or chronic evolution.[1,2,3] It is caused by a neurotropic encapsulated yeast, *Cryptococcus Neoformans*, whose most frequent clinical presentation is meningoencephalitis.[2] This is a common infection in immunocompromised patients, and its incidence has increased with the advent of HIV infection.[4,5,6] The first cases of neuro-meningeal cryptococcosis (NMC) in children in Africa were described in 1996 involving 3 children in Malawi.[7] Although HIV is the leading cause of immunosuppression in Africa and should be routinely investigated, other causes of immunosuppression are possible. These are mainly malnutrition, which is relatively common in sub-Saharan Africa, connective tissue disorders, and visceral or solid tumours.

Depending on the region, NMC is present in 2 to 30% of HIV-infected patients, particularly those with less than 100 CD4+/mm3.[5,8] It is estimated that the disease is responsible for more than 600,000 deaths per year worldwide.[9] In Africa, cryptococcal meningitis is responsible for 13-42% of all deaths in HIV-infected people.[8] Sub-Saharan Africa has the highest estimated annual burden with a median incidence in HIV patients of 3.2% and high mortality of 13-40%.[5] A study in Cameroon showed that 42.2% of patients with the neuro-meningeal cryptococcal disease died within 21 days of diagnosis, despite being on antifungal treatment with fluconazole.[10]

Compared to the number of adults, the number of children who acquire cryptococcosis has been inexplicably low, with fewer than 1000 cases of cryptococcosis described in children, including those

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who are immunocompromised.[11] Vertical transmission of the infection is possible, with a few cases in neonates found in the literature.[12] In Colombia, the reported prevalence was 2.6%.[13] In South Africa, studies have estimated the occurrence of neuromeningeal cryptococcosis to occur in 0.9-2% of cases in children under 15 years of age.[11,14] In Cameroon, most studies of neuromeningeal cryptococcosis have been conducted in the adult population only.[5,10] The aim of our study was to study the clinical, paraclinical, and prognostic profile of neuromeningeal cryptococcosis in children.

Methods & Materials

A retrospective study was conducted from March 1, 2010 to March 31, 2018 after approval of the institutional ethics committee. Included in this study were all children under 15 years of age admitted to the Infectious Diseases Department of the Mother and Child Centre of the Chantal Biya Foundation in Yaounde for neuromeningeal cryptococcosis. All children whose records were incomplete were excluded. The following parameters were evaluated: age, gender, length of stay in the hospital, clinical signs at presentation, cerebrospinal fluid (CSF) examination results, the evolution of the disease, total lymphocyte and/or CD4 lymphocyte counts and/or plasma HIV viral load in known HIV infected children and brain CT scan results. Direct examination of the CSF and subsequent staining with India ink and/or culture on Sabouraud medium and an antifungal culture was performed in all patients at the medical analysis laboratory of the Centre Pasteur of Cameroon. Hypercytorachia was considered when white blood cell count in the CSF greater than 5 cells/HPF, hypoglycorrhachia was considered when CSF glucose level of less than 0.4 g/l and raised intracranial hypertension (ICH) was considered when CSF pressure greater than 15 cm of water. The collection of the treatments used (antifungal and antiretroviral treatment (ART)) the evolution and prognosis of the patients (cure, sequelae, death) completed these variables.

The data were processed with EPI Info 3.3.2 software (CDC Atlanta, USA). Quantitative variables were expressed as means ± standard deviation, with the ranges. Qualitative variables were expressed as numbers and percentages. Comparisons of the qualitative variables were done using the chi-square test, while the quantitative variables were analyzed by the Student's t-test. The univariate logistic regression model was used to retrieve factors associated with prognosis. The significance level of the comparison was $p < 0.05$.

Results

A total of 331 children were hospitalized for meningitis during the study period of which 12 (3.6%) had NMC. The average age of children with NMC was 11 years with a range from 1-15 years. There were 5 boys (41.7%) with a male: female ratio of 0.7. The peak of disease occurrence was in 2017 with 3 cases (25%). All patients were HIV infected. Nine children (75%) were already known to be immunocompromised with HIV and under antiretroviral therapy (ART) but all of them were not complying with the established protocol; on the other hand, 3 (25%) of them were detected to be HIV infected by Elisa during hospitalization for NMC. The common clinical symptoms were headache in 9 (75%), fever in 8 (66.7%), nausea or vomiting in 7 (58.3%), convulsions in 7 (58.3%) and altered sensorium in 5 (41.7%). Clinical examination revealed signs of meningeal irritation in 10 (83.5%), focal neurological signs in 2 (16.7%) and raised intracranial tension in 3 (25%). CSF India ink staining was positive in 11 (91.7%) children; cryptococcal antigen was positive in only one child (8.3%). Culture on Sabouraud substrate revealed the presence of cryptococcus neoformans in all the children. CSF was macroscopically clear in 9 (75%) of cases. Mean CSF glucose was 0.5467± 0.1546 g/l [range 0.35 to 0.55 g/l]. The mean CSF cell count was 8 cells/HPF [range 5-14]. Mean CSF proteins were 0.7658±.3415 g/l [range 0.3 to 1.5]. The median CD4 count was 29 [10-100] cells /µl. The mean value of the HIV viral load was 3867 copies/ml [2084-8000]. Brain CT scan was performed in 4 patients (33.3%) and in each of the cases, one abnormality was found, namely: indirect signs of ICH, left multifocal encephalitis, tri-ventricular hydrocephalus, and progressive multifocal leukoencephalopathy. The average time between the onset of clinical signs and hospitalization was 11 days [range 4.5-14 days] with a median time to care of 4 days after the admission [range 3-6.5 days]. All children received fluconazole antifungal therapy as monotherapy. Seven (58.3%) children had a degradation in the Glasgow coma score in the first week of treatment. Two children (16.7%) had sequelae, which included blindness and psychomotor retardation and 7 (58.3%) died. Hypercytorachia, hypoglycorrhachia, high HIV viral load and deterioration of the Glasgow coma score in the first week of treatment were associated with poor prognosis of children with NMC disease (Table 1).

Discussion

Prevalence of NMC was 3.6% among all patients of meningitis in our study and all of them were HIV infected. The rate of infection in immunocompromised patients can be as high as 5-10%, and as high as 30% in AIDS patients.[16] Joshi et al studied patients

Table 1. Paraclinical and evolutionary factors associated with the prognosis of the study population

Variables	Deaths (n=7)	Survivors (n=4)	P value	OR (95% CI)
Hypercytorachia	0	3 (75%)	0.04	
Hypoglycorachia	4 (57.1%)	1 (25%)	0.04	
Mean HIV viral load (copies/ml)	8000 [Range 4000-10000]	2447 [Range 1652-3335]	0.03	2 (0.19-20.6)
Glasgow coma score deterioration	7 (100%)	0	0.001	

with cryptococcal disease in 42 children›s hospitals in the United States between 2003 and 2008, and the results showed that 16% of the patients were infected with HIV, 63% of the patients had other potential immunodeficiency factors and 21% of the patients were immunocompetent.[15] Our prevalence was similar to the Likasitwattanakul[16], Komi[1] and Mullan[17] studies that found 3% and 2.4% respectively.

In most studies, the mean age of children with the cryptococcal disease was 9.8 years, and a few cases of cryptococcal disease were reported in children younger than 1 year of age.[11] In comparison, we have documented that the highest incidence occurs in children over 10 years of age. This finding may reflect the fact that HIV-related opportunistic infections are more frequent with increasing age and rarely occur in the first two years after HIV infection (except for Pneumocystis carinii pneumonia).[18] This age group corresponds to the period of adolescence during which any medical approach should take into account the underlying physical, emotional, intellectual and psychosocial transformation that is most often responsible for interruptions or even discontinuation of medical care, particularly in the case of long-term illness. Mullan in Botswana and Owusu in Ghana reported similar results.[17,19]

We had a second peak in incidence in children aged 5-10 years. Like most pediatric HIV infections in Cameroon, they are transmitted vertically from mother to child, and since cryptococcosis is a disease characteristic of AIDS, the bimodal distribution of incidence rates of cryptococcosis in children can be explained by the occurrence of cryptococcosis in both rapid and slow progressors of HIV.

In our study, we had a female predominance. This contrasts with data from most studies where the male sex was preferentially affected.[3,11,14,15,16] This male predominance contrasts with the trend toward the feminization of HIV infection. Male dominance is more evident in adults, particularly in the HIV-infected population.[13]

The incidence of AIDS-related cryptococcosis has decreased significantly with the increased use of highly active antiretroviral therapy.[20] Our results showed that most cases of NMC occurred in HIV-infected children with very low absolute CD4+ T-cell counts and that 75% were on ART but not adherent at the time of illness. Immunosuppression was severe, with an average CD4 count of 29 CD4/mm³. Severe immune deficiency with a CD4 count <100 cells/mm³ is very often the main factor in NMC.[1,21] The only associated factor found in all children in our study was HIV immunosuppression. In most studies, virtually all children were immunocompromised against HIV.[11,16,18] In South Africa, 2% of the clinical isolates of cryptococcus species came from children and 96% of them were HIV immunocompromised.[2] This finding confirms the importance of co-infection between NMC and HIV.

The clinical picture of the children in our study was dominated by headache, fever, nausea or vomiting, convulsions, and signs of meningeal irritation. Most studies conducted on children with NMC described a similar picture[16,18,20]. The presence of these clinical signs in an HIV-immunocompromised child should therefore necessitate early detection of NMC. Direct examination with India ink was positive in nine out of 10 cases, but sensitivity was even higher in Sabouraud's CSF culture as reported by Assogba, et al.[1] These results were similar to those reported by other authors and emphasize the relevance of direct and culture studies in the diagnosis of cryptococcosis.[11,16,18,22]

The CSFs were clear, cloudy or xanthochromic with no correlation with the disease as previously observed[5][6,40]. The weak cellular response observed during episodes of cryptococcosis (mean of 8 elements/mm³) expressed a minimal inflammatory response. This was observed in a previous study where about 55% of cases of AIDS-related cryptococcal meningitis had a minimal inflammatory response characterized by <10 lymphocytes/mm³ of CSF.[9] This weak CSF cellular response is thought to be related to the decline in cell-mediated immunity during AIDS.[24] This was the case in our study population where three-quarters of the children showed severe immunosuppression. In several cohorts, nearly half of the HIV-positive patients with cryptococcal meningitis had normal CSF, meaning that an apparently normal CSF should therefore not exclude the possibility of cryptococcal infection.[6,16,23]

We were unable to assess the CBC in these children, but the study by Luo et al found that 46.45% of patients with disseminated cryptococcosis had an increased number of eosinophils in the peripheral blood; therefore, a diagnosis of possible disseminated cryptococcosis should be considered in children with cryptococcosis who had an increased number of eosinophils in the peripheral blood.[20] They also demonstrated that peripheral blood eosinophil levels decreased as the patient's condition improved with clinical treatment, indicating that an increase in the proportion of eosinophils may be a hematologic feature of the acute phase of cryptococcosis and that a decrease in the proportion of eosinophils may contribute to the evaluation of clinical treatment.

In our study, only four children conducted CT scans as this is done at the expense of the parents. Nevertheless, abnormalities were identified. During NMC, brain CT scan is often normal but may show non-specific abnormalities such as micro-abscesses, aspects of inflammatory granuloma of the meninges which, in the context of acute or subacute meningitis, may be of interest.[25]

In our study, we noted a delay in consultation after the onset of the first symptoms and a 4-day delay in treatment which could be explained by the fact that the examinations were paid for by the parents and the vast majority of the population did not have social assistance. This average consultation time was close to that of Gumbo et al, who found a 9-day delay.[6] In our series, the average time between the onset of clinical signs and hospitalization was 11 days, similar to what is reported in the literature, which averaged 10 to 15 days.[5,6,11] In a quarter of the cases, NMC had occurred in patients whose HIV status was unknown, in which case the bacterial origin was mentioned first and only in the absence of clinical improvement under antibiotic

treatment was a fungal etiology sought.

In a review of the characteristics of NMC in sub-Saharan Africa, it was found that fluconazole and amphotericin B were used alone or in combination.[1] Fluconazole is currently widely used alone, at 81.25%,[1,24] as in our study or in combination with flucytosine.[26] One week of amphotericin B plus flucytosine and two weeks of fluconazole plus flucytosine have been effective as induction therapy for cryptococcal meningitis in resource-limited settings.[26] Numerous studies in recent years have noted the superiority of amphotericin B and 5-fluorocytosine over fluconazole or amphotericin monotherapy.[26] This was not the case in our study because the affordability and availability of antifungal molecules limited the use of this dual therapy. A good therapeutic approach is often difficult to achieve in our communities because of the high cost of care and the unavailability of drugs.[1] Amphotericin B is often not readily available and difficult to handle in our regions.[1,24] In a study conducted in Spain in 2000, all five adult patients treated with intravenous amphotericin B in combination with flucytosine and fluconazole were discharged favorably.[27] In a series from Dakar, mortality with fluconazole was high in 71.1% of cases.[24] In children, the treatment is less codified and therefore the management is more delicate. Although there are no controlled studies in children, the results of studies in adults have been extrapolated to children and their use has been recommended by international guidelines for the management of this disease.[28]

In our study, intra-hospital mortality was high, accounting for more than half of the patients. This mortality was significantly associated with hypercytorachia, hypoglycorrhachia, high HIV viral load and deterioration of the Glasgow coma score in the first week of treatment. It is similar to that found by Gumbo et al (43%), where mortality was significantly related to the deterioration of the children's state of consciousness.[6] On the other hand, it was lower than those found by Likasiwattanakul and Joshi who found respectively 28.5% and 9.5% where the initial treatment included combinations of Amphotericin B, fluconazole and 5-fluorocytosine.[15,16] In sub-Saharan Africa, mortality is high with 45.9% of deaths (range 42.2% to 71.1%), with nearly half of the patients dying in most studies.[3,10,21] NMCs suffer from high mortality in the tropical regions of low-income countries.[1] This is due to several factors: the high cost and the unavailability of drugs, the ineffectiveness of adapted treatments and the limited financial resources of affected patients, in addition to the delay in diagnosis due either to a rudimentary technical platform or to non-specific signs of the disease.

Conclusion

Neuromeningeal cryptococcosis is a severe opportunistic fungal infection in HIV-infected children. Its prevalence remains low. It should be considered in the context of headache, a fever associated with meningeal syndrome in HIV immunocompromised children. Mycological examination of the CSF makes it possible to confirm the diagnosis, isolate and identify the yeast and monitor its progress. It has a high mortality rate in this study, hence the urgency for early diagnosis and appropriate treatment to improve the prognosis.

Authors Contribution

All the authors contributed to the realization of this study.

Compliance with Ethical Standards

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