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ARTIGO ORIGINAL

Epidemiological Findings of Neurocryptococcosis in Immunocompetent Patients: Case Reports from a Public Hospital in Joinville, Brazil

Achados Epidemiológicos de Neurocriptococose em Pacientes Imunocompetentes: Relato de Casos de um Hospital Público de Joinville, Brasil

Hallazgos epidemiológicos sobre neurocriptococosis en pacientes inmunocompetentes: relato de casos en hospital público de Joinville-Brasil

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ABSTRACT

Background and Objectives: Neurocryptococcosis is a fungal disease that affects mainly immunocompromised patients. Cases in immunocompetent patients have been described in some case reports. However, as its reporting was not mandatory in Brazil until 2020, little is known about its epidemiology in the South Region of the country. The present study had the objective of describing epidemiological aspects related to the disease in presumably immunocompetent patients. **Methods:** A retrospective and observational study was developed, based on cases of patients who received care in a public hospital in Joinville, Santa Catarina, Brazil, between 2018 and 2019. Patients with a clinical diagnosis confirmed by the presence of the fungus Cryptococcus spp. in cerebrospinal fluid by means of the Chinese ink staining were evaluated regarding clinical aspects, treatment, and complications during hospitalization. **Results:** The diagnosis of the disease was confirmed for two patients in 2018 and six patients in 2019. All of them showed no apparent factors for immunodeficiency and no evident environmental risk factors. Most were men with an average age of 39 years. Fever and mental confusion were the most common symptoms at admission. The variant *C. neoformans* was found in 75% of the cases. All patients received amphotericin B for at least 13 days with or without combined fluconazole. Six patients had nephrotoxicity due to amphotericin B, two evolved to in-hospital death, and two had neurological sequelae. **Conclusion:** Mortality and complications related to the treatment of neurocryptococcosis in immunocompetent people showed high rates in the studied sample. The recent inclusion of this disease as a mandatory reporting pathology can improve epidemiological data, which will be used to achieve better understanding and prevention of this problem.

Keywords: *Cryptococcal Meningitis. Meningitis. Epidemiology. Immunocompetence.*

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RESUMO

Justificativa e Objetivos: Neurocriptococose é uma doença fúngica que acomete principalmente pacientes imunocomprometidos. Casos em pacientes imunocompetentes têm sido descritos em alguns relatos de casos; no entanto, por não ser uma doença de notificação compulsória no Brasil até 2020, ainda pouco se sabe sobre sua epidemiologia no sul do país. O presente estudo teve como objetivo descrever aspectos epidemiológicos relacionados à doença em pacientes supostamente imunocompetentes. **Métodos:** Estudo retrospectivo, observacional, baseado em uma série de casos atendidos entre 2018 e 2019 em um hospital público de Joinville, Santa Catarina, Brasil. Pacientes com diagnóstico clínico confirmado pela presença do fungo do gênero *Cryptococcus* spp. no líquido cefalorraquidiano pelo método tinta da China foram avaliados quanto aos aspectos clínicos, ao tratamento e às complicações durante o período de internação. **Resultados:** Houve dois pacientes em 2018 e seis pacientes em 2019 com diagnóstico confirmado. Todos sem fatores aparentes para imunocomprometimento e sem fator de risco ambiental evidente. A maioria eram homens com média de idade de 39 anos. Febre e confusão mental foram os achados mais comuns na apresentação. A variante *C. neoformans* foi encontrada em 75% dos casos. Todos receberam Anfotericina B, no mínimo, durante 13 dias, associado ou não a Fluconazol. Seis pacientes apresentaram nefrotoxicidade causada pela Anfotericina B, dois evoluíram para óbito intra-hospitalar e dois permaneceram com sequelas neurológicas. **Conclusão:** A mortalidade e as complicações relacionadas ao tratamento da neurocriptococose em pessoas imunocompetentes foram altas na amostra estudada. A recente inclusão da doença como uma patologia de notificação compulsória poderá aprimorar dados epidemiológicos para o melhor entendimento e a prevenção dessa doença.

Descritores: *Meningite Criptocócica. Meningite. Epidemiologia. Imunocompetência.*

RESUMEN

Justificación y Objetivos: La neurocriptococosis es una enfermedad fúngica que afecta especialmente a pacientes inmunocomprometidos. Fueron citados casos en pacientes inmunocompetentes en algunos relatos. Por no considerársela de notificación obligatoria en Brasil hasta 2020, poco se sabe aún sobre su epidemiología en el sur del país. El estudio objetivó describir aspectos epidemiológicos relativos a la enfermedad en pacientes supuestamente inmunocompetentes. **Métodos:** Estudio retrospectivo, observacional, en base a una serie de casos atendidos entre 2018 y 2019 en un hospital público de Joinville, Santa Catarina. Pacientes con diagnóstico clínico confirmado por presencia de *Cryptococcus* spp., utilizándose el método de tinta china en líquido cefalorraquídeo fueron evaluados respecto de aspectos clínicos, tratamiento y complicaciones durante su internación. **Resultados:** Hubo 2 pacientes en 2018 y 6 en 2019 con diagnóstico confirmado, todos sin factores aparentes de inmunocompromiso y sin factor de riesgo ambiental evidente. Mayoría de hombre, media etaria de 39 años. Fueron hallazgos comunes en su presentación la fiebre y confusión mental. La variante *C. neoformans* fue hallada en 75% de los casos. Todos recibieron anfotericina B como mínimo durante 13 días, en asociación o no con fluconazol. Seis pacientes presentaron nefrotoxicidad por anfotericina B, dos sufrieron fallecimiento intrahospitalario, y dos resultaron con secuelas neurológicas. **Conclusión:** La mortalidad y las complicaciones relativas al tratamiento de la neurocriptococosis en inmunocompetentes fueron altas en la muestra estudiada. La inclusión de la enfermedad como patología de notificación obligatoria podrá mejorar los datos epidemiológicos para entender mejor y prevenir la enfermedad.

Descriptores: *Meningitis Criptocócica. Meningitis. Epidemiología. Inmunocompetencia.*

INTRODUCTION

Cryptococcosis is a systemic fungal disease that affects mostly people with immunodeficiency and is the main cause of meningoencephalitides in patients with the human immunodeficiency virus (HIV), with a mortality rate of 15% in this group of patients.[1] The disease is a potentially lethal condition caused by an encapsulated fungus of the genus *Cryptococcus* spp.[2] The presence of meningoencephalitis caused by *Cryptococcus* in immunocompetent patients has been described in some case reports over the world.[3-9] The Brazilian Ministry of Health began to consider cryptococcosis a mandatory reporting disease only in February 2020. Consequently, the prevalence of neurocryptococcosis in presumably immunocompetent patients has varied, ranging from 5% to 43% of the endemic cases described in the Southeast and North Regions of Brazil.[10-13] However, little is known about the occurrence of this disease in the South Region of the country.

Before the emergence of HIV, cryptococcosis had a low incidence and was often a complication associated with other chronic diseases or the use of medications, including those used to treat neoplasias, corticosteroids used chronically, and immunosuppressive and chemotherapy drugs.[2] From the 1980s onwards, cryptococcosis became more frequent in the clinical setting and a remarkable increase in its incidence in tropical and subtropical areas was observed.[1] Two species of this fungus genus have been associated with the disease in humans: *Cryptococcus neoformans* and *Cryptococcus gattii,*[14] which have different sources of contamination. *C. neoformans* is

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usually isolated in soil contaminated with bird excrement, whereas *C. gattii* is more commonly found in areas with eucalyptus leaves or decaying tree wood in tropical and subtropical regions.[12,14] The only mode of transmission described in the literature is by inhaling the fungus in the environment.[2,14] In the North and Northeast Regions of Brazil, the presence of the *C. gattii* form has been more often found in immunocompetent patients.[10-13] In the South Region, the cases of cryptococcosis diagnosed in immunosuppressed patients have been predominantly caused by *C. neoformans*.[10]

Cryptococcosis has been the second cause of mortality in patients affected by systemic mycoses in Brazil.[15] According to DATASUS, there were around 22,000 hospitalizations in Brazil over the past five years because of systemic mycoses, and 45% of these hospital admissions occurred in the Northeast Region of the country.[16] In the state of Santa Catarina, the average number of hospitalizations prompted by systemic mycoses has been 100 per year, which is one third of the annual number of hospital admissions caused by leptospirosis, a disease with mandatory reporting.[16] Although the occurrence of cases of systemic mycoses is an important cause of morbidity and hospitalization, there is a lack of epidemiological studies specifically addressing meningoencephalitis caused by *Cryptococcus* spp. in immunocompetent patients in the South Region of Brazil.

The present study had the objective of describing epidemiological aspects related to neurological findings linked to cryptococcosis in presumably immunocompetent patients.

METHODS

This was a report of a series of cases that characterized a retrospective, descriptive, and observational study based on the review of patient records of all the confirmed cases of neurocryptococcosis in immunocompetent patients admitted to São José Municipal Hospital, in Joinville, state of Santa Catarina, Brazil, from February 2018 to January 2020. This is a public general hospital, with a medical residency program in several areas, including neurology. All the patients 18 years old or older with a diagnosis of neurocryptococcosis confirmed by identification of the fungus *Cryptococcus* spp. in the cerebrospinal fluid by means of the direct mycological test carried out with Chinese ink staining were included in the sample. The other evaluated data were gender, age, place of residence, symptoms, routine laboratory and imaging tests, treatment carried out, and outcomes such as mortality, kidney failure, or neurological sequelae identified until hospital discharge. The proposal was approved by the hospital research ethics committee (report no. 3.919.390/CAAE 29503320.5.0000.5362).

RESULTS

Eight cases of neurocryptococcosis were found for the analyzed period, with five men (62.5%) and three (37.5%) women. The average age was 39.25 ± 14.51 years. Two cases were diagnosed in 2018 (cases 1 and 2) and the others were confirmed in 2019. Two patients lived in Barra Velha, a coastal municipality in the north of Santa Catarina, 55 km away from Joinville. The other six patients lived in the study city, and the distance between their places of residence ranged from 3 to 6.5 km. In this subgroup with six patients, two were prisoners at the local penitentiary. Regarding symptoms, all the patients complained about headache at hospital admission, three (37.5%) showed mental confusion, and three (37.5%) had fever. Only two patients (25%) showed signs of meningeal irritation during physical examination. All patients were evaluated for the presence of previous diseases or therapies that could be associated with an immunodeficiency status, such as cancer, contamination with HIV, liver disease, severe malnutrition, and use of immunosuppressants and/or treatment with corticoids. No patient had clinical or laboratory findings related to immunodeficiency. Two patients did not have associated comorbidities and, in the remaining six patients, the most common previous comorbidities were hypertension (37.5%) and drug addiction (37.5%). Other characteristics of the sample are shown in table 1.

Cellularity in the cerebrospinal fluid over 200 leukocytes/mm^3 was found in 87.5% of the cases in the first analysis of the fluid, with the presence of hypoglycorrhachia (a value 60% lower than that found for blood serum glycemia) in all cases. The species *Cryptococcus neoformans* was found in the cerebrospinal fluid of 75% of the examined cases, and the fungus species was not identified in cases 2 and 3. Only one patient (case 5) did not show alterations in brain imaging (computerized tomography or magnetic resonance). The images obtained with the latter technique indicated ventriculitis, increased thalamic perivascular spaces, subcortical nodular lesions, multiple cystic lesions, and dural enhancement. The former imaging method showed the presence of diffuse cerebral edema, cerebellar hyperdensity with hypodense halo, and lesion with perilesional edema.

All patients received 1 mg/kg/day endovenous amphotericin B deoxycholate over a period that ranged from 13 to 74 days. This time variation occurred because of the time necessary for the cerebrospinal liquid culture to show a negative result according to the tests carried out at the support laboratory. For two patients (cases 1 and 4), part of the treatment was carried out with 6 mg/kg/day liposomal amphotericin based on the availability of the medication at the institution. The use of fluconazole in the consolidation phase happened over a period between the 12th and the 110th day (cases 2 and 6 to 8). One patient (case 2) had a consolidation treatment with 400 mg/day fluconazole over around 10 weeks and a maintenance period of six weeks.

Regarding the complications related to the treatment, hypokalemia associated with the use of amphotericin B was observed in all patients. Additionally, the presence of acute kidney lesion caused by nephrotoxicity

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Table 1. General characteristics of the analyzed cases (n=8).

					Cerebrospinal fluid analysis											
Case	**Gender**	**Age**	**Origin**	**Previous diseases**	**Cells (no./ mm³)**	**Seg (%)**	**Lymphomono (%)**	**Prot (mg/dL)**	**Glic (mg/dL)**	**Positive culture**	**Treatment (days)**	**Hospi-talization (days)**	**Death**	**AKL**	**Hepatoto-xicity**	**Neurological sequela**
1	M	54	Joinville	1. SAH 2. Previous stroke	308	75	0	0	18	Yes	Ampho Dex/LipA (27)	28	No	No	No	No
2	F	50	Joinville	1. SAH	320	49	0	0	25	No	Ampho Dex (54) Fluco (110)	167	Yes	Yes	Yes	
3	M	53	Joinville	1. SAH 2. Smoking 3. Alcoholism	578	0	56	96	56	No	Ampho Dex (14)	20	No	No	Yes	No
4	F	54	Joinville		26	0	80	15	44	Yes	Ampho Dex/ LipA (74)	177	No	Yes	Yes	Yes
5	M	26	Barra Velha	1. Drug addiction	538	0	66	65	42	Yes	Ampho Dex (13)	21	No	Yes	No	No
6	M	27	Joinville	1. Smoking 2. Alcoholism 3. Drug addiction	395	0	96	108	51	Yes	Ampho Dex (17) Fluco (12)	17	Yes	Yes	Yes	
7	M	24	Joinville		380	0	70	100	31	Yes	Ampho Dex (61) Fluco (61)	61	No	Yes	No	No
8	F	26	Barra Velha	1. Drug addiction	217	0	39	73	28	Yes	Ampho Dex (69) Fluco (69)	69	No	Yes	No	Yes

SAH: systemic arterial hypertension; Seg: segmented; Lymphomono: lymphocytes and monocytes; Prot: proteins; Gluc: glucose; AKL: acute kidney lesion; Ampho Dex: amphotericin deoxycholate; LipA: liposomal amphotericin; Fluco: fluconazole; Reference values for the cerebrospinal fluid: cellularity of 0-4 leukocytes/mm3; segmented: < 5%; lymphomonocytes: 30-70%; proteins < 40mg/dL; glucose > 45mg/dL.

triggered by amphotericin B was found in six patients (75%). Four patients (50%) had hepatotoxicity, two of whom during consolidation with fluconazole. Two patients evolved to death during hospitalization and two had a neurological sequela (cases 4 and 8, both with ophthalmoplegia).

DISCUSSION

Based on the review carried out by the authors, it is possible to state that this is the first study to evaluate epidemiological aspects of neurocryptococcosis in immunocompetent patients at a hospital in the South of Brazil. There was an increase in the number of cases over the two analyzed years, predominantly of the *Cryptococcus neoformans* variant, with a higher prevalence in non-elderly men and non-negligible mortality and renal complications resulting from treatment.

A retrospective study carried out in the Brazilian state of Minas Gerais found a high rate of neurocryptococcosis in immunosuppressed patients, and 96% of the cases were caused by the *C. neoformans* variant.[13] In the 278 cases reviewed by the authors, covering a period of 20 years, only four cases of neurocryptococcosis in apparently immunocompetent patients were found, all of them caused by the *C. gattii* species.[13] A similar result was reported by another study in the same Brazilian region, in which a review of neurocryptococcosis cases registered between 1998 and 2010 identified only six cases in immunocompetent patients, also infected with *C.gattii*.[11] A reduced number of cases of meningitis caused by *C. gattii* have been detected in immunocompetent children and adolescents in the far North of the country, in the state of Piauí.[10] It is believed that the variants of the species *C. gattii* have their origin in the Amazon tropical forest region and are responsible for outbreaks that occurred in other parts of the world with migrant birds as vectors.[17,18] The present study identified an increase in the number of spontaneous cases over the two considered years and a predominance of the fungus *C. neoformans*. It is known that this species is often found in patients

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with HIV in the South of Brazil. The fact that a remarkable share of the examined sample lived in the biggest city of Santa Catarina and the growing anthropic action observed in great urban areas may justify that the number of immunocompetent people exposed to this fungus is increasing.

The symptoms of neurocryptococcosis cases have varied considerably, in both immunocompetent patients and people with diseases associated with HIV.[11,19] Alteration of the mental state, meningitis symptoms, and fever have been most commonly found in patients with neurocryptococcosis.[11,13,19] The predominant clinical status in the patients analyzed in the present study was compatible with meningitis. However, a small number of these patients had nuchal rigidity as one of the results of their physical examination, indicating the importance of diagnostic suspicion and of complementing the investigation by analyzing the cerebrospinal fluid. This procedure is mandatory in cases like these, in which a variable increase in cellularity, with predominance of lymphomonocytes, together with a low glucose level and an increased concentration of proteins in the cerebrospinal liquid, may suggest meningitis.[2] The use of Chinese ink staining allows to visualize yeasts that are highly suggestive of diseases caused by fungi.[2] Culture is a key element, for both characterizing the fungus species and guiding the response to the treatment, since Chinese ink does not distinguish between active and inactive fungi, which means that the method cannot be used to confirm treated diseases.[2]

Treatment scheme and time have varied in different studies.[3,13,19] The best evidence for the treatment of neurocryptococcosis is based on studies involving immunosuppressed patients.[20] The Brazilian Health Ministry has been instituting a protocol with three phases: induction, consolidation, and maintenance.[21] The induction phase is characterized by the use of amphotericin combined or not with flucytosine, which is not traded in Brazil, until the sterilization of the cerebrospinal fluid, that is, until the etiologic agent is no longer identified in the sample of the cerebrospinal fluid culture. The consolidation phase involves administration of fluconazole over six to 12 weeks. The last phase, maintenance, has a variable duration, and for immunocompetent patients it is carried out according to medical indication.[21] In the present study, the time of use of amphotericin B showed disparate intervals, because of both the lack of a defined institutional protocol and the time to process the cerebrospinal fluid samples until culture negativation was reached in the analyses carried out by the reference laboratory in the state, located in a different city. After the publication of the last neurocryptococcosis treatment guidelines by the Brazilian Health Ministry in 2019,[21] verifying negativation in the cerebrospinal fluid before moving to the consolidation phase began to be a standard conduct, and in-hospital deaths were not registered in the examined samples from that point onwards. Because of the severity of the symptoms, the physicians opted for a short maintenance for one of the cases, with the administration of fluconazole, a situation provided for the Brazilian Ministry of Health treatment guidelines, although without a clear definition of severity for the indication.

The mortality associated with neurocryptococcosis in immunocompetent patients has ranged from 25% to 50% in some Brazilian studies.[10,13] Some of the explanations for this wide mortality rate are epidemiological characteristics of the patients, applied therapeutic plans, and local difficulties for diagnosis and treatment. Adverse effects associated with the treatment, especially the use of amphotericin, have been reported frequently.[10,11,13] The present study showed a noticeable prevalence of nephrotoxic acute kidney lesion caused by the use of amphotericin B.

Cryptococcosis is a disease typical of tropical and subtropical countries and, because some of these areas are occupied by underdeveloped and developing countries, it has become a potentially neglected disease.[1,11] Cases in which other diseases that lead to immunosuppression are associated have been more frequently found. However, because the reporting of the disease became mandatory only very recently, there is a lack of epidemiological data obtained with standardized information collection that could provide resources to develop prevention actions, run epidemiological analyses, and better evaluate therapeutic conducts.

The present study has limitations that have to be taken into account. As it is retrospective, other data that could be relevant, such as occupational risk factors, could not be analyzed. Additionally, follow-up was limited during hospitalization, and the risk of relapse or other complications after hospital discharge could not be assessed. The limited sample did not allow to explore data analytically, but these can be relevant to improve the epidemiological understanding of the disease and its occurrence in immunocompetent patients.

In conclusion, the data pointed to a possible increase in the number of local cases regarding neurocryptococcosis in immunocompetent patients. Considering the severity of the disease and the potential complications associated with the treatment and sequelae, the results can provide resources to expand the knowledge of the health problem and demonstrate the importance of the recent inclusion of neurocryptococcosis in the list of mandatory reporting diseases adopted in Brazil for the understanding of the epidemiological evolution of the disease and monitoring of the responses to the advocated treatments.

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AUTHORS' CONTRIBUTIONS

All the authors contributed to the study conception, manuscript outlining, data analysis, writing of the article and final approval. All the authors approved the final version to be published and are responsible for all the aspects of the study, including the guarantee of its accuracy and integrity.

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