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Prognostic Factors in Neuromeningeal Cryptococcosis at Brazzaville University Hospital

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ABSTRACT

Objective: *Helping to improve the management of neuromeningeal cryptococcosis at Brazzaville University Hospital*

Patients and Method: *Descriptive and analytical cross-sectional study of neuromeningeal cryptococcosis cases hospitalized in the infectious diseases department between January 1, 2021 and October 31, 2024 in HIV-infected patients, receiving or not highly active antiretroviral therapy and having given free and informed consent to participate in the present study.*

Results: *A total of 2170 patients were hospitalized during the study period, including 79 for neuromeningeal cryptococcosis, i.e. 3.6% of admissions. Mean age was 43.7 ± 11 (19-74) years, female (n=45 ;57%), housewife (n=19 ;24.1%), single (n=59 ;74.7%) and urban resident (n=76 ;96.2%).*

Fever (n=30;38%) and disturbed consciousness (n=23;29.1%) were the main reasons for consultation for more than 15 days (29;36.7%). The mean Glasgow score was 9.8 ± 3.2 (2-13), with neck stiffness (n=30;38%). Oral candidiasis (n=22;27.8%) and silky trichopathy (n=33;42%) were present. The CSF was clear in 100% of cases, with mean lymphocyte counts of 85.7 ± 23.9 (14-100) and mean glycorrhaphy of 0.9 ± 0.7 (0.5-4). Direct examination with India ink was positive in 64.6% of cases (n=51), and culture was performed in 5 patients. Cerebral CT scans, when performed (n=21), revealed ventricular dilatation in 14 patients (17.7%). The mean time to treatment was 5.7± 6.1 (1-31) days. Fluconazole was used as monotherapy (n=68;86.1%), combined with Oncotyl (n=12;15.2%). Corticosteroid therapy was prescribed (n=71;89 ,9%). The mean length of hospital stay was 18.9 ± 11.3 (2-44) days, and the outcome was unfavorable in 55.7% of cases (n=44). IRIS and ICH occurred in 10 and 12 cases respectively. Case fatality was 55.7%. Poor prognostic factors were age (p=0.006), ventricular dilatation (p=0.001), radiographic abnormality (p=0.001) and neurological disorders (P<0.0001).

Conclusion: *The hospital prevalence of neuromeningeal cryptococcosis remains high at Brazzaville University Hospital.*

The poor prognostic factors identified are those described in the literature. Lethality remains high, linked to neurological and CT scan disorders. Prevention remains the only effective measure, and involves early detection and management of HIV/AIDS infection.

Keywords
Neuromeningeal cryptococcosis, Prognosis, Prevalence, CHU-Brazzaville.

Introduction
Neuromeningeal cryptococcosis is a deep-seated mycotic infection common in populations immunocompromised by HIV-AIDS, and poses a real public health problem in sub-Saharan Africa [1]. Worldwide, the prevalence of this condition remains high, with 80% of the population having anti-cryptococcal antibodies, but it is those with weakened immune systems who pay the heaviest price, as in the Congo [2]. Its lethality remains high despite the therapeutic strategies available in different contexts. The aim of this study was to determine the current prevalence of CNM in HIV-positive patients and to identify the various prognostic factors for this condition.

Patients and Method
This was a descriptive and analytical cross-sectional study of cases of neuromeningeal cryptococcosis hospitalized in the Infectious Diseases Department between January 1, 2021 and October 31, 2024 in HIV-infected patients, whether or not receiving highly active antiretroviral therapy, who had given free and informed consent to participate in the present study. Data were analyzed using Epi.Info 3.2.0 software. Categorical variables were presented as numbers and percentages, and qualitative variables as mean and standard deviation. Statistical tests were used according to their applicability criteria, particularly for prognostic factors. For all these tests, the significance threshold was set at 0.05.

Results
A total of 2170 patients were hospitalized during the study period, including 79 for neuromeningeal cryptococcosis, i.e. 3.6% of admissions. Mean age was 43.7± 11 (19-74) years, female (n=45;57%), housewife (n=19;24.1%), single (n=59;74.7%) and urban resident (n=76;96.2%). The age distribution of patients is shown in Table 1.

Table 1: Breakdown of patients by age group.

Age group (years)	Fréquency	Percentage (%)
<20	1	1,3
20-29	4	5,1
30-39	25	31,6
40-49	28	35,4
50-59	14	17,7
≥60	7	8,9
Total	79	100,0

Fever (n=30;38%) and disturbed consciousness (n=23;29.1%) were the main reasons for consultation for more than 15 days (29;36.7%). The mean Glasgow score was 9.8 ±3.2 (2-13), with neck stiffness (n=30;38%). Oral candidiasis (n=22;27.8%) and silky trichopathy (n=33;42%) were present. The CSF was clear in 100% of cases, with mean lymphocyte counts of 85.7± 23.9 (14-100) and mean glycorrhaphy of 0.9 ± 0.7 (0.5-4). Direct examination with India ink was positive in 64.6% of cases (n=51), and culture was performed in 5 patients. Cerebral CT scans, when performed (n=21), revealed ventricular dilatation in 14 patients (17.7%) (Figure 1). The mean time to treatment was 5.7± 6.1 (1-31) days. Fluconazole was used as monotherapy (n=68;86.1%), combined with Oncotyl (n=12;15.2%). Corticosteroid therapy was prescribed (n=71;89 ,9%). The average length of hospital stay was 18.9± 11.3 (2-44) days, and the outcome was unfavorable in 55.7% of cases (n=44). IRIS and ICH occurred in 10 and 12 cases respectively. Case fatality was 55.7%. Poor prognostic factors were age (p=0.006), ventricular dilatation (p=0.001), radiographic abnormality (p=0.001) and neurological disorders (P<0.0001) (Table 2).

Table 2: Prognostic factors.

Items	EVOLUTION				OR	IC95%	P-Value
	Death (n=44)		Cured (n=35)				
	n	%	n	%			
Age (years)							
40-59	37	84,1	31	88,6	0,6	0,03-0,8	**0,001**
Corticotherapy	39	88,6	32	91,4	0,7	0,1-3,2	0,6
Psychotherapy	9	20,5	19	54,2	0,2	0,08-0,5	**0,001**
Ventricular dilatation	12	27,3	5	14,2	2,2	0,1-0,8	**0,000**
Fluconazol	27	34,2	21	26,6	0, 8	0,1-2,5	0,5

Discussion
The present study, carried out in the infectious diseases department of the Brazzaville University Hospital, a national reference in the management of neuromeningeal cryptococcosis, an opportunistic infection classifying at the AIDS stage, presents some selection bias due to its nature. Other unidentified care sites, difficulty of access to culture on specific media, missing information in certain patient files. In spite of these classic limitations related to the methodology used, the present work has the merit of lifting the veil on the prognostic factors of neuromeningeal Cryptococcosis in the infectious diseases department of Brazzaville University Hospital.

The prevalence of neuromeningeal cryptococcosis was high in the present study (3.6%), lower than that reported in previous studies carried out in the same department [3]. It appears higher than that reported in 2013 in the infectious diseases department of the FANN National University Hospital in Dakar, Senegal [4]. However, the prevalence of neuromeningeal cryptococcosis remains high in the African sub-region, in line with the literature (5,6). Diagnosis of CNM is based on the analysis of body fluids, particularly the LCS, using several techniques such as direct examination with Indian ink, cryptococcal antigen testing in blood and urine, and above all culture of the LCS on SABOURAUD medium - tests which are still not available in our resource-constrained country, and which largely justify the possibility of missing cases of CNM. These difficulties have been reported by several African authors [3,5,7].

Young adults are the most affected, with a high frequency

among those aged between 40 and 49. This finding corroborates those found in the literature [3,5]. This is the population most affected by HIV infection, which is the main breeding ground for Cryptococcosis in the sub-region. The Infectious Diseases Department is designed to hospitalize adults. According to the literature, the number of children with CNM is very low [8]. This relative resistance of children to infection is difficult to explain, since the fungus is present in the environment and children, like adults, are capable of producing anti-cryptococcal antibodies [8].

The high proportion of CNM cases among women is nothing new, since similar results have been reported in Abidjan, Côte d'Ivoire, and Dakar, Senegal. In any case, these results are largely linked to the feminization of HIV/AIDS infection, which is the main bed of CNM in sub-Saharan Africa, as reported by the World Health Organization [9]

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Patients in low-income professions, with a low standard of living, as well as housewives, are the most affected in the present study. These include the unemployed, pupils/students and blue-collar workers. This finding corroborates that made by several authors in the sub-region [3,4,6,7].

Patients with neuromeningeal cryptococcosis were single in 75% of cases, and married in 11%. As a rule, HIV infection is transmitted heterosexually, and single people are intensely sexual. These data are similar to those found in a study carried out in Abidjan on the epidemiological, diagnostic, therapeutic and evolutionary aspects of neuromeningeal cryptococcosis, and to that already reported in the same department by Ossibi Ibara and colleagues [3,10]. In Senegal, 57.9% of cases involved married couples, and 51.5% polygamous couples [4]. These differences may be explained by socio-cultural particularities specific to the populations studied. Patients with neuromeningeal cryptococcosis were immunosuppressed by HIV in 78.5% of cases. These results are similar to those obtained in the same department and in the African sub-region [3-7]. Western data report the same rates (). Indeed, the prevalence of cryptococcosis remains high in general, since 80% of people worldwide have anti-cryptococcal antibodies, and only those who are immunosuppressed develop the disease [2].

The neurological tropism of cryptococci for the central nervous system is in line with the main reasons for patient consultations. Disturbed consciousness (29%) and fever (38%) were the main reasons for admission. The nervous system remains an antibody-poor tissue, and the anti-cryptococcal antibodies present in the blood are absent in the cerebrospinal fluid, which constitutes a veritable culture broth for cryptococci, justifying the predominance of neurological localization, such as the convulsive seizures found in 15% of cases [3-5].

The long consultation times found in our patients are similar to those reported in the literature. In this study, 36% of patients were seen within more than 2 weeks. In Abidjan, Bissagnéné et al. reported a delay of 19 days, while Soumaré et al. in Senegal reported a delay of 23 days. These long delays can be largely explained by patients' late recourse to health facilities for symptoms they have traditionally consulted or self-medicated, a classic behavior in Africa [11,12].

Cryptococcosis is one of the causes of sub-acute meningoencephalitis with basilar signs, as reported in the literature [11]. We report a high frequency of neurological signs associated with meningeal involvement, notably neck stiffness in the context of fever in 38% of cases, and coma in 19%. These results are similar to those found in the same department in Brazzaville and Burkina Faso by Millogo and colleagues [3,13]. Cerebrospinal fluid was clear in 69% of cases in this study, and 72% of cases in Dakar (4). The clear appearance of CSF in neuromeningeal cryptococcosis is usually found in African series. The results obtained after analysis of the CSF and staining with India ink are similar to those described by Sow in Dakar, Bissagnéné in Abidjan and Kivukutu in the DRC [5,11,14]. However, the sensitivity of direct examination after Indian ink staining is lower than that of culture and antigen testing, which are not available in our context of a country with limited resources. Culture could only be performed in a small proportion of patients, even though its specificity and sensitivity are close to 100%.

Frontal chest radiographs revealed abnormalities in 9 patients. Interstitial syndrome and tuberculous miliaria were present in 18% of cases. The tuberculosis-cryptococcosis association is not new, having already been identified in the same department by Ossibi Ibara and colleagues [3].

Cerebral CT scans revealed scanographic abnormalities such as ventricular dilatation and cortico-subcortical atrophy in the patients. These abnormalities are poor prognostic factors, as reported in the literature [5,6,13]. The first-line treatment for neuro-meningeal cryptococcosis is amphotericin B in its lipid formulation, a drug not available in our context. Fluconazole was used as monotherapy in 86% of patients, and in 15% of cases, it was combined with 5-Fluocytosine. Numerous studies have demonstrated the superiority of the amphotericin B+ 5-fluorocytosine combination over fluconazole monotherapy. The fluconazole+5-fluorocytosine combination is also superior to fluconazole alone, despite greater toxicity [10].

Antiretroviral treatment was administered in 48% of cases. This consisted of the combination of Tenofovir+ Lamivudine+ Dolutegravir in all cases, in accordance with the new World Health Organization guidelines. Under this treatment, 5 cases of immune restoration were identified, justifying the addition of corticosteroid therapy in these patients. The initiation of highly active antiretroviral therapy after diagnosis of cryptococcosis must be early to avoid the occurrence of other opportunistic infections, but must also take into account the risk of inflammatory immune reconstitution syndrome [15]. In cases of confirmed cryptococcosis undergoing treatment, triple antiretroviral therapy should be deferred for 2 to 4 weeks. The length of hospital stay appears long in the present study, and is similar to that obtained in previous studies in the same department and at sub-regional level.

These long delays, which are typical in tropical environments, are partly justified by the late consultation of health care facilities, leaving patients at an advanced stage of immunodepression. The corollary of this is the appearance of opportunistic infections, the management of which is complex in our context of resource-limited countries [3].

Neuromeningeal cryptococcosis remains a serious infection with a high mortality rate. More than half the patients affected by this condition died in the present study, i.e. a case-fatality rate of 55.7%. This result corroborates those obtained by Ossibi Ibara in Dakar and Brazzaville, Eholié in Abidjan and Seydi in Dakar [3,4,5,16]. The poor prognostic factors identified in the present study are similar to those found in the literature. Age (P= 0.006) remains the most frequently identified factor in the African region. Ventricular dilatation (P=0.000) complicates the natural course of cryptococcosis in HIV-immunosuppressed patients.

Conclusion

In the Congo, CNM remains a real public health problem in HIV-immunocompromised populations. Its conventional management still poses the problem of the availability of first-line drugs and diagnostics in our context of a country with limited resources. The prognostic factors identified are in line with those described in the literature. Lethality remains high, due to the intracranial hypertension and immune restoration syndrome specific to the populations concerned. Prevention remains the only cost-effective measure, and requires first and foremost early dete
ction and management of HIV infection.

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