

## Epidemiological, Clinical and Paraclinical Outcomes of Neuromeningeal Cryptococcosis among HIV Inpatients at the Armed Forces Training Hospital Omar BONGO ONDIMBA in Gabon

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### ABSTRACT

**Background:** The Human Immunodeficiency Virus (HIV) is a chronic pathology, progressively evolving towards a severe immunodepression without antiretroviral treatment. This severe immunodepression corresponds to the Acquired Immunodeficiency Syndrome (AIDS) stage, which favoring the occurrence of opportunistic infections. like Cryptococcosis, a systemic fungal infection with a neuromeningeal tropism due to a mycosis called *Cryptococcus neoformans* (opportunistic yeast fungus). In Gabon, the last study was conducted in 2016 at Lambaréné Hospital Center, where the authors reported two cases of neuromeningeal cryptococcosis (NMC) with HIV in a rural area, who were not adhering to antiretroviral treatment (ART).

**Objective:** Determine the prevalence, clinical and paraclinical feature of Neuromeningeal Cryptococcosis (NMC) associated with people living with HIV (PLHIV) in the internal medicine department.

**Materials and Methods:** This were a retrospective study of adult inpatient who presented with neuromeningeal cryptococcosis associated with HIV in the internal medicine department of HIA-OBO over a period of 6 years from December 01, 2015 to December 31, 2021.

**Results:** The prevalence was 8,4%. We collected 6 PLHIV inpatients, two men and four women. The most affected age group was 40 to 50 years old with a female predominance. The clinical feature was dominated by the deterioration of the general state (100%), headaches (50%), hemiplegia and fever in 50% of the cases. The main CSF cytochemical outcome were hyperproteinorachia (100%) and hypoglycorachia (83.3%). The diagnosis of NMC was suspected on clinical and biological signs, then confirmed with the identification of cryptococci either by a direct exam with India ink or by culture of the CSF (83.3%). The level of CD4 cells was  $\leq 100$  cells/mm<sup>3</sup> in 66.7% of cases. Thus, classifying PLHIV with this opportunistic disease at stage C3 AIDS according to the CDC Atlanta classification.

**Conclusion:** The clinical signs, the HIV context, the stage of clinical and immunological immunosuppression in PLHIV helped in the diagnosis of NMC; confirmed by the results of direct examination (India ink test) and/or CSF culture on Sabouraud medium to detect *Cryptococcus neoformans*.

**Keywords:** Neuromeningeal cryptococcosis; HIV/AIDS; Cerebrospinal fluid; India ink; Gabon

## INTRODUCTION

The Human Immunodeficiency Virus (HIV) is a major public health problem worldwide.<sup>[1]</sup> In 2020, the number of people living with HIV (PLHIV) was estimated at 37.7 million, of which more than two thirds, or 25.4 million, are in Africa.<sup>[1]</sup> HIV is a chronic pathology, progressively evolving towards severe immunosuppression in the absence of antiretroviral treatments; this severe immunosuppression corresponds to the phase of Acquired Immunodeficiency Syndrome (AIDS), thus favoring the occurrence of opportunistic pathologies. This is particularly the case of Cryptococcosis, a systemic fungal infection with neuromeningeal tropism due to a mycosis called *Cryptococcus neoformans* (an opportunistic yeast-like fungus)<sup>[2,3]</sup> This fungal infection is generally associated with the advanced stages of HIV/AIDS and can reveal HIV infection in 29% of cases and the United States (USA) and 15 to 35% in Central Africa<sup>[2,3,4]</sup> In Africa, and particularly in sub-Saharan Africa. Mortality linked to neuromeningeal cryptococcosis (CNM) is 100% in the absence of adequate treatment and 20 to 40% despite treatment. In a tropical context, any delay in early diagnosis and treatment further increases the risk of mortality related to this opportunistic condition in PLHIV<sup>[4]</sup>

In a tropical context, any delay in early diagnosis and treatment further increases the risk of mortality related to this opportunistic condition in PLHIV.<sup>[4]</sup> The clinical forms of cryptococcosis are multiple, the most frequent being the cerebro-meningeal, cutaneous and pulmonary forms.<sup>[5]</sup> In Gabon, very few studies on the prevalence of neuromeningeal Cryptococcosis in PLHIV are available. The latest was in 2016, which reported 2 cases of Cryptococcosis with HIV, not adhering to antiretroviral treatment at Lambaréné Hospital.<sup>[6]</sup>

In these circumstances, we conducted a retrospective study at the Omar BONGO ODIMBA Army Training Hospital to determine the prevalence, clinical and paraclinical features of neuromeningeal cryptococcosis (NMC) among people living with HIV (PLHIV) in the internal medicine department.

## PATIENTS AND METHODS

### Type-setting-study period

This was a retrospective, single-center study of patients living with HIV who presented with neuromeningeal cryptococcosis between December 2015 and December 2021.

### Patients

The study population consisted of all PLHIV aged over 18, admitted to hospitalization in the internal medicine department of the Omar BONGO ONDIMBA Armed Forces Training Hospital (HIA OBO) during the period of study.

### Objective and study variables

The main objective was to determine the epidemiological aspects; identify the clinical signs and paraclinical signs of neuromeningeal cryptococcosis in PLHIV and assess immunosuppression using clinical categories and

TCD4 lymphocyte cell counts, according to classification from Atlanta CDC in the Department of Internal Medicine at HIA-OBO.

The variables studied were age, sex and profession on the one hand, and functional, general signs and physical signs suggestive of meningitis or meningoencephalitis on the other. This study also included cerebrospinal fluid (CSF) samples, Indian ink test, and culture on Sabouraud medium, as well as blood samples for cryptococcal antigen, CD4 T lymphocyte assay, and brain scan with and without injection of contrast medium. Additionally, HIV immunocompromised status was confirmed by HIV serology, whether it was discovered pre- or per-hospitalization, and whether or not the individual was receiving antiretroviral treatment.

The diagnosis of NMC was made based on the presence of encapsulated budding yeasts after a direct examination with India ink. The detection of the cryptococcal antigen was performed using an agglutination test, and the culture was conducted aseptically on Sabouraud medium to confirm that the strains were indeed cryptococci.

### **Data analysis**

Data analysis was conducted using Epi Info software version 6.04 (CDC/WHO).

### **Ethical considerations**

Permission to access patient records during the study period was obtained from the head of the HIA OBO.

## **RESULTS**

We collected seventy-one records of HIV patients presenting with clinical aspects of meningitis or meningoencephalitis from the internal medicine department of the HIA OBO. All patients were of the HIV-1 serotype. Among this population, six HIV-positive patients presented with neuromeningeal cryptococcosis, resulting in a prevalence of 8.45%.

### **Sociodemographic aspects**

The age group most affected was 40-50 years old, accounting for 50% of cases, followed by those over 50 years old at 33.3% and 30-40 years old at 16.7%. The age range of patients was 36-55 years old. Women were more represented than men, making up 66.7% (n=4) of cases, with a sex ratio of 0.5 (male/female). The most common profession among patients was housewife, accounting for 33.3% of cases. Other professions were hairdresser (16.6%), accountant (16.6%), mechanic (16.6%), and construction worker (16.6%).

### **Clinical and morphological feature**

The most common clinical signs were headaches (50%), followed by nausea (16.7%), vomiting (16.7%), and photophobia (16.7%). On admission, fever was present in 50% of patients. All HIV-positive patients had a deterioration in their general condition. One patient had an altered state of consciousness (16.7%). Motor deficits, such as hemiplegia, were identified in 50% of cases, followed by neck stiffness (33.3%) and restlessness (33.3%). Kernig's sign and delirium were observed in 33.3% of cases. A brain scan was performed on all patients, and it was normal in 83.3% (n=5) of the cases."

**CSF analysis after lumbar puncture and cryptococcus antigen assay in the blood**

Lumbar puncture with Cerebrospinal Fluid (CSF) analysis was performed in 5 (83.3%) of our patients. The macroscopic appearance of CSF was clear (or crystal water) in 66.7% (n=4) of samples. Hyperproteinorachia was observed in 83.3% (n=5) (Table 1), hypoglycorachia in 83.3% (Table 2); Indian ink test was positive in 66.7% (n=4) (Table 3) and CSF culture on Sabouraud medium was sterile in 66.7% (n=4) of patients (Table 4). The cryptococcal antigen in the blood had not been achieved in 83.3% of patients (Table 5).

**Immunological outcomes among PLHIV**

According to the Atlanta CDC (Centers for disease control) classification, 66.7% (n=4) of PLHIV who underwent a TCD4 lymphocytes blood test had a rate less than or equal to 100 cells/mm<sup>3</sup>. All patients were classified as C3 due to a TCD4 level less than 200/mm<sup>3</sup> and the presence of a cryptococcosis infection (Table 6).

**Table 1:** Distribution of patients according to proteinorachia

Proteinorachia (g/L)	Effective	Pourcentage %
[0,5-1,5[	2	33,3
[1,5-3[	2	33,3
≥ 3	1	16,7
Not done	1	16,7
<b>Total</b>	<b>6</b>	<b>100</b>

**Table 2:** Distribution of patients according to glycorachia

Glycorachia (g/L)	Effective	Pourcentage %
[1-2 [	5	83,3
Not done	1	16,7
<b>Total</b>	<b>6</b>	<b>100</b>

**Table 3:** Breakdown by Indian ink test

Indian ink test	Effective	Pourcentage %
Positive	4	66,7
Negative	1	16,7
Not done	1	16,7
<b>Total</b>	<b>6</b>	<b>100</b>

**Table 4:** CSF culture on Sabouraud medium

CSF culture on Sabouraud medium	Effective	Pourcentage %
Positive culture	1	16,7
Sterile	4	66,7

Not done	1	16,7
<b>Total</b>	<b>6</b>	<b>100</b>

**Table 5:** Cryptococcal Antigen in the blood

Cryptococcal Antigen in the blood	Effective	Pourcentage %
Positif	1	16,7
Not done	5	83,3
<b>Total</b>	<b>6</b>	<b>100</b>

**Table 6:** CDC Atlanta classification

TCD4 cells (/mm <sup>3</sup> )	Effective	Pourcentage%	CDC
≤ 100	4	66,7	C3
>100	1	16,7	C3
Not done	1	16,7	C3
<b>Total</b>	<b>6</b>	<b>100</b>	<b>C3</b>

## DISCUSSION

We conducted a retrospective study on the epidemiological, clinical and paraclinical profiles of HIV-positive patients hospitalized for neuromeningeal cryptococcosis over a period of 6 years, from December 2015 to December 2021, in the Internal Medicine department of the HIA OBO. In this study, the prevalence of neuromeningeal cryptococcosis was 8.45% among PLHIV.

Our results were higher than those reported by Minta et al in Mali and Bedia-Tanoh et al in Côte d'Ivoire, who reported respectively 5,1% in 2011, 3.6% in 2018.<sup>[7,8]</sup>

Our findings can be attributed to the high prevalence of HIV in Gabon, which is estimated at 3% [2.4-3.9] among adults aged 15-49 in 2021.<sup>[9]</sup> The most affected age group was between 40 and 50 years old. This could be due to the fact that cryptococci has become a marker of HIV infection and that this age group is likely more sexually active.<sup>[10]</sup>

In our study, female patients predominated (66.7%) compared to male subjects, with a sex ratio of 0.5 (Male/Female). This is similar to what was observed by Gbangba-Ngai et al. in Bangui (67.8%),<sup>[11]</sup> and by Ossibi Ibara et al. in Brazzaville (57.3%).<sup>[12]</sup> This female predominance can be explained by the feminization of HIV infection in sub-Saharan Africa, and specifically in Gabon. In 2021, Gabon had a prevalence of 4.6% [3.6-6.0] among women aged 15-49, compared to 1.5 [1.0-2.0] among men.<sup>[9]</sup>

In our series, the most common profession among patients was housewife, accounting for 33.3% of cases. This was similar to what was observed by Minta et al. in Mali, where 28.6% of patients with NMC were housewives.

<sup>[7]</sup> These results may be attributed to economic, educational, psychological, and socio-cultural factors that disproportionately affect this female population.<sup>[11]</sup>

However, both women and men were equally likely to be infected with *Cryptococcus* spp. Our study also found that all HIV-positive patients were involved in community activities (such as mechanics, hairdressers, construction workers), which may have exposed them to the presence of this pathogen in the environment. All HIV-positive patients had an altered general condition upon admission, i.e., 100% of cases. The most common symptoms observed were headaches, fever, and motor deficit (hemiplegia).

Our results were similar to those of Konate et al. in Côte d'Ivoire, who found fever as the predominant symptom in 100% of cases.<sup>[12]</sup> Kadjo K et al. in Côte d'Ivoire and Ondounda M et al. in Gabon also reported headaches as the most common symptom in NMC, with 95.4% and 100% of HIV-positive cases respectively.<sup>[13,14]</sup> Additionally, Gbangba-Ngai et al. in Bangui reported a predominance of headaches in 98.3% and fever in 95% of NMC among HIV-positive individuals.<sup>[11]</sup>

Our results were in agreement with those of Minta et al. in Mali, who reported a predominance of headaches in 85.7% of CNM cases.<sup>[7]</sup> This could be due to intracranial hypertension caused by the pathogen. Motor deficits and neck stiffness were observed in 50% and 33% of cases, respectively. These findings were similar to those reported by Sow et al. The presence of neurological deficits may indicate the location and severity of cryptococcal neurological lesions.<sup>[15]</sup> The analysis of CSF showed a clear liquid with hyperproteinorachia, hypoglycorachia, and the presence of encapsulated yeasts on direct examination after staining with Indian ink. This cytochemical presentation of CSF is characteristic of NMC as a type of clear fluid meningitis.<sup>[13,10]</sup>

It is therefore important to repeat the lumbar puncture while respecting strict aseptic gestures as proposed by certain authors, in the face of a sterile CSF, clinical signs of neuromeningeal expectation, the HIV background and severe immunosuppression that may raise suspicion of NMC. Therefore, repeating the lumbar puncture could improve the profitability of this examination.<sup>[16]</sup>

Only one of our patients had a negative direct India ink examination. In this context, the diagnosis of NMC was based on a set of clinical and morphological arguments (brain scan) then confirmed secondarily by CSF culture on Sabouraud-chloramphenicol medium. This could be explained by the low amount of cryptococci in the CSF. It is therefore important to repeat the lumbar puncture while respecting strict aseptic gestures as some authors suggest, in the face of a sterile CSF, clinical signs of neuromeningeal expectation, the HIV background and severe immunosuppression which may lead to suspicion of NMC. Thus, repeating the lumbar puncture could improve the profitability of this examination.

If the technical platform allows it, in the event of negativity of the direct examination, the diagnosis will then be confirmed either by the presence of soluble cryptococcal antigens by the latex particle agglutination test in the CSF which has a sensitivity and a specificity between 90 to 95% or by culture of CSF on Sabouraud medium, the sensitivity and specificity of which are close to 100%.<sup>[12,17-20]</sup>

The latter will then be carried out for diagnostic and subtractive purposes to improve patients' headaches. If the technical platform allows it, in the event of negativity of the direct examination, the diagnosis will then be confirmed either by the presence of soluble cryptococcal antigens using the agglutination test for latex particles

in the CSF which has a sensitivity and a specificity of between 90 to 95% or by CSF culture on Sabouraud medium where the sensitivity and specificity are close to 100%.<sup>[12,17-20]</sup>

A TCD4 lymphocyte count of less than or equal to 100 cells/mm<sup>3</sup>, or 66.7%, was found in four of six NMCs among the HIV population with extremes ranging from 10 to 176 cells/mm<sup>3</sup>.

All patients had been classified at stage C3 according to the Atlanta CDC classification, due to an objective TCD4 level of less than 200/mm<sup>3</sup> and the presence of a cryptococcosis infection. These results were in agreement with certain authors of the literature and could confirm the fact that NMC in the HIV population would readily occur at an advanced stage of immunosuppression, therefore at an AIDS stage with a low TCD4 lymphocyte count  $\leq$  100 cells/mm<sup>3</sup>.<sup>[21, 5]</sup>

## CONCLUSION

Despite its small sample size, this monocentric observational study confirms the data found in literature, particularly studies conducted by certain authors in sub-Saharan Africa, showing that neuromeningeal cryptococcosis is a common infectious emergency in tropical diseases, specifically during the severe immunosuppression stage of HIV/AIDS.

Therefore, it is important to systematically search for neuromeningeal cryptococcosis in the presence of any febrile or non-febrile meningial syndrome, or even in the presence of headaches associated with fever in people living with HIV (PLHIV). To confirm the diagnosis of neuromeningeal cryptococcosis, we relied on the results of direct examination (India ink test) and/or culture of cerebrospinal fluid (CSF) on Sabouraud medium for the detection of *Cryptococcus neoformans*."

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