Epidemiological approach to Cryptococcus meningitis and related species in northeast Brazil: a scoping review

Abordagem epidemiológica à meningite por Cryptococcus e espécies relacionadas no nordeste do Brasil: uma revisão de escopo

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Introduction: Cryptococcosis is a fungal infection associated with yeast of the *Cryptococcus* genus. It is an opportunistic infection, more prevalent in individuals with AIDS, primarily manifesting as meningitis. Although there are numerous cases of cryptococcosis in northeastern Brazil, little is reported in the literature regarding meningitis cases. Objective: This study aimed to conduct a scoping review of meningitis cases associated with the *Cryptococcus* genus reported in the northeastern region of Brazil. Methodology: Four databases were utilized. Twenty-one studies were selected, totaling 492 cases. All states had publications on cryptococcal meningitis cases. RESULTS: The results revealed few studies on *Cryptococcus* meningitis in the region, with 492 identified cases. The majority were caused by *Cryptococcus neoformans* (356 cases), followed by *C. gattii* (98 cases), and other related species. AIDS was the primary underlying condition, associated with high mortality. Genetic research was underutilized. Conclusion: There is a need to enhance diagnostic methods in conjunction with increased case reporting to obtain a more detailed and comprehensive understanding of the epidemiology of neurocryptococcosis in northeastern Brazil.

**Keywords**: *Cryptococcus*, meningitis, Cryptococcosis, epidemiological aspects, Northeast, Brazil, fungal infections, CNS.
1 INTRODUCTION

Cryptococcosis is a fungal infection associated with Cryptococcus yeasts (Chen et al., 2021). These yeasts are primarily transmitted in urban areas through the inhalation of fungal propagules found in pigeon and captive bird droppings (Farrer et al., 2021). The infection primarily affects the lungs and the central nervous system, with potential involvement of other organs as it progresses (Adams et al., 2020). Immunocompromised individuals, particularly those with Acquired Immunodeficiency Syndrome (AIDS) or undergoing antineoplastic treatment, are more vulnerable (Smith et al., 2023).

Implicated species belong to the Cryptococcus neoformans/Cryptococcus gattii complex (Santos et al., 2020). The predominant clinical presentation is cryptococcal meningoencephalitis, characterized by neurological symptoms such as headaches, confusion, visual disturbances, and seizures (Xavier et al., 2020). Other forms include pulmonary cryptococcosis, marked by respiratory symptoms, and the disseminated form, where Cryptococcus yeasts can infiltrate multiple organs through the bloodstream (Khan et al., 2020), as illustrated in Figure 1. Cryptococcosis is a fungal infection associated with Cryptococcus yeasts (Chen et al., 2021). These yeasts are primarily transmitted in urban areas through the inhalation of fungal propagules found in pigeon and captive bird droppings (Farrer et al., 2021). The infection primarily affects the lungs and the central nervous system, with potential involvement of other organs as it progresses (Adams et al., 2020). Immunocompromised individuals, particularly those with Acquired Immunodeficiency Syndrome (AIDS) or undergoing antineoplastic treatment, are more vulnerable (Smith et al., 2023).

Diagnosis relies on identifying Cryptococcus cells in cerebrospinal fluid, blood, pulmonary secretions, biopsies, and serological tests (Larone 2018). Prevention of cryptococcosis necessitates measures to avoid fungal exposure, early intervention (Ministério da Saúde, 2018), and personalized treatment for immunocompromised patients, such as those with AIDS.
Preventing exposure to Cryptococcus and, consequently, cryptococcosis, involves avoiding contact with bird excreta, especially pigeon droppings, and activities that might expose individuals to contaminated dust or soil. Additionally, it entails steering clear of contaminated food and water, maintaining personal hygiene, bolstering the immune system, and utilizing appropriate protective gear in environments at risk of contamination (CDCP, 2022).

The treatment of cryptococcosis involves antifungal agents such as amphotericin B and fluconazole. The duration of the regimen depends on the overall health of the host and can extend over several months (Lima et al., 2018). The treatment prognosis correlates with the severity of the disease and the patient's immune status (Dromer; Ronin., 2021).

In Northeast Brazil, cryptococcosis is a growing public health problem characterized by high incidence and mortality rates (Macêdo et al., 2019). Studies conducted by Barbosa et al (2018), indicate a higher prevalence among men and HIV-positive patients. Regions with high HIV cases, such as Piauí, Bahia, and Ceará, report the most cases of cryptococcosis (Macêdo et al., 2019).

Despite existing case studies on cryptococcosis throughout Brazil, there is no comprehensive review of the status of this fungal infection in the Northeastern region of the country. Consequently, this monograph underscores the need for a narrative literature review on cryptococcosis in Northeast Brazil, encompassing epidemiological, clinical, and therapeutic aspects. The aim is to enhance understanding of the disease's situation in the region, facilitating the development of more effective prevention, diagnosis, and treatment strategies tailored to local needs (Lima; Melo e Silva, 2021).

2 METHODOLOGY

2.1 PROTOCOL

This is a scoping review study focused on cryptococcosis in Northeast Brazil. It adheres to the Joanna Briggs Institute guidelines and follows PRISMAScR reporting standards.

The study utilized the PICO framework:
Population: Patients with Cryptococcus-related meningitis in Northeast Brazil.

Intervention: Epidemiological analysis of Cryptococcus-related meningitis in Northeast Brazil.

Comparison: Not applicable; the emphasis was on the epidemiological approach itself.

Outcome: Identification of risk factors, incidence patterns, geographical distribution, clinical and epidemiological characteristics, and mortality rates related to Cryptococcus meningitis in Northeast Brazil.

The study aimed to answer the question: "What are the epidemiological patterns of cryptococcal meningitis in Northeast Brazil?" The protocol was registered on the Open Science Framework under DOI: 10.17605/OSF.IO/JW6S5.

2.2 SEARCH MECHANISM

Two reviewers (G.C.A.S and R.E.C.N) independently selected references from PubMed, Scopus, Scielo, and Google Scholar using predefined inclusion and exclusion criteria. The search strategy involved Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), utilizing Boolean operators "AND" and "OR". The search commenced in PubMed and extended to Scopus, Scielo, and Google Scholar. Publications up to May 10, 2023, were included, without restrictions on publication year or language. Duplicate removal was conducted using the Rayyan software.

2.3 STUDY SELECTION

To ensure consistency, the reviewers discussed the eligibility criteria and applied them to a 20% sample of retrieved references for inter-rater reliability assessment (Kappa ≥ 0.80). Once agreement was established, all studies were reviewed. This stage comprised two phases: in phase 1, titles and abstracts were screened, and studies aligned with the review topic proceeded to phase 2 for fulltext evaluation. The reference lists of included studies were also scrutinized for relevant research. Ineligible studies were documented with exclusion reasons. Discrepancies were resolved by a third reviewer (W.P.S.R).
2.4 DATA EXTRACTION

Data extraction involved two assessors using a designated spreadsheet. In case of discrepancies, a third reviewer was consulted. A flowchart following PRISMA-ScR guidelines was generated to illustrate the article selection process (Figure 2).

3 RESULTS

3.1 SEARCH MECHANISM

Eight hundred and two studies were identified in bibliographic databases. After removing duplicates, 728 records remained for title and abstract screening. Among these, 687 were excluded as they did not relate to the research question. Following full-text assessment, 21 articles were selected for qualitative analysis based on the inclusion criteria (Figure 2).

3.2 MENINGITIS DUE TO CRYPTOCOCCUS IN NORTHEAST BRAZIL

The Northeast region of Brazil has limited studies on Cryptococcus meningitis. Among the reported cases, cryptococcosis is significantly common in patients with HIV/AIDS (Rodrigues et al., 2020). Until May 2023, 21 articles documenting these cases have been found. The case density per state is represented in Figure 3, and the data is summarized in Table 01.

A total of 492 cases of neurocryptococosis were identified, including 356 caused by the \textit{C. neoformans} complex, 98 by the \textit{C. gattii} complex, and 35 identified only at the genus level. Some correlated species were identified: 01 Papiliotrema laurentii, 01 Naganishia diffluens, and 01 Naganishia albida.

Analyzing only the 356 isolates from the \textit{C. neoformans} complex, genotyping was conducted on 93 of them, with 91 corresponding to genotype VNI, 01 to VNII, totaling 92 \textit{C. neoformans} sensu stricto (current nomenclature) and 01 VNIII, corresponding to the hybrid form \textit{C. neoformans} \textit{x} \textit{C. deneoformans} (current nomenclature).

When analyzing the 98 isolates from the \textit{C. gattii} complex, genotyping was conducted on 60 isolates, with 59 corresponding to genotype VGII (current C.
deuterogattii) and 01 corresponding to genotype VGI (current C. gattii sensu stricto). All states reported cases of neurocryptococcosis, as indicated in Figure 3.

3.2.1 Alagoas

In a study conducted by Maranhão et al (2020), a case of Cryptococcus spp. infection in Alagoas state was reported. The patient, a 44-year-old immunocompetent male, worked in an area with a high concentration of pigeons. He presented with facial lesions, persistent headaches, and night fever. Cryptococcus neoformans, genotype VNI, was isolated from the cerebrospinal fluid. The patient was successfully treated with amphotericin B and was discharged after 75 days of hospitalization.

3.2.2 Bahia

Neurocryptococcosis in Bahia state has been reported in four studies, totaling 185 cases. A comprehensive study by Darzé et al (1999), documented 104 cases, predominantly in AIDS patients. Matos et al (2012), examined 62 Cryptococcus isolates, comprising 49 cases of C. neoformans (genotype VNI) and 13 of C. gattii (genotype VGII). Trillhes et al (2008), included 8 cases related to C. gattii (genotype VGII). Additionally, Oliveira et al (2021), identified 9 cases associated with C. deuterogattii and 2 cases of C. neoformans. No additional information was provided about these cases.

3.2.3 Ceará

Ceará state reported 7 cases distributed across 3 articles. In a study by Meneses et al (2002), 5 cases of Cryptococcus neoformans were detected in HIV patients. Aragão et al (2008), described a case of bilateral amaurosis due to cryptococcal meningitis in a patient from Ceará. Daher et al (2015), reported a fatal case of cryptococcosis in a 23-year-old man with HIV and diabetes mellitus. Additional details about these cases were not provided.
3.2.4 Maranhão

In Maranhão state, an epidemiological study conducted in the year 2010 identified 2 cases of *Cryptococcus neoformans* in cerebrospinal fluid samples. However, no clinical details or patient outcomes were provided Magalhães *et al* (2015).

3.2.5 Paraíba

In a study conducted by Romulo e Sousa (2013), 24 cases of neurocryptococcosis were recorded in Paraíba state. The majority of patients were male, and 8 of them had AIDS. Common symptoms included disorientation, unconsciousness, fever, vomiting, and headache. No additional information was provided regarding the outcomes of these cases.

3.2.6 Pernambuco

In Pernambuco state, 44 cases of neurocryptococcosis were documented across 4 publications. Oliveira and colleagues (2022), reported a case of meningitis in a patient undergoing tuberculosis treatment. Vechi and colleagues (2019), described a case in an HIV-positive patient. No additional details about these cases were provided.

3.2.7 Piauí

Piauí state had the highest number of studies on neurocryptococcosis, with 127 cases documented in 7 articles. Soares *et al* (2008), reported 28 cases in HIV-positive patients. Martins and colleagues, 2011 (30), described 63 cases, mostly in male patients with HIV. Trilles *et al* (2008b), presented 9 cases related to *C. neoformans* and 8 cases related to *C. gattii*. Vieira and colleagues (2013 and 2015) described cases in HIV-positive patients but did not provide details on outcomes. Meyer *et al* (2021) reported 6 cases, while Trilles *et al* (2003b), isolated 2 cases of *C. gattii*. No additional details were provided about these cases.
3.2.8 Rio Grande do Norte

In Rio Grande do Norte state, a study reported 12 cases of Cryptococcus neoformans and 10 cases of C. deuterogattii in cerebrospinal fluid samples from patients with meningitis. Clinical details and outcomes were not provided (Aragão et al., 2008).

3.2.9 Sergipe

In Sergipe state, Barbosa Júnior et al (2006), identified 41 cases of Cryptococcus neoformans meningitis. No demographic or outcome details were provided for these cases. In another study by Barbosa Júnior et al (2013), 35 clinical isolates of Cryptococcus were presented, with 26 cases of C. neoformans and 9 of C. gattii. No additional details were provided about these cases.

4 DISCUSSION

Cryptococcal meningitis, a globally distributed fungal infection with high mortality, is particularly concerning in patients with HIV/AIDS (Carrijo et al., 2021). Despite its presence throughout the territory, the Northeast region of Brazil lacks in-depth studies on neurocryptococcosis (Alves et al., 2022).

The lack of awareness about cryptococcal meningitis, its etiological agents, transmission, and symptoms can lead to delays in diagnosis in underserved regions, increasing the severity and difficulty of disease treatment (Souto et al., 2017). Lack of access to appropriate diagnostic resources and treatments, as well as adherence to long-term treatments, can contribute to the high mortality rate from Cryptococcus in the region (Alves et al., 2022). Globally, it is estimated that cryptococcal meningitis causes 152,000 deaths in patients with HIV/AIDS, accounting for 19% of AIDS-related deaths (Kabir, 2022). The mortality rate from Cryptococcus in Northeast Brazil is high, with an observed rate of 44.8% in this study. However, this rate is based only on studies that mentioned patient outcomes, potentially underestimating the reality. The high incidence of HIV/AIDS in the Northeast region is one of the factors contributing to this rate, along with the lack of access to adequate healthcare in underserved areas (Lins et al., 2019).
The lack of mandatory reporting of cryptococcosis in Brazil hampers effective disease monitoring by public health authorities. Without accurate data on cases and distribution, prevention and control strategies are compromised, and resource allocation for research and treatment is affected (Barbosa et al., 2019). Underreporting is exacerbated by the lack of complete and digitized patient records in hospitals in the region (Vidal; Penalva de Oliveira e fink, 2013; Pappalardo et al., 2019).

Research on cryptococcal meningitis in Brazil is uneven, with most robust studies concentrated in other regions of the country (Pappalardo et al., 2019; Silva-Vergara et al., 2021). This is partly due to the lack of funding and dedicated research groups on the topic in the Northeast region. Addressing this imbalance is crucial to develop effective interventions across all regions and improve the diagnosis and treatment of neurocryptococcosis Silva-Vergara et al., 2021).

In summary, neurocryptococcosis is a severe fungal infection that mainly affects patients with HIV/AIDS, necessitating more accessible diagnostic methods and early treatment (Carrijo et al., 2021). Antiretroviral therapy is crucial to reducing the incidence of cryptococcosis in HIV/AIDS patients, and preventive measures are essential to avoid disease development (Da Silva et al., 2021).

5 CONCLUSION

Based on the analyzed data, we can conclude that Bahia has the highest number of reported cases in the literature, while Piauí is the state with the most available studies. Maranhão and Alagoas have the lowest number of reports. Cryptococcus neoformans is the most common species, followed by C. deuterogattii. AIDS is the primary underlying disease in cases of cryptococcal meningitis, with a high mortality rate. Few studies have utilized proteomic analysis or genetic sequencing methods over the years. The lack of mandatory reporting hampers obtaining precise data, and the disparity in research on the disease in Brazil needs to be addressed to develop effective health policies (45).
AUTHORS’ CONTRIBUTIONS

Author Contributions: G.C.A.S.: Conducted the research, performed the data analysis, and wrote the article; R.E.D.C.N.: Conducted the research and performed the data analysis; W.P.D.S.-R.: Designed the article, guided the research, and corrected the writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

AIDS – Acquired Immunodeficiency Syndrome
BBB – Blood-Brain Barrier
GXM – Glucuronoxylomannan
HIV – Human Immunodeficiency Virus
CSF – Cerebrospinal Fluid
RFLP – Restriction Fragment Length Polymorphism
CNS – Central Nervous System
ART – Antiretroviral Therapy
PCR – Polymerase Chain Reaction
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ANNEXES

Figure 1. Trojan Horse Mechanism

a) Fungal propagules found in feces of colonized birds or organic material are inhaled. b) In the lungs, blastoconidia are phagocytosed. c) Stress-resistant cells remain inside phagocytes and are transported through the bloodstream. d) Phagocytes freely cross the blood-brain barrier, facilitating yeast access to this anatomical site. e) Free blastoconidia, causing infection in the central nervous system.

Source: Own authorship.

Figure 2. PRISMA Flow Diagram of Study Selection for Scoping Review

Identification: databases searched and references retrieved; Screening: number of references included and excluded according to the eligibility criteria; Included: how many new references were included after the initial screening.

Source: Adapted from PRISMA.
Figure 3. Density of Cryptococcal Meningitis Cases in Northeast Brazil

DISTRIBUTION OF NEUROCRIPTOCOCOSIS CASES IN THE NORTHEAST REGION OF BRAZIL

- BAHIA / BA - 185
- PIAUÍ / PI - 127
- SERGIPE / SE - 76
- PERNAMBUCO / PE - 44
- RIO GRANDE DO NORTE / RN - 26
- PARAÍBA / PB - 24
- CEARÁ / CE - 7
- MARANHÃO / MA - 2
- ALAGOAS / AL - 1

Numbers of cases of neurocryptococcosis in the northeast region of Brazil.
Source: Own authorship.