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Epidemiological and space analysis of cryptococcosis in children in the mesoregions of the state of Pará, Eastern Amazon, from 2000 to 2017

Análise epidemiológica e espacial da criptococose em crianças nas mesorregiões do estado do Pará, Amazônia Oriental, de 2000 a 2017

Análisis epidemiológico y espacial de la criptococosis en niños de las mesorregiones del estado de Pará, Amazonía Oriental, de 2000 a 2017

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Abstract
Cryptococcosis is a fungal disease, which until the year 2020 was not compulsory notification, and until this period there were no exact data on its occurrence in Brazil. Objective: To analyze the clinical, laboratory, and epidemiological characteristics, beyond the spatial distribution and occurrence, of cryptococcosis in children living in the Brazilian Oriental Amazônia from 2000 to 2017. Methodology: This descriptive and transversal study was conducted at the University Hospital João de Barros Barreto (HUJBB), Belém-Pará, through data obtained from records of children aged up to 13 years old who were hospitalized with the diagnosis of cryptococcosis from 2000 to 2017. A descriptive analysis was performed using calculation of frequency, median age, and standard deviation using IBM SPSS 24.05.0. The significance level was set at p=0.05 (α=5%). The data were purified using the Table Win v. XX program. The laboratorial georeferencing of data for the creation of geographic data (BDGeo) was performed using ArcGIS 10.2 and TerraView 4.0. Results: Predominance infections happened in the rural areas, principally from *C. gattii*. Georeferencing demonstrated heterogenic distribution of the disease in mesoregions of Pará state, having a direct relation with deforested. Conclusion: The largest occurrence was in the northeastern mesoregion of Pará likely due to the environmental impact of deforestation.
Keywords: *Cryptococcus*; Cryptococcosis in children; Georeferencing Pará mesoregions.

Resumo
A criptococose é uma doença fúngica, que até o ano de 2020 não era de notificação compulsória, não existindo até esse período dados exatos sobre sua ocorrência no Brasil. Objetivo: Analisar as características clínicas, laboratoriais e epidemiológicas, além da distribuição espacial e ocorrência, da criptococose em crianças residentes na Amazônia Oriental Brasileira de 2000 a 2017. Metodologia: Estudo descritivo e transversal realizado no Hospital Universitário João de Barros Barreto (HUJBB), Belém-Pará, por meio de dados obtidos de prontuários de crianças de até 13 anos internadas com diagnóstico de criptococose no período de 2000 a 2017. Foi realizada análise descritiva por meio de cálculo de frequência, mediana de idade e desvio padrão usando IBM SPSS 24.05.0. O nível de significância foi estabelecido em p=0,05 (α=5%). Os dados foram purificados usando o programa Table Win v. XX. O georreferenciamento laboratorial de dados para criação de dados geográficos (BDGeo) foi realizado utilizando ArcGIS 10.2 e TerraView 4.0. Resultados: As infecções predominantes ocorreram nas áreas rurais, principalmente por *C. gattii*. O georreferenciamento demonstrou distribuição heterogênea da doença nas mesorregiões do estado do Pará, tendo relação direta com o desmatamento. Conclusão: A maior ocorrência foi na mesorregião nordeste do Pará provavelmente devido ao impacto ambiental do desmatamento.
Palavras-chave: *Cryptococcus*; Criptococose em crianças; Georreferenciamento das mesorregiões do Pará.

Resumen
La criptococosis es una enfermedad fúngica, que hasta el año 2020 no era de notificación obligatoria, y hasta ese período no había datos exactos sobre su ocurrencia en Brasil. Objetivo: Analizar las características clínicas, de laboratorio y epidemiológicas, más allá de la distribución espacial y la ocurrencia, de la criptococosis en niños residentes en la Amazonía Oriental Brasileña de 2000 a 2017. Metodología: Este estudio descriptivo y transversal fue realizado en el Hospital Universitario João de Barros Barreto (HUJBB), Belém-Pará, a través de datos obtenidos de prontuarios de niños de hasta 13 años que fueron hospitalizados con el diagnóstico de criptococosis de 2000 a 2017. Se realizó un análisis descriptivo mediante cálculo de frecuencia, mediana de edad y desviación estándar utilizando IBM SPSS 24.05.0. El nivel de significancia se fijó en p=0,05 (α=5%). Los datos se purificaron utilizando el programa Table Win v. XX. La georreferenciación laboratorial de datos para la creación de datos geográficos (BDGeo) se realizó utilizando ArcGIS 10.2 y TerraView 4.0. Resultados: Predominaron las infecciones en las zonas rurales, principalmente por *C. gattii*. La georreferenciación demostró una distribución heterogénea de la enfermedad en las mesorregiones del estado de Pará, teniendo una relación directa con la deforestación. Conclusión: La mayor ocurrencia fue en la mesorregión nororiental de Pará probablemente debido al impacto ambiental de la deforestación.
Palabras clave: Criptococo; Criptococosis en niños; Georreferenciación de las mesorregiones de Pará.

1. Introduction

Cryptococcosis, also known as torulose, European blastomicose, or Busse-Buschke disease, is a systemic ringworm infection acquired by inhalation of propágulos (basidiósporos) of the fungus *Cryptococcus*. It is a disease that occurs worldwide, with majority of the cases seen in Africa and Asia, followed by South America and Central America. It is considered a fatal disease that affects immunocompromised as well as immunocompetent patients, is caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, and is rare in the pediatric age range, but common among immunocompromised patients with predilection to the central nervous system (SNC). The scarcity of data regarding cases in children may be due to unfavorable outcomes and a large number of cases with significant neurological sequelae (Luo *et al.*, 2015 and Ministério da Saúde, 2021a).

Brazil is the fourth country with the largest number of isolates after South Africa, China, and the United States (Cagliat, 2013); however, the annual incidence of cryptococcosis is not well defined, because Cryptococcosis is a fungal disease, which until the year 2020, in Brazil, was not compulsory notification (Ministério da Saúde, 2020). The literature shows that in more than 215,000 patients registered with HIV between 1980 and 2002, 6% were diagnosed with cryptococcosis at the time of being diagnosed with AIDS (Santos & Figueiredo, 2021, Ministério da Saúde, 2021b and Carrijo *et al.*, 2021). Reichert-Lima *et al.* (2016) highlights that in the period 1998–2006, 125,633 patients died of AIDS in Brazil, with 5,898 deaths related to some fungal infection, and that cryptococcosis was responsible for 50% of cases. In the state of Pará, the focus of this study, very little is known about the occurrence of this disease in children due to the lack of obligatory notification of this disease, considerable mortality, and increased number of sequelae observed, making it necessary to understand how this infection behaves in different mesoregions of the state of Pará.

In 2014, cryptococcosis appeared to be responsible for 15% of deaths related to AIDS worldwide, with a third of cases occurring in Sub-Saharan Africa. In the same year, the global incidence of cryptococcosis infection was estimated to be approximately 223,100 cases yearly, resulting in 181,000 deaths. A total of 73% of cases occurred in Sub-Saharan Africa, resulting in 135,900 deaths annually, demonstrating that having a cryptococcosis infection signifies failure in the treatment of HIV (Rajasingham *et al.*, 2017 and WHO, 2018).

Given the importance of the disease for public health and immunosuppressed individuals, as well as the relevant lack of studies about the occurrence of cryptococcosis in Brazilian Amazônia, the aim of the present study was to analyze the context of clinical, laboratory, and epidemiologic management as well as the spatial distribution of cryptococcosis in children in the mesoregions of Pará state (Amazônia Oriental), from 2000 to 2017.

Considering the ecology of *Cryptococcus*, its most frequent habitat is the rural zone area, with 38 cases in this study,

and comprised 69.09% of cases in a study by Corrêa *et al.* (1999) and Guo *et al.* (2016). Certainly, the presence of organic substrates due to the decomposition of lumber as well as large areas of deforestation would create a favorable environment for the replication of the life cycle of the fungus, thus causing infection by *C. gattii* to be more common in children in these regions (Pinto Junior, 2010).

2. Methodology

This is a descriptive and transversal study (Campana, 1999a, 1999b, Lopes, 2018, Lopes & Lima, 2018) conducted at the University Hospital João de Barros Barreto (HUJBB), Belém-Pará, which is a reference for the treatment of parasitic infectious diseases in the state. From July 2017 to March 2018, data were collected from the Medical Archive Division (DAME) using the records of children up to 13 years of age hospitalized with a diagnosis of cryptococcosis between 2000 and 2017. The collected information was then placed into an electronic table using Excel 7.0. This study was approved by the Ethics Committee of Research of the referred hospital (number 2.095.052). Patient data were kept anonymous.

Descriptive analysis was performed using frequencies and standard deviations. To make a statistical calculation, IBM SPSS 24.05.0 was used, while for the study of variables, a test of qui-quadrate (X^2) with an interval of confidence corresponding to 95% was used. The level of significance adopted was p=0.05 (α=5%).

For the spatial analysis, demographic and cartographic data were obtained from the Brazilian Institute of Geography and Statistics (IBGE) (Pinto Junior, 2010 and IBGE, 2010), and the environmental data obtained from the System of Monitoring of Deforestation of Legal Amazonia from the PRODES project of the National Institute of Spatial Research (INPE). Then, the data were analyzed using TabWin v. XX and laboratory georeferencing through geographic coordinate indexing obtained through the System of Projection LAT/LONG with DATUM WGS 84, generated Geographic DATA (BDGeo), using the softwares ArcGis 10.2 and TerraView 4.0. For the data analysis, thematic maps of deforesting and special distribution of patients with cryptococcosis were created. In this phase, geoprocessing techniques were used (GEO) for the analysis of the flow and algebra of the maps. The method chosen to analyze the special standard of cryptococcosis occurrence was the temporal distribution of cases.

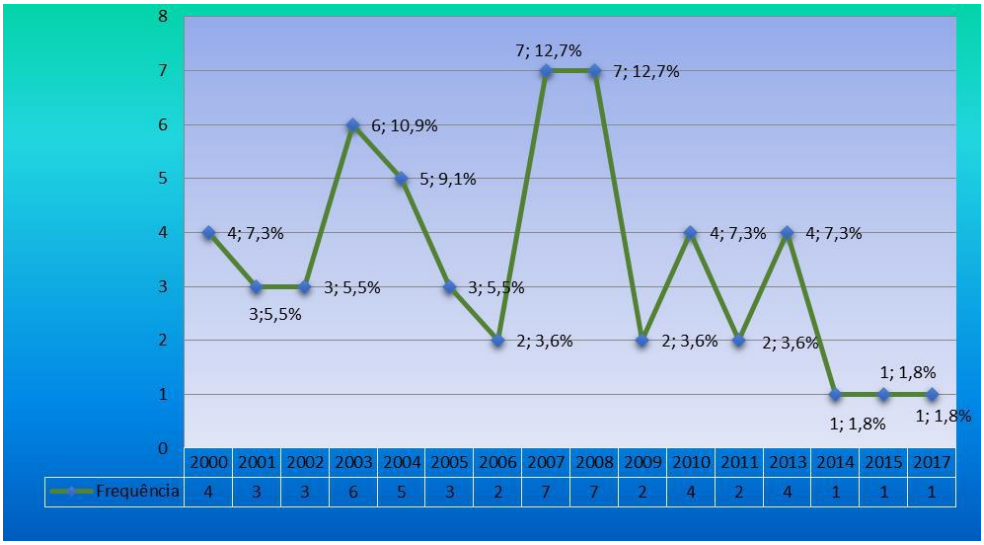
3. Results

After conducting a survey in the Medical Archive of Division and Statistics (DAME) of University Hospital João de Barros Barreto, data of a total of 60 children up to 13 years of age with cryptococcosis diagnosed from January 2000 to December 2017 were taken. Of these, 55 were included in this study, while 5 were excluded because of lack of complete data in the inbuilt records

3.1 Clinical-epidemiological analysis

A distribution of cases in the period of study revealed that majority of cases occurred in 2007 and 2008 (n=7 ;12.7 % / year), with an annual rate of 3.4 cases (DP= 2.0 cases), as Figure 1:

Figure 1 – Distribution of Cryptococcosis cases by Year in children admitted to the HUJBB, in the period 2000–2017.



Source: Prepared by the author (2019).

The age range varied from 5 to 13 years, with a median of 8.9 years, and majority of cases affecting children aged 10–13 years old (n=27; 49.1%). The disease was more predominant in males (n=34; 61.8%), those with brown skin, (n=46; 83.6%), and those in rural areas (n=38; 60.1%; P=0.824).

In 37 cases (67.3%) whose causative species were identified, *C. gattii* was found to be responsible for 29 cases (52.7%), while *C. neoformans* was responsible for 8 cases (14.5%).

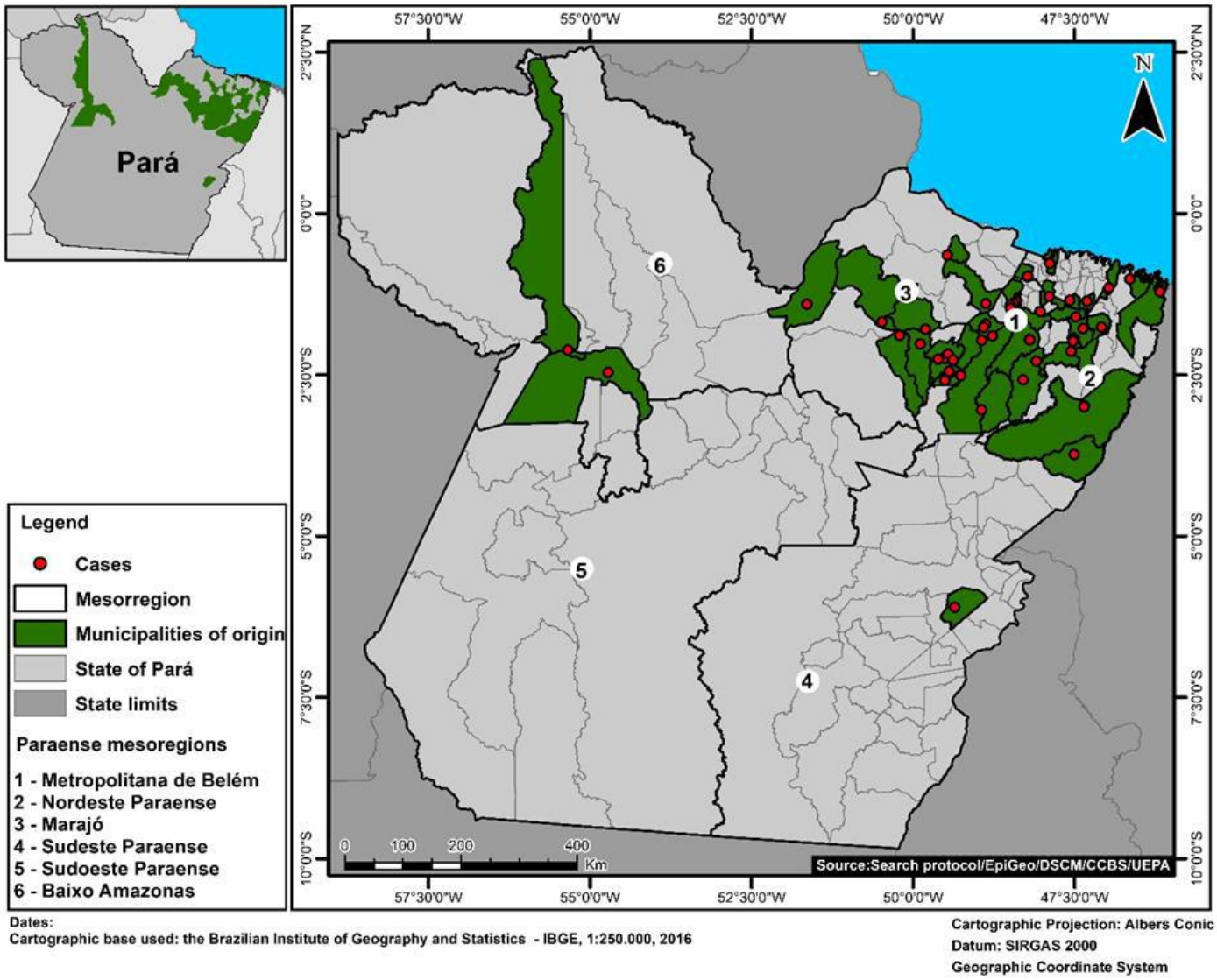
Meningoencephalitis occurred in 51 cases (92.7%), followed by 3 cases of meningoencephalitis associated with pulmonary cryptococcosis (5.5%) and one case of meningoencephalitis associated with cryptococcosis tegumentar (1.8%). There was a predominance of headache (n=53; 93.4%; P=0.494), vomiting (n=49; 89.1%, P=0.860) and fever (n=49; 89.1%; P=0.369). The occurrence of sequelae was frequent, with a predominance of headache (n=27; 49.1%, P=0.104) and alteration of visual acuity (n=20; 36.4%, P=0.005). Of the total patients who developed headache, 18 (66.7%) underwent a ventriculoperitoneal shunt.

Fifty patients (90.9%) were treated in the induction phase with Anfotericina B desoxicolato, 4 cases (7.3%) with Anfotericina B desoxicolato associated with fluconazole, and one patient (1.8%) received only fluconazole. Of all the patients, 42 (76.4%) showed clinical improvement, while 9 patients (16.3%) died.

3.2 Analysis of spatial distribution of cases in the state of Pará

Analysis of the spatial distribution of cases showed an inhomogeneous pattern in the municipalities of Pará, with a major concentration in the mesoregions of north-east Para (35 cases, 63.6%). Nevertheless, no case was registered in the southeast of Pará. In the meantime, the mesoregion of Low Amazon registered only 2 cases (3.6%), the South-east of Pará registered four cases (7.3%), Marajó Island registered six cases (10.9%), and the metropolitan mesoregion of Belém registered 8 cases (14.5%). Municipalities that reported a higher number of cases were Cametá and Mocajuba, with 7 and 5 cases, respectively. The other municipalities had only 1–2 cases, as Figure 2.

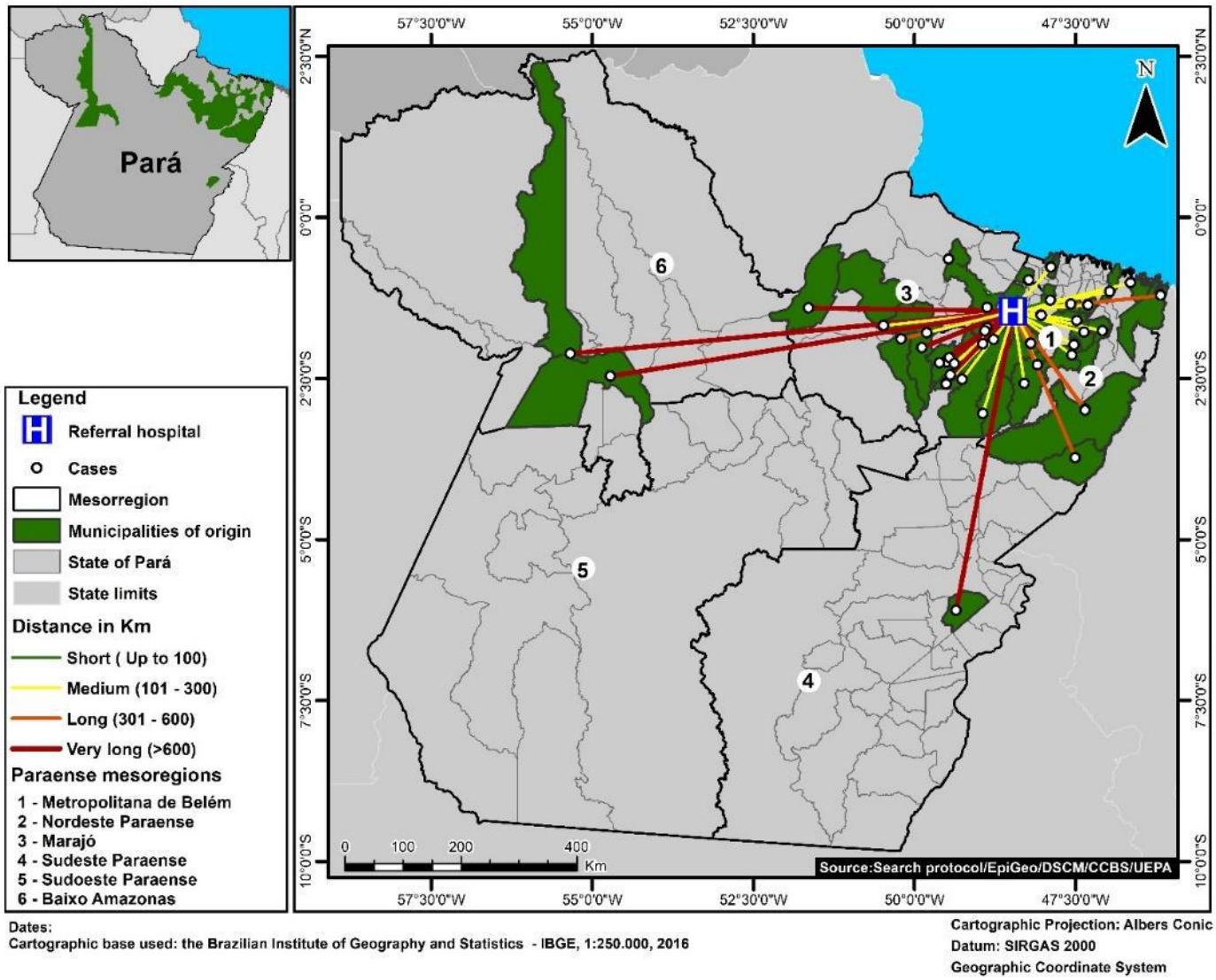
Figure 2 – Spatial distribution of cases of cryptococcosis in the state of Pará from 2000 to 2017.



Source: Research Protocol/EPIGEO/DSCM/CCBS/UEPA – 2018.

An analysis of the map of flow (Figure 3) was created to visually express a relation between the distance and the municipalities where the cases of cryptococcosis were recorded, which shows that distance influences access to health service, with the smaller the distance, the bigger the number of flow origin/destination of cases needing to be attended to.

Figure 3 – Origin and destination of demand-service of cryptococcosis in Pará State from 2000 to 2017.

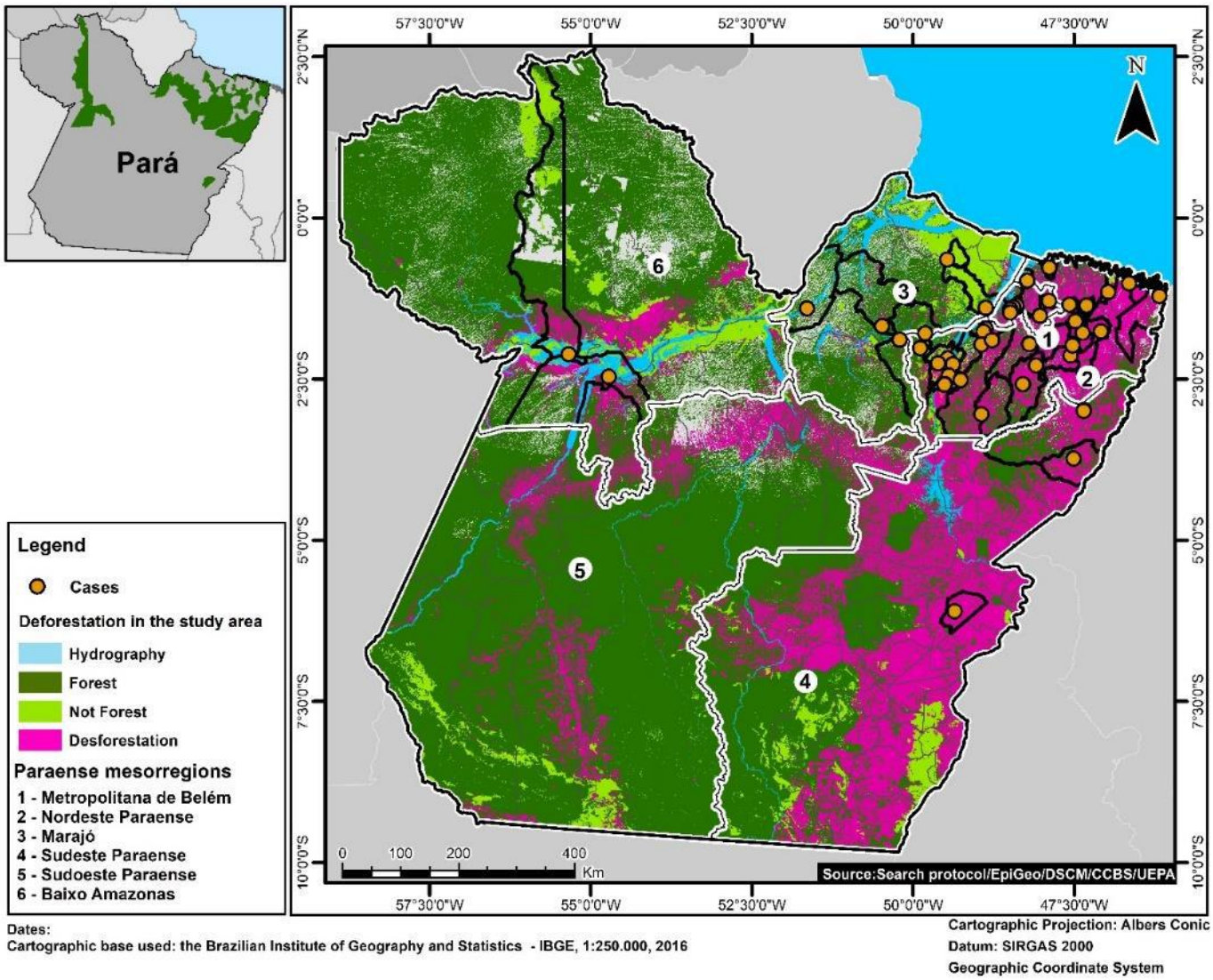


Source: Research Protocol/EPIGEO/DSCM/CCBS/UEPA – 2018.

This way, it is possible to observe that the pursuit for service of care and attention attributed to cryptococcosis emerged with higher percentage in municipalities that had short (21.8%) and medium (50.9%) distances in relation to the place of service offered. On the other hand, municipalities that had long distances (9.1%) and very long distances (18.2%) were those that presented a minor number of attended cases.

It can be seen from the map, which illustrates the areas of deforestation (Figure 3) during this period, that removal of the native forest cover in Pará has happened in a heterogenous way in its variable municipalities, and that according to the data of INPE, the total area of vegetation removed in the interval of analysis (2000 and 2017) was estimated to be 79.5 mil km² (INPE, 2018). It was possible to observe that the period between the years 2000 and 2011 were the most critical, where vegetation of 66,000 km² was deforested, which corresponds to approximately 83.0% of the total estimated in the period. The highest number of cases diagnosed with cryptococcosis and those hospitalized in the hospital of reference was also highest during this period (48 cases), which corresponds to 87.3% of the total cases. On the other hand, in the period between 2012 and 2017, the state deforested about 1,35,000 km² of forest cover, which was the period with the least amount of deforestation done in the period of study (Figure 4).

Figure 4 – Deforestation of the area of study from 2000 to 2017.



Source: Research Protocol/EPIGEO/DSCM/CCBS/UEPA – 2018.

Data from IBGE (INPE, 2018) showed that in the period between 2000 and 2004, due to tax charged with deforesting in Pará, there was a considerable increase of up to 9.000k²/year. This study shows that in the same period, the highest number of *Cryptococcus* cases was registered (26 cases, 47.28%). Since 2005, it has been observed that after the tax charged with deforesting slowed down, which varied from 6.000–3.000k²/year, the number of cryptococcosis cases dropped to 22, corresponding to 40.0% of the total cases. In the period between 2012 and 2017, deforesting was around 13.5 mil km², the smallest during the period studied; consequently, this was the smallest number of cases registered for cryptococcosis, with only seven registrations corresponding to 12.7%.

4. Discussion

After the completion of data collection and its treatment in Pará, which represents 29.7% of the Brazilian Amazon and 14.6% of the national territory, we identified that in the period between 2000 and 2017, 60 children were hospitalized with a diagnosis of cryptococcosis at the University Hospital João de Barros Barreto, which is a hospital of reference for these cases in Pará. In the current study, 55 cases were included and five were excluded, as they lacked information in the medical records.

The distribution by age in this study showed that the largest occurrence of cases was in children aged 5–13 years old, with an average age of 8.9 years, as observed in the work published by Corrêa *et al.* (1999) and Lizarazo *et al.* (2014). There was no case of affected children younger than 2 years old in our study, which was also similar to the results of Goldman *et al.* (2001), who when analyzing immunologically competent children observed that children younger than 2 years old had minimum reactivity to the *C. neoformans* protein, while children over 2 years old showed increasing reactivity, reaching up to 70% in children over 5 years old. Several other authors have also described the same presentations of cryptococcosis in children (Corrêa *et al.*, 1999, Santos *et al.*, 2008 & Severo *et al.*, 2011).

In our study, there was a predominance of cases affecting males (61.82%) as compared with females (38.18%). This higher incidence related to sex has also been described in other studies conducted in South Africa, China, the United States, and Colombia (Guo *et al.*, 2016, Lizarazo *et al.*, 2014, Miglia *et al.*, 2011 & Joshi *et al.*, 2010).

Apparently, cryptococcosis in the Amazon region has a preference for brown-colored skin, which represented about 83.63% of the total cases (46 cases). However, this distribution is probably more related to an intense miscegenation of races that occurs in the Amazon Region due to ethnic predilection related to some specific groups, since the contribution of genetic inheritance, mainly indigenous and to a lesser extent African, determines that 73% of the population of the State of Pará is brown (Pará, 2016).

There are risk factors for acquisition of the disease, other than the presence or mention of a clinical or other condition that causes immunosuppression. This has been shown in a study conducted in Pará, described by Corrêa *et al.* (1999), as well as a study conducted in China by Yuanjie *et al.* (2012). Some studies in the literature also point to the presence of some kind of immunosuppression as a predisposing factor to infection in children, as seen in the patients evaluated by Guo *et al.* (2012), Huang *et al.* (2010), Lizarazo *et al.* (2014) and Guo *et al.* 2016.

The clinical evolution of our cryptococcosis showed similarity to existing literature, with almost all patients presenting with meningoencephalic involvement. The neurotropism of *Cryptococcus* by SNC is attributed to the presence of an adequate concentration of nutrients assimilated by the fungus, as well as lack of activity of system compliance and nonexistence, or a deficient inflammatory response of brain tissue (Jongwutiwes, et al., 2008).

Majority of cases were diagnosed only after 30 days from the beginning of symptoms as observed in other studies (Corrêa *et al.*, 1999, Lizarazo *et al.*, 2014, Lizarazo *et al.*, 2007 & Escandón *et al.*, 2012), and that clinical presentations of cryptococcosis were more commonly in the form of headache, fever, and vomiting, as well as neck stiffness. It is important to note that in prior studies, there was no evidence of measurement of intracranial pressure in patients with hydrocephalus according to Lizarazo *et al.* (2014). These data are rare, despite being part of the treatment guidelines for neurocryptococcosis.

CSF cytochemical analysis and direct mycological examination using ink from China were performed in 100% of the cases, and all were positive. Latex agglutination was performed in only nine cases, with positivity was observed in seven cases (77.77%). Culture for fungus on LCR was performed in 46 cases, and from these, 41 (74.55%) were positive for *Cryptococcus* in only 2 cases cultured in other tissues, with all being 100% positive. In relation to diagnosed species, 29 cases (53%) were identified as *C. gattii*, 8 cases (14%) were identified as *C. neoformans*, while the species implicated in 18 cases (33%) were not identified, thus showing that Pará can be considered endemic for *C. gattii*. This variety of laboratory characteristics have also been described in various studies conducted in endemic areas for the disease, such as the Amazonia, especially for Pará, as an endemic area for cryptococcosis mainly caused by *C. gattii* (Corrêa *et al.*, 1999 & Darzé, 2000).

Regarding pharmacological management and clinical outcomes, 100% of the cases received induction of amphotericin B followed by the use of fluconazole, as recommended by the World Health Organization. However, the rate of fatality (16.38%) can be considered high when compared with data described by Joshi *et al.* (2010) in the United States of America, but on the other hand, low when compared with a tax described by the states of Pará and Rio Grande do Sul in the work

published by Corrêa *et al.* (1999), Severo *et al.* (2009) and in China by Luo *et al.* (2015) and Guo *et al.* (2016).

With regard to clinical sequelae, computed skull tomography data showed that the most frequent finding was hydrocephalus (49.09%), which was represented by 18 cases requiring ventriculoperitoneal shunt. This percentage exceeds the 18.8% seen in a study by Lizarazo *et al.* (2014) and 38.9% in a study by Guo *et al.* (2016).

In order to better elucidate the data discussed so far, geoprocessing techniques were used. This showed heterogeneity of records of this disease in the studied areas, and it can be observed that the northeast of Pará mesoregion, as previously mentioned, had the largest number of municipalities with treated cases (35 cases). On the other hand, the southeast mesoregion of Pará has not registered any cases, with the smallest number of described cases from the mesoregion of Low Amazon, which registered only two cases.

The mesoregions of Pará presented sociodemographic characteristics that favor the occurrence of cryptococcosis, according to Pereira and Barros (2012). From an epidemiologic point of view, *C. neoformans* is considered cosmopolitan and therefore is found in different geographic regions, and being saprophytic, this fungus is related to various organic substrates. On the other hand, *C. gattii* can be isolated in regions of tropical and subtropical weather apart from regions having warm climate, with its incidence in the environment strongly related to the presence of wood in decomposition, which can be favored by intense deforestation as a consequence of exporting and other developing projects that are characterized in many regions of the Brazilian Amazon.

When we observed that during the study period, removal of the native cover in Pará state was heterogeneous in its various municipalities, a similar distribution of the cases of cryptococcosis also occurred in a heterogeneous way. This analysis identified a relationship between deforestation and the occurrence of disease in most of the studied municipalities, considering that the number of cases is related to greater or lesser deforestation. Although studies of species isolation of *Cryptococcus* in environmental samples are scarce in the northern region, it is important to stress that *Cryptococcus* can also be isolated from domestic dust, as shown by Costa (2008) and Brito-Santos *et al.* (2015), which related the presence of fungus in domestic dust in the municipality of Santa Izabel do Rio Negro (Amazonas).

A geographic distance from the place of occurrence of infection to the hospital of reference for the adequate treatment is shown by the map of flow, and it was possible to observe a direct relationship between the occurrence of treatment and distance. Certainly, there was a greater search for patients living in municipalities that have short and medium distances in relation to specialized health services. This can be justified probably by greater facility access, or because of the shorter distance traveled, as well as the greater availability of transport offered in the area. As related in Pará (2012), in Pará state, access to health services is not associated to its existence or nonexistence, but also to the demographic, socio-economical, and cultural condition of the population.

5. Conclusion

Cryptococcosis is still a challenge in clinical practice in Brazil, especially in the northern region. Unfortunately, there is a lack of multicenter studies on the condition, especially those with prospective characteristics. This study permitted the association of reference data with clinical and epidemiological characteristics to geotechnology, favoring knowledge of the environmental condition of the places of occurrence, and of the sociodemographic indicators. The use of geoprocessing permitted the analysis of the service demand in the hospital of reference, identifying places of occurrence of the disease, as well as its demographic and socio-economic characterization, which provided relevant information about the spatial behavior of this disease, with the current study finding higher disease occurrence in the rural environment and in areas with prevalent deforesting.

The identification of endemic areas for cryptococcosis is also of fundamental importance, because from this

knowledge it is possible to implement public policies to improve the social conditions of these areas and thus reduce the number of cases. Consequently, reducing the number of deaths and severe neurological sequelae, since, according to what was found in this study, the highest occurrence occurred in the rural area of Pará's mesoregions, where the socioeconomic situation is unfavorable.

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