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Current Aspects of Neuromeningeal Cryptococcosis in the Infectious Diseases Unit at Brazzaville University Hospital

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Abstract **Objectives**: To determine the current prevalence of neuromeningeal cryptococcosis (CNM) at the Brazzaville University Hospital and to identify the associated factors. **Patients and method:** This is a cross-sectional, descriptive and analytical study of CNM cases admitted to the infectious diseases unit between January 1, 2018 and March 31, 2021, i.e. 39 months. The diagnosis was made by positive direct examination of the LCS after India ink staining. **Results:** Eighty-three hospitalized patients (3.4% of admissions) with average age 40.5 ± 10.8 years (17-72 years), female (n = 51; 61.4%). The sex ratio was 0.6. They were civil servants (n = 22; 26.5%), single (n = 54; 65.1%). These patients lived in cities (n = 82; 98.8%), with a high school education (n = 42; 50.6%). They were immunocompromised in particular to HIV (n = 78; 94%), leukaemia (n =2; 2,4%), detected in hospital (n = 34; 44.9%) where they consulted for fever and headache respectively in 55 cases (66, 3%) and 44 cases (53%). Glasgow ranged from 8-13 in 34.9% (n = 29). Tuberculosis was the associated opportunistic infection in 25.3% of cases (n = 21). The mean cytorachia was 95.2 ± 200.6 (1-1300) / mm3 and the mean proteinorachia was 1.3 ± 0.9 (0.4-2.6) g / l. LCS pressure was> 250 in 5 cases (6%). The direct LCS examination was positive for all patients (100%). CD4 was <200 in 56.6% (n = 47) Fluconazole was administered between 1200-2000 mg in 72 patients (86.7%) and 15 of them (18.1%) had received a discharge puncture. ART was prescribed in 63.9% (n = 53) and it was combined with TDF + FTC + EFV in 41% (n = 34). The outcome was death in 50.6% (n = 42) due mainly to HIC (n = 16; 19.3%) and related to tuberculosis (p = 0.004). **Conclusion:** CNM remains an opportunistic infection in adults and young people, frequent at Brazzaville University Hospital, occurring after advanced immunosuppression, often in association with tuberculosis. Its lethality is still high in connection with intracranial hypertension. Its prevention involves detection and early management of HIV infection.

Keywords: *Neuromeningeal cryptococcosis, current aspects, CHU, Brazzaville*

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1. Introduction

Neuromeningeal cryptococcosis is a systemic mycosis that mostly affects patients immunosuppressed by HIV in the AIDS stage. It is responsible for fatal subacute meningoencephalitis in the absence of adequate management. It is a pathology of immune restoration [1]. Globally, 80% of the population have anti-cryptococcal antibodies, but not all of them develop the disease. Immunosuppression is therefore an important contributing factor as reported in the literature [2].

In Senegal, the frequency of CNM increased from 2.9% in 2001 to 7.9% in 2003 with a lethality case of 61.4% in 2013 and 57.6% in 2018 [3,4,5].

In Côte d'Ivoire, CNM has experienced significant growth since the advent of HIV/AIDS; its frequency has increased between 1969 1980 from 4 cases to 149 from 1985 to 1993 with a lethality case increasing from 87% to 41.2% since the advent of highly active ARVs [6,7].

In Burkina Faso, the overall prevalence of CNM is 1.8% and the prevalence has declined from 3.1% in 2002 to 0.2% in 2010 [8].

In Congo, the last study carried out in the infectious diseases unit in 2013 showed a prevalence of 4.3% of

adults of average age of 40.2 ± 10.4 (17-64) years and a death case of 74% [9]. Since then, no study has been carried out in this same unit targeting the current situation of this pathology, hence the object of this present work whose general objective was to determine the current prevalence of CNM at the Brazzaville University Hospital and to identify the factors associated with the unfavourable outcome of the patients.

2. Patients and Method

This was a cross-sectional study with a descriptive and analytical aim of CNM cases hospitalized in the infectious diseases unit at Brazzaville University Hospital during the period from January 1, 2018 to March 31, 2021 and diagnosed in the parasitology-mycology laboratory at Brazzaville University Hospital after LCS analysis and staining with Indian ink. The culture on Sabouraud-chloramphenicol medium is not available in our context.

Patients aged at least 17 years regardless of immunological status, receiving or not receiving antiretroviral therapy were included in this study.

The study variables were epidemiological (age, sex, profession, marital status as well as place of residence), clinical (reason for consultation and signs of examination), paraclinical (LCS study, HIV status, CD4), therapeutic and progressive (processing time, dosage of FCZ, antiretroviral molecules, therapeutic results).

Data were processed using EPI info 3.3.2 software (CDC Atlanta, USA) with the determination of descriptive and analytical statistics for all subjects. For all tests, the significance level was set at 5%.

3. Results

3.1. Epidemiological Data

During the study period, 2,440 patients were hospitalized including eighty-three patients for CNM (3.4% of admissions), mean age 40.5 ± 10.8 years (17-72 years), female (n = 51; 61.4%), male (n = 32; 38.6%) (Table 1). They were civil servants (n = 22; 26.5%), jobless (n = 16; 19.3%), housewife (n = 15; 18.1%). The marital status is shown in Figure 1. These patients lived in the city (n = 82; 98.8%), having a secondary education (n = 42; 50.6%) and primary schooling (n = 31; 37.3%).

3.2. Clinical Data

The patients were immunosuppressed to HIV (n = 78; 94%), leukaemia (n =2; 2,4%), detected in hospital (n = 34; 44.9%) where they consulted for fever and headache respectively in 55 cases (66.3%) and 44 cases (53 %). Glasgow was between 8 to 13 in 34.9% (n = 29) and <8 in 2 cases (2.4%). In 33 patients (39.8%) meningeal stiffness was noted with Kernig's sign present (n = 17; 20.5%) and neurological deficit (n = 15; 18.1%). Signs of immunosuppression were prurigo (n = 37; 44.6%), oral thrush (n = 24; 28.9%) and silky trychopathy (n = 43; 51.8%). The crackling rales were present in 20.5% of cases (n = 17). Tuberculosis and toxoplasmosis were the associated opportunistic infections in 25.3% of cases (n = 21) and 6% (n = 5), respectively.

3.3. Paraclinical Data

The mean cytorachia was 95.2 ± 200.6 (1-1300) / mm3 and the mean proteinorachia was 1.3 ± 0.9 (0.4-2.6) g / l. LCS pressure was> 250 in 5 cases (6%). The direct LCS examination was positive in all patients (100%). CD4 was <200 in 56.6% (n = 47) for a mean of 210.7 ± 46.2 (199-499). Patients were immunosuppressed by HIV in 78 cases (94%) and there was HIV1 in 67 cases (85.9%), dual in 10 cases (12.8%) and HIV2 in 1 case (1.3%). They were diagnosed with HIV during hospitalization in 44.9% of cases (n = 35). The brain scan when it was performed, had objectified the image of abscess cockade in 5 cases. The Genexpert in gastric tubing fluid had identified Mycobacterium tuberculosis without resistance to rifampicin in 21 cases (25.3%).

3.4. Therapeutic Data

Fluconazole was the only antifungal available and administered between 1200-2000 mg in 72 patients (86.7%) and 15 of them (18.1%) had received a lumbar discharge puncture. ART was prescribed in 63.9% (n = 53) and it was coupled with the combination of TDF + FTC + EFV in 41% (n = 34). Dolutegravir (DTG), a new molecule recommended as first-line treatment, was administered in combination with Tenofovir (TDF) and lamivudine (3TC) in 13 cases (4.8%). Fifty-five patients (66.3%) were on bactrim chemoprophylaxis. The mean time to anti-crypto treatment after HIV was 32.3 ± 11.8 days.

3.5. Evolving Data

The mean hospital stay was 38, 5± 10,3 days (6-42). The outcome was favourable in 45.8% of cases (n = 38). The immune restoration syndrome was found in 6 cases (7.2%). The overall lethality case was 54.2% (n = 45) due mainly to intracranial hypertension (n = 16; 19.3%) and anaemic shock (n = 9; 10.8%). It was higher in women with a statistically significant association with tuberculosis (Table 2).

Table 1. Distribution of patients according to age and sex

Age scale	Sex				Total	
	M		F			
	n	%	n	%	n	%
17-29 years	3	9,4	11	21,6	14	16,9
30-39 years	7	21,9	20	39,2	27	32,5
40-49 years	11	34,4	13	25,5	24	28,9
50-59 years	10	31,3	5	9,8	15	18,1
60-69 years	1	3,1	1	2;0	2	2,4
≥70 years	0	0	1	2,0	1	1,2
Total	32	100	51	100	83	100

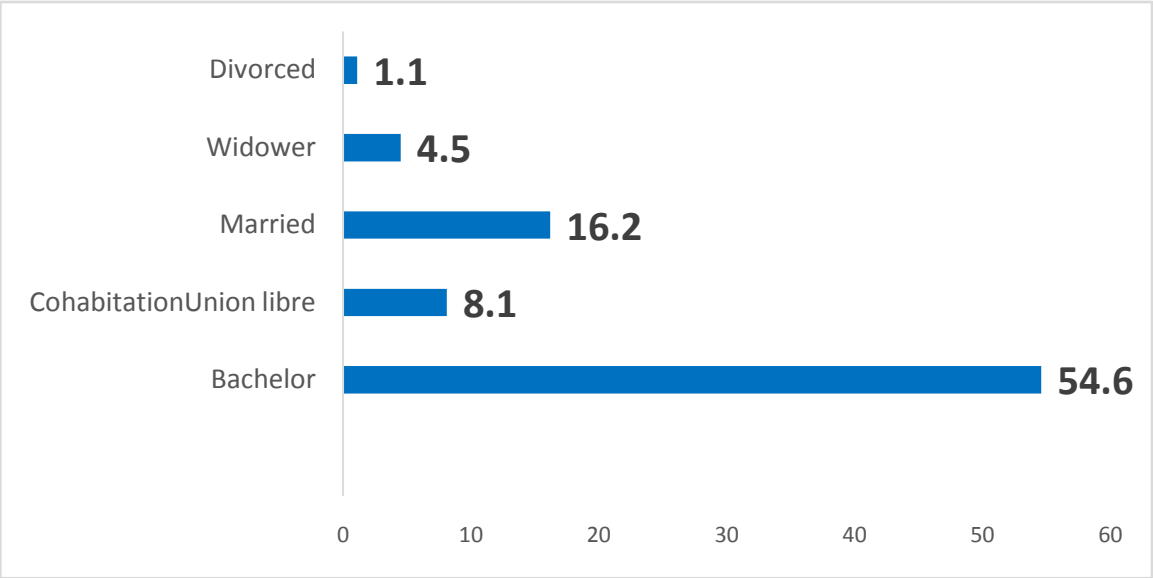

Figure 1. Distribution of patients by marital status

Table 2. Factors associated with the therapeutic outcome

	Evolution		OR	IC95%	P-value
	Death	Cured			
	n(%)	n(%)			
Sex					
M	17(40,5)	13(34,2)	1,3	0,5-3,2	0,5
F	25(59,5)	25(65,8)	0,7	0,3-1,9	0,5
Opportunistic Infections					
Tuberculosis	15(35,7)	6(15,8)	2,9	1,01-8,6	**0,04**
Coccidiosis	2(4,8)	1(2,6)	1,8	0,1-21,2	0,6
Toxoplasmosis	1(2,4)	1(2,6)	0,9	0,05-14,9	0,9
HIV					
Positive	41(97,6)	34(89,5)	4,8	0,5-45,2	0,1
Negative	1(2,4)	4(10,5)	0,2	0,02-1,9	0,1
India ink					
Positive	42(100)	36(94,7)			0,1
Negative	0(0,0)	2(5,3)			0,1
GenXpert					
Positive	7(16,7)	3(7,9)	2,3	0,5-9,7	0,2
Negative	35(83,3)	35(92,1)	0,4	0,1-1,7	0,2
Discharge Puncture					
Yes	5(11,9)	8(21,1)	0,5	0,1-1,7	0,2
No	37(88,1)	30(78,9)	1,9	0,5-6,6	0,2
Glasgow					
<8	1(2,4)	1(2,6)	0,9	0,05-14,9	0,9
≥8	41(97,6)	37(97,4)	1,1	0,06-18,3	0,9
Cytology					
<10	9(21,4)	7(18,4)	1,2	0,4-3,6	0,7
≥10	33(78,6)	31(81,6)	0,8	0,2-2,4	0,7
FCZ					
400-1200	8(19,0)	3(7,9)	2,7	0,6-11,2	0,1
˃ 1200-2000	34(81,0)	35(92,1)	0,3	0,08-1,4	0,1
TARV					
Yes	29(69,0)	22(57,9)	1,6	0,6-4,06	0,3
No	13(31,0)	16(42,1)	0,6	0,2-1,5	0,3
Bactrim Chemoprophylaxis					
Yes	28(66,7)	24(63,2)	1,1	0,4-2,9	0,7
No	14(33,3)	14(36,8)	0,8	0,3-2,1	0,7

4. Discussion

The prevalence of CNM remains high in the infectious diseases unit at Brazzaville University Hospital. It is lower compared to that found in 2013 [9]. This always concerns adults-young people linked to HIV infection affecting a sexually active population. Contrary to 2013 data and those in the literature, women are the most affected by CNM, although it seems that genetic and hormonal factors protected this population [3,10].

The female predominance here may be related to the feminization of HIV infection which is the bed of the onset of cryptococcosis [11]. Single people represented more than half of the patients concerned with a low socioeconomic level; which corroborates the data in the literature [7,9,12]. CNM is still an affection for the subject immunocompromised by HIV whose main reasons for late consultation remain fever and headaches. The long consultation times observed are similar to those found at the level of the sub-region, the reasons being denial of the disease, hidden consultations and the low socio-economic level preventing consultation in a hospital structure [4,9].

Almost half of the patients were tested HIV positive during per-hospitalization, thus distorting the first item of the WHO 90-90-90 objective which expects that 90% of seropositive patients be aware of their serological status within the deadlines by means of early detection [12]. The CNM always carries out a meningoencephalitis characterized here by the disorders of consciousness and a stiffness of the neck found in the patients. The association of CNM with other opportunistic infections such as tuberculosis and toxoplasmosis found in the present study is not a new fact since it has been reported in Dakar and Abidjan [5,9]. We must welcome the advent of Genexpert which, in the present study, permitted to reveal 21 cases of tuberculosis in patients with a persistent infectious syndrome associated with crackling rales in cases of CNM. Advanced immunosuppression justifies this possible association since 56.6% of patients had CD4 counts <200 / mm3 on admission. All cases of CNM were confirmed by direct examination of the LCS after India ink staining. Sensitive examinations such as culture on Sabouraud-Chloramphenicol medium and cryptococcal antigenemia, not available in our context, would have enabled the identification of other cases. These difficulties linked to the weakness of the technical platform are also recognized elsewhere [5,13].

Fluconazole is still the only antifungal molecule available in Congo and it has been used in large doses in 86.7% of cases. No adverse effects were found in these patients. The first-line treatment for CNM is based on polyenes, in particular amphotericin B combined with 5-fluorocytosine. This combination has always been shown to be effective compared to fluconazole alone [14]. In Malawi, the combination of Fluconazole and Flucytosine significantly reduced the death rate within 2 weeks of its introduction [15]. In order to reduce intracranial hypertension, lumbar discharge punctures have been performed in some patients in 18% of cases. These punctures were conditioned by measuring the pressure of the LCS at the patient's bed by means of an infuser as shown in Figure 2. The pressure measurement of the LCS can also be done in a seated position or in lateral decubitus. The advantage here is to easily collect the liquid with good pressure. Antiretroviral treatment had been prescribed in 64% and it was the TDF + combination. FTC + EFV in 41% of cases. Currently, WHO recommends the combination TDF + 3TC + DTG as first-line antiretroviral therapy in adults - young people, as found in other series [16].

The long observation times found in patients are related to the advanced immunosuppression caused by late consultations. This corroborates previous work carried out in the same unit and elsewhere [4,7,9].

Figure 2. Bedside LCS Pressure Measurement Technique (Source: photo Dr. Ossibi Ibara)

Eight years later, the prognosis of CNM remains poor since we find a lethality of 54.2% in connection with intracranial hypertension itself favored by the component of the polysaccharide capsule which induces deleterious effects for the host. Note that this lethality is lower compared to that obtained in 2013, namely 74%. This difference can be explained partly by the high number of lumbar puncture of discharge associated with the availability of antifungal molecules in the unit. Our study found a high lethality in women and in association with tuberculosis with a statistically significant difference. The current lethality of CNM is 61.4% in Senegal and 41.2% in Cote d'Ivoire. The methodological, diagnostic and therapeutic differences largely justify these lethality rates observed at the sub regional level [4,7].

5. Conclusion

CNM is still a frequent disease responsible for high lethality at Brazzaville CHU despite the availability of ARVs. Its prognosis remains severe in connection with other associated infections such as tuberculosis. This shows the value of early detection and management of HIV infection.

Conflict of Interest

The authors declare that they have no conflict of interest in relation to this study.

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