

Full Length Research Paper

Seasonal variations in cryptococcosis diagnosis in the CeDReS laboratory of the University Hospital of Treichville in the era of HAART: A retrospective study from 2011 to 2018

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Cryptococcal meningitis, the second leading cause of death in people living with advanced-stage HIV infection, was the focus of the current study aimed at assessing the features of patients with this condition at the CeDReS laboratory. Participants were individuals with confirmed diagnoses of cryptococcal meningitis conducted by the CeDReS laboratory of the University Hospital of Treichville, in Abidjan, Ivory Coast. The study spanned cases reported from January 2011 to December 2018, with data collection performed using the computerized laboratory information system. Among the 2,623 participants with suspected meningitis, 290 cases were identified as cryptococcal meningitis (11.2%). The frequency of cryptococcal meningitis increased from 5.8% in 2011 to 15.2% in 2017, coinciding with a rise in the number of people living with HIV referred to the laboratory. Notably, while the prevalence of cryptococcal meningitis was on the rise, the number of participants under anti-retroviral therapy remained consistent throughout the study period. The median CD4 T cell count was 56/mm³. Most cases of cryptococcal meningitis were diagnosed during the months of February (29 out of 202, 14.4%) and June (40 out of 243, 16.5%). In Ivory Coast, February is considered the warmest month, while June is one of the rainiest. These results serve as a crucial database on the seasonal occurrence of cryptococcal meningitis in Ivory Coast and provide a foundation for comparison studies between clinical and environmental isolates.

Key words: Cryptococcosis, positivity rate, dry season, wet season, HIV/AIDS.

INTRODUCTION

Over the past two decades, antiretroviral therapy (ART) has been massively scaled up in low- and middle-income

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countries. By the end of 2022, almost 39 million people globally were receiving ART (UNAIDS, 2023). In line with the 90-90-90 strategy, the latest HIV treatment guidelines recommend that all people living with HIV should initiate ART regardless of clinical stage and CD4 cell count, facilitating early management of opportunistic infections (Fuge et al, 2022 ; Haas et al., 2018). Cryptococcosis, caused by yeast species complexes of *Cryptococcus neoformans* and *C. gattii*, is a fungal disease affecting immunocompromised individuals (Kwon-Chung et al., 2014; Rajasingham et al., 2017). In most cases, the disease progresses to cryptococcal meningitis, which is often deadly. In 2014, the yearly number of related deaths was estimated at 181,100 worldwide, with 75% of cases occurring in Africa alone (Rajasingham et al., 2017). Cryptococcosis accounts for 15% of deaths in people living with HIV worldwide and is particularly burdensome in African countries.

Previous studies conducted in Ivory Coast have highlighted the fact that before the widespread use of ART, a diagnosis of cryptococcosis equated to a death sentence (Bissagn  n   et al., 1994; Eholi   et al., 2000). From 1969 to 1980, the disease was rarely reported in hospital wards across the country, with only four cases documented during that time frame (Odehouri et al., 1991). However, since 1985, there has been a surge in the number of cases diagnosed, especially among HIV-infected individuals. Nowadays, ARTs are readily available in Ivory Coast, leading to a significant decrease in the number of cases of cryptococcal meningitis, although the disease remains severe and deadly for the few reported cases (Aoussi et al., 2012; Kassi et al., 2018; Kouakou et al., 2017). The severity of the illness is attributed to the yeast's tropism for the central nervous system. Typically, the main sources of these clinically relevant yeasts are soils and trees contaminated with pigeon droppings (Akaihe and Nweze, 2021; Cogliati et al., 2016).

In Europe, it has been reported that the percentage of trees harboring *Cryptococcus spp* is subject to seasonal variations. Indeed, these microorganisms were less likely to be isolated in August, which is the warmest and driest month of the year around the Mediterranean Sea. This suggests that some variations could depend on the period of the year (Cogliati et al., 2016). This observation was independently confirmed by a report from Columbia showing that *Cryptococcus spp* could not be recovered from trees when there was less rain (Nnadi et al., 2016). In Sub-Saharan Africa, the epidemiological features of cryptococcosis are difficult to ascertain for two reasons. One reason is that most reports solely focus on the clinical features of the disease (Fuge et al, 2022). The second reason is that there are very few reports on the environmental yeast in countries such as Nigeria, South Africa, Kenya, Egypt, Libya, Cameroon, and Ivory Coast (Ellabib et al., 2016; Kassi et al., 2018). In the latter, an ecological study was implemented to collect information on its influence on the features of the disease in patients

(Kassi et al., 2018).

Based in the teaching hospital of Treichville, the Center for Diagnosis and Research on AIDS and Other Infectious Diseases (CeDReS) is a national reference institution for mycology diagnosis. Every year, more than 50,000 patients undergo biological analysis in this center. Some of them are infected with HIV and under antiretroviral treatment, routinely followed up.

In this center, high rates of positive cerebrospinal fluid cryptococcosis diagnosis were noticed for only two months every year. However, the link between seasons and the occurrence of the fungal infection has not been established yet. The objective of this study is to determine if there is any correlation between rainy and dry seasons and Cryptococcosis infection and to what extent these parameters are useful to forecast Cryptococcosis transmission in Abidjan, Ivory Coast.

MATERIALS AND METHODS

Study participants and methods

The present study is a cross-sectional study on cryptococcal meningitis diagnosed in the CeDReS laboratory from January 2011 to December 2018, an eight-year period. Data were recovered from the computerized laboratory information system (LIS). Patients suspected of cryptococcal meningitis whose diagnostic was confirmed by the CeDReS laboratory were included. The diagnostic confirmation required that a cerebrospinal fluid (CSF) sample undergo microscopic examination with Chinese Ink and/or a successful culture on Sabouraud-chloramphenicol medium.

Cultures were kept at 37°C for 2 to 7 days. Further characterization of the successful culture involved biochemical assays using identification gallery ID32C and a urease test. In some cases and upon the express request from a physician, some CSFs were subject to an agglutination test to detect cryptococcal antigen using the Pastorex Crypto Plus kit (Bio-Rad, France) following the manufacturer's instructions. Data on the sex and age as well as the biological parameters of the CSF, the HIV status, and the CD4 T cells count were recorded. Frequencies and rates were computed, and differences were assessed for each month of a calendar year.

Weather data

In Ivory Coast, there are two main seasons: a rainy season from April to October and a dry season from September to March. During the rainy season, June stands out as the rainiest month, especially in the western part of the country. This season is characterized by high winds and high humidity rates along the seaside, with dry, hot air prevailing inland. In contrast, during the dry season, the air is filled with moisture, and temperatures reach their peak. Occasional rainfall may occur during this period as well. Between 2011 and 2018, temperatures ranged from 27 to 29°C in the southern part of the country. Monthly rainfall varied on average from 76 to 679 mm, and humidity rates ranged from about 84 to 90% (Sodexam, 2019). Since the early 2000s, average annual temperatures have consistently remained above those of the 1981 to 2010 reference period. The average annual temperature recorded in 2018 was 27.3°C, indicating an increase of +1.19°C compared to the 1981 to 2010 period (26.2°C). This marks the highest rise since 1961, followed by 2010 (+0.8°C) and 2018 (+0.7°C). Additionally, the average relative humidity increased by approximately +3% in 2018 compared to the reference period of 1981-2010, observed in the north, center, and some areas in the south.

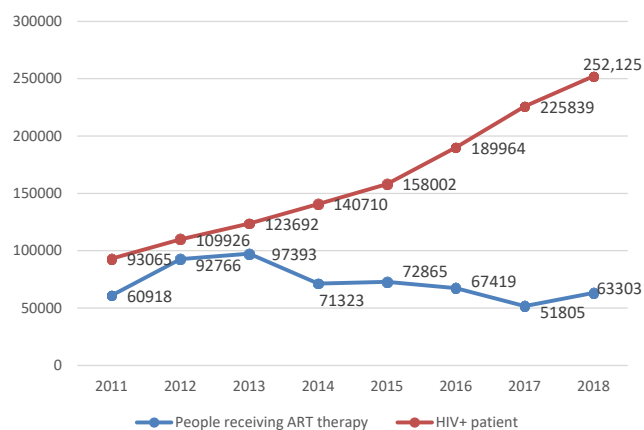


Figure 1. Total numbers of HIV-infected individuals and numbers of those under ART from 2011 to 2018.

Statistical analysis

The data collected were analyzed using the Statistical Package for Social Science (SPSS) version 21.1.0 software. The relationship between two variables was tested with Pearson's chi-square test or Fisher's exact test with a 5% risk of error.

RESULTS

Age and sex of the patients

Overall, 2,623 files were examined from the computerized LIS from which and 290 cases of cryptococcal meningitis were identified. The sex ratio among the 290 cases was 0.96; hence there were a similar number of male (142 out of 290, 48.9%) and female (142 out of 290, 51.1%) patients. The average age was 35.2 years (± 5.7 years) with extremes at 18 and 78 years. The age groups of 31-45 years and 46-60 years had high rates of positive CSF at respectively 12% and 11.2%.

HIV status

The HIV-positive status was clearly indicated in the medical files for 119 patients. Among these individuals, the positivity rate for cryptococcal meningitis was 97.4% (116 out of 119). The unknown HIV status of the other participants did not allow for a comparison between HIV-infected and HIV-uninfected individuals. From 2011 to 2018, the number of HIV-infected individuals rose from 93,065 to 252,125 in Ivory Coast. The number of those receiving ART did not significantly change, remaining between 60,918 and 63,303, as shown in Figure 1 (UNAIDS, 2018).

CD4 T cells count

The CD4 T cells count was readily available for 201

participants (69.3%). The average CD4 T cells count was $63/\text{mm}^3$ with extremes at 5 and $498/\text{mm}^3$. Among the 201 participants, 181 (90%) were immune compromised with a CD4 T cells count below $200/\text{mm}^3$.

CSF examination

The macroscopic examination of all 2,623 CSF samples sent to the laboratory showed that the CSFs were clear in 63.2% of the cases, while some were blurry (32.2%), and a small portion were bloody (4.6%). The biochemical examination of the CSF samples revealed an average glucose level of 0.58 ± 0.57 G/L, with extremes at 0.04 and 3.72 G/L. The average protein level in the CSFs was 0.75 ± 0.65 G/L, with extremes at 0.02 and 4.05 G/L. Microscopic examination detected the vegetative forms of *Cryptococcus* in 285 out of 290 cases (98.3%). Culture on specific medium grew in all 285 microscopy-positive CSFs (100%), as well as in three additional samples that were microscopy-negative. Physicians requested an agglutination test for 40 out of 290 CSFs (13.8%), and the test was positive in all 40 CSFs, confirming the results of the microscopy and culture.

Frequency of the cryptococcal meningitis

The frequency of the cryptococcal meningitis over the study period was 11.2% as shown in Table 1. A statistically significant increase in the frequency of cryptococcal meningitis was observed from 2011 to 2017, rising from 5.8 to 15.2%. The years 2017 and 2018 saw peaks in cases of cryptococcal meningitis, with a yearly average of 58.5 cases. Over the eight-year period, the Parasitology and Mycology Unit of the CeDReS laboratory diagnosed a total of 290 cases, resulting in an overall average yearly number of cases of 36.2. Additionally, a statistically significant relationship between frequencies in CSF positivity rates from 2011 to 2018 ($p=0.0005$) was observed.

Trends in cryptococcal meningitis diagnosis

The cumulative monthly positivity rates from 2011 to 2018 are shown in Figure 2. Spikes in positivity rates were observed in June (16.5%) and February (14.4%). A statistically significant relationship between cryptococcal meningitis positivity rates from 2011 to 2018 and the different month of years ($p=0.0184$) was observed.

Distribution of the seasonal cases

The seasonal positivity rates are shown in Figure 3. The positivity rates of the cryptococcal meningitis during the rainy season seemed similar to that of the dry season,

Table 1. Frequencies in CSF positivity rates from 2011 to 2018.

| Years | # of examined CSFs | # of positive CSFs | CSF positivity rates % |
|-------|--------------------|--------------------|------------------------|
| 2011 | 347 | 20 | 5.8 |
| 2012 | 108 | 10 | 9.3 |
| 2013 | 348 | 38 | 10.9 |
| 2014 | 302 | 28 | 9.3 |
| 2015 | 310 | 34 | 11 |
| 2016 | 360 | 43 | 11.9 |
| 2017 | 401 | 61 | 15.2 |
| 2018 | 447 | 56 | 12.5 |
| Total | 2,623 | 290 | 11.1 |

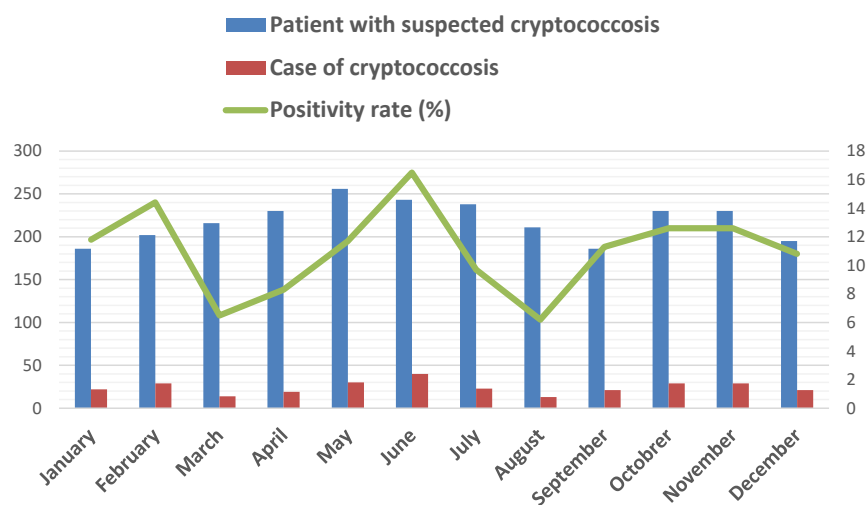


Figure 2. Trends in cryptococcal meningitis positivity rates from 2011 to 2018.

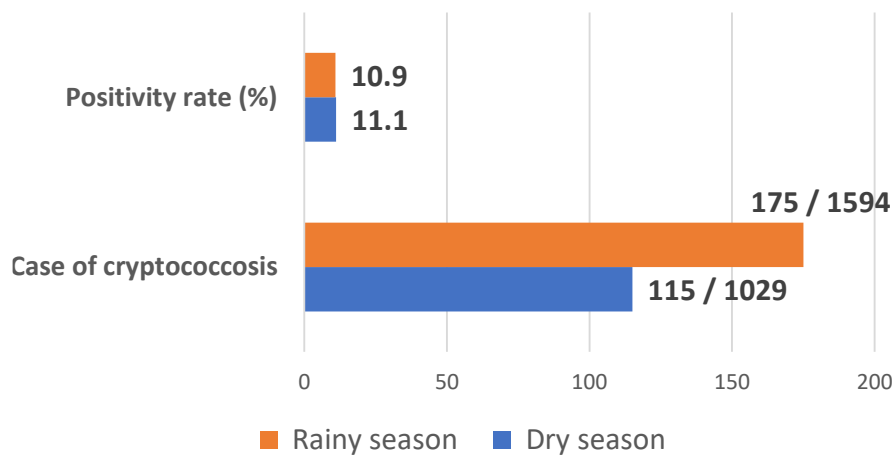


Figure 3. Seasonal positivity rates of cryptococcal meningitis.

11.1% versus 10.9% (115 out of 1029 versus 175 out of 1594). No statistically significant relationship between rain

or dry season and positivity rates of cryptococcal meningitis ($p=0.9255$) was observed.

DISCUSSION

From 1996 onwards, antiretroviral drugs have changed the outcome of HIV infection by reducing opportunistic diseases and mortality rates in both Western countries and Africa (UNAIDS, 2013, 2018). However, tuberculosis, invasive bacterial, and fungal infections remain the main causes of opportunistic diseases and deaths in Sub-Saharan Africa despite the widespread use of ART (Anglaret et al., 2012; Eholié et al., 2000; Moh et al., 2007). *Cryptococcus* spp is considered the main cause of non-viral meningitis in HIV-infected individuals, accounting for 87.5% of cases in Abidjan (Eholié et al., 2000). The average yearly number of cases found in this study exceeded previously published figures from the same laboratory, with 16 cases per year ($p < 0.0001$) reported from 1999 to 2005, and 20 cases per year ($p < 0.0001$) reported from 2006 to 2010 (Bedia-Tanoh et al., 2018). This suggests that the number of cryptococcal meningitis cases appears to be increasing from 1999 to 2018. A report from the Tropical Infectious Diseases ward of the same University Hospital indicated that from August 2008 to August 2011, 46 individuals with cryptococcal meningitis were hospitalized, representing 2.5% of all in-patient admissions, with a yearly rate of 16 cases, less than half the rate reported by the current study (Cogliati et al., 2016). In Bobo-Dioulasso, Burkina Faso, a neighboring West-African country, the yearly rate reported for in-patients with cryptococcal meningitis hospitalized at the Internal Medicine ward from 1999 to 2001 was three times lower, with 12 cases ($p < 0.0001$) (Bamba et al., 2011).

These differences could be explained by the fact that the CeDReS laboratory collected samples from various wards at the University Hospital of Treichville, as well as from outpatients and surrounding hospitals. Moreover, the laboratory is situated near the Tropical Infectious Diseases ward, which serves as the national reference service for HIV care in Ivory Coast. Each year, up to 2,400 patients are hospitalized there, with HIV-infected patients constituting 95% of that number (Aoussi et al. 2012). The results of this study are likely related to the high-quality facilities of the CeDReS laboratory, enabling a comprehensive set of biological examinations to be routinely performed. Cryptococcal meningitis is considered an emergency that requires rapid and reliable microscopic examination, along with an agglutination test within a few hours following sample collection. Additionally, the CeDReS laboratory serves as a national reference laboratory for HIV and multi-drug-resistant tuberculosis diagnosis. Since 2011, it has been committed to a standardization process, culminating in being the first Ivorian public laboratory accredited in 2021 according to ISO 15189 (2012 version) standards. These factors make the laboratory attractive for CSF examination seekers, suggesting that the rate uncovered by this study should be fairly close to the actual one.

Microscopic examination is typically successful in

detecting 72 to 84% of cryptococcal meningitis cases, but this sensitivity is considered lower than that of CSF culture, which ranges from 94 to 100% (El Fane et al., 2015).

Therefore, culture on specific medium remains the gold standard diagnostic for cryptococcal meningitis (Bicanic and Harrison, 2004). The current study reported a microscopic examination sensitivity of 98.3%, similar to the 100% previously reported in Ivory Coast by Bedia et al. (2018), and in Burkina Faso by Bamba et al. (2012). The few missed positive samples could be samples harboring mutant *Cryptococcus* spp lacking the capsule (Qiu et al., 2013), which can be identified with the agglutination test (Bedia-Tanoh et al., 2018), as demonstrated in this study with a sensitivity of 100%, similar to previous reports (El Fane et al., 2015).

Three times more HIV-infected individuals were found in this study, but the number of those under ART remained the same from 2011 to 2018. The increase in the number of HIV cases might have driven the rise in the number of cases of cryptococcal meningitis. Indeed, Ivory Coast remains one of the most affected countries in West Africa by HIV infection, with a frequency of 2.8% in 2018, down from 3.6% in 2010, despite sustained successes in HIV care since 2010 (MSLS, 2015). Most of the patients were female adults (51%), consistent with HIV infection becoming a female disease in Ivory Coast, where 60% of HIV-infected individuals were female (MSLS, 2015).

Cryptococcal meningitis predominantly affected young adults, consistent with previous reports. In Ivory Coast, Bedia et al. (2018) showed an average age of 38.9 ± 8.68 years, while Kouakou et al. (2017) reported a high frequency for people aged 35 to 47 years (Bedia-Tanoh et al., 2018; Cogliati et al., 2016). In Burkina Faso, the average age was 32.9 ± 4.3 years (Bamba et al., 2012). These observations may be related to the high proportion of young people among HIV-infected individuals in Ivory Coast and Burkina Faso, and to the susceptibility of these immunocompromised young adults to cryptococcal meningitis (Moh et al., 2007).

Biochemical and cytological examinations showed lymphocytic-rich clear CSFs with high protein content, likely due to leaks into the blood-brain barrier (BBB) during inflammation. The low glucose content in the CSF could suggest either the utilization of this energy source by the fungi and the inflammatory host cells, or alterations in the BBB glucose transport systems. Notably, these observations are common in lymphocytic-rich clear CSF meningitis (Eholié et al., 2000; UNAIDS, 2017). Eighty percent of cryptococcal meningitis cases occurred in people with severe cellular immune suppression, with CD4 T cell counts below $100 /\text{mm}^3$ (Park et al., 2009). In this study, 90% of the cases had CD4 T cell counts below $200/\text{mm}^3$. However, 10% of the participants had more than $200 \text{ cells}/\text{mm}^3$, suggesting that cryptococcal meningitis could occur in immune-competent individuals, as reported before in Ivory Coast and elsewhere (Bellet et al., 2021; Favalessa et al., 2014).

To the best of our knowledge, this is the first report on the frequencies of seasonal cases of cryptococcal meningitis in Ivory Coast. It could be of interest to assess data from the environment in Abidjan to look into the correlation with the trends in clinical cases. However, such comparison studies were performed in Thailand and the USA (Chariyalertsak et al., 1996; Sorvillo et al., 1997).

Using weather information, we explored the effects of climatological parameters on the occurrence of cryptococcosis cases at CeDReS, Abidjan, located in a wet and rainy tropical region at 5.3°N. The correlation found with monthly frequencies in CSF positivity rates from 2011 to 2018 appears to be a simple correlation without biological plausibility. In this study, high frequencies were observed in June and February. In Ivory Coast, it is widely accepted that February is the warmest month of the year, while June experiences significant rainfall. A cross-sectional study combining environmental and clinical assessments will be needed to determine the implications of changes in seasonal frequencies of cryptococcal meningitis for human health. Similar works from the USA demonstrated significantly high frequencies during the Fall and Winter seasons (Kidd et al., 2007). Conversely, in Thailand, 793 cases were reported in people living with HIV at the University Hospital of Chiang Mai. The analysis of their seasonal frequencies (rainy versus dry seasons) showed no significant difference. In a study on environmental fungi in the British Columbia province of Canada and the northwestern Pacific side of the United States, Kidd et al. (2007) reported seasonal variations in the shedding of yeasts from chicken stools, with the highest frequencies measured during the Spring and Summer seasons (Randhawa et al., 2011). This report was confirmed by an independent study in Europe showing that while *C. neoformans* can be recovered at various temperatures, *C. gattii* was only isolated when the average outside temperatures were above 10°C (Cogliati et al., 2016).

Conclusion

A large cross-sectional study was conducted to collect clinical and environmental data on *Cryptococcus*, aiming to understand the seasonal variations in the frequencies of cryptococcal meningitis in Ivory Coast.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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