

Epidemiological Profile of Cryptococcal Meningitis Patients in Rio Grande do Sul, Brazil

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Abstract Cryptococcosis is a major opportunistic mycosis which has meningitis as its most frequent clinical presentation and can be fatal in the absence of antifungal therapy. The aetiological agents are *Cryptococcus neoformans*, which affects mainly immunocompromised subjects, and *C. gattii*, the aetiological agent for cryptococcosis in healthy individuals. A recent outbreak of cryptococcosis on Vancouver Island, Canada, raised the level of concern about the epidemiology of this disease. In Brazil, between 1980 and 2002, six per cent of AIDS patients had cryptococcosis in course at the time of diagnosis. To identify the profile of cryptococcal meningitis patients in Rio Grande do Sul (RS), Brazil, a retroactive study was realized using data from patients registered at Laboratório Central de Saúde Pública IPB-LACEN/RS from 2000 to 2005. Most of the patients were men (77.12%), Caucasian (83.5%), median age between thirty and thirty-nine years old (46.24%) and HIV positive (95%).

Keywords Cryptococcosis · Meningitis · AIDS · Epidemiological profile

Introduction

Cryptococcosis is an infection manifested mainly as lung disease or meningitis, which can be rapidly fatal if untreated. This infection can be caused by both *Cryptococcus neoformans* and *Cryptococcus gattii*. *C. neoformans* var. *grubii* (serotype A) and *C. neoformans* var. *neoformans* (serotype D) are cosmopolitan and affect mostly immunocompromised individuals, especially those infected by HIV. *Cryptococcus gattii* affects healthy individuals and was considered to be restricted to tropical and subtropical regions of the world [1, 2] until recently, when it was isolated from humans, animals and from many different environmental locations on Vancouver Island, British Columbia, and from surrounding areas of the Canadian and USA mainland [3–6].

In Brazil, 215,810 cases of AIDS were registered from 1980 to 2002. Six per cent of these patients had cryptococcosis in course at the time of diagnosis [7]. Several molecular typing methods have been used in epidemiological analysis of clinical and environmental isolates of *C. neoformans* and *C. gattii* and important reports have shown the epidemiological aspects of isolates of these yeasts in Rio Grande do Sul state [8–10]. However, these reports did not

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explore the patients' characteristics. Considering the importance of this disease and the lack of data about those patients, a retrospective investigation was conducted in order to verify the profile of patients with cryptococcal meningitis in South Brazil.

Patients and Methods

Data from 126 patients with cryptococcal meningitis who reported to the Laboratório Central de Saúde Pública IPB-LACEN/RS between 2000 and 2005 were used to assess the epidemiological profile of the cryptococcal meningitis patients. The parameters considered for analysis were race, gender, age, HIV and other risk factors for the disease and related symptoms. The number of patients (n) for each parameter was variable, according to the data available, as not all the records were properly filled in. A control group was formed with 220 patients who were suspected to have meningitis, but whose cerebrospinal fluid (CSF) had shown negative results for *C. neoformans* and *C. gattii* using India ink preparations, culture in Sabouraud Dextrose Agar, and latex agglutination test. The statistical analyses were performed using the χ^2 test with or without the Yates correction and *Kappa* test (SPSS vs. 13.0).

Results and Discussion

Epidemiological analysis revealed that the majority of patients were men (77.12%), Caucasian (83.5%) and HIV infected (95%). The data are summarized in Table 1. Most patients were between 30 and 39 years old (46.24%) (Table 2). Race, HIV infection and age were statistically different ($\chi^2 P = 0.0001$) between patient and control groups. The symptoms were mainly chronic headache (80%), fever (22.86%), vomiting (17.14%), sensory loss (14.29%) and stiff neck (11.43%). Chronic headache, sensory loss and stiff neck were statistically different ($\chi^2 P = 0.0001$) between patient and control groups.

We found 95.42% (126 samples) of *C. neoformans* var. *grubii* (serotype A) and 4.58% (6 samples) of *C. gattii* (serotype B). These data are in agreement with the world literature, which points out as predominant the infection caused by variety *grubii* [1, 11]. *Cryptococcus neoformans* var. *neoformans*

(serotype D), which is predominant in temperate climates, was not found. A previous study conducted in our state showed a prevalence of 89.52% and 10.48% for the varieties *grubii* and *gattii*, respectively. However, the percentage of *C. gattii* might be overestimated, since the samples were not randomly obtained [8].

Regarding the epidemiological profile, 95% of the patients were HIV positive, reinforcing the HIV infection as the main risk factor for cryptococcosis. The frequency of HIV infection was significantly higher in the patients with cryptococcal meningitis than in those of the control group ($P = 0.0001$). Our results also agree with the literature about gender, finding 77.12% of men compared to 22.88% of women. In France, a study with 2,125 cases showed a men:women ratio of 6.8 among the HIV-infected patients and 1.7 among the non-infected [12]. The IberoAmerican Cryptococcal Study Group, in nine countries including Brazil, obtained 5.1-fold more infected men than women as a research result [13]. Apparently, men are highly susceptible to infections caused by *C. neoformans* and *C. gattii*.

Other invasive mycosis also appears to be more frequent in men, such as paracoccidioidomycosis, studies of which have shown the influence of female hormones along the course of infection. For *Paracoccidioides brasiliensis*, the rate of subclinical infection is the same for both men and women, but the progression of the disease is higher in men. Male and female mice were infected with conidia (infectious form) and, after 48 hours, the conidia had started to develop into yeast (pathogenic form) in males, but not in females [14, 15]. It is possible that female hormones have an important role in host defence against cryptococcosis; yet, in studies with mice, females infected with *C. neoformans* produced higher levels of cytokines in plasma and higher levels of TNF- α and IFN- γ in spleen and blood than did males [16].

Most cases (46.24%) occurred in 30–39-year-olds, which was statistically different from the control group ($P = 0.0001$). Similar data was found in Austria, Germany and Switzerland, where the age group comprehended 31 and 40 years old for men and 21 and 30 years old for women [17]. In France, Dromer et al. [12] found an age group between 26 and 35 years old for HIV-positive patients and more than 46 years old for HIV-negative patients.

Table 1 Demographic characteristics of the analysed individuals

		Cryptococcal meningitis patients		Control group patients	
		Number	Total	Number	Total
Race	Caucasian*	86 (83.5%)	103	142 (65.44%)	217
	Not Caucasian	17 (16.5%)	103	75 (35.56%)	217
Gender	Male	91 (77.12%)	118	137 (62.56%)	219
	Female	27 (22.88%)	118	82 (37.44%)	219
HIV	Positive*	95 (95%)	100	130 (86.67%)	150
	Negative	5 (5%)	100	20 (13.33%)	150

* The difference is statistically significant according to χ^2 ($P < 0.0001$)

Table 2 Age ranges among all analysed individuals

	Cryptococcal meningitis patients		Control group patients	
	n	%	n	%
From 10 to 19 years old	2	2.15	5	2.86
From 20 to 29 years old	15	16.13	50	28.57
From 30 to 39 years old*	43	46.24	63	36.00
From 40 to 49 years old	24	25.81	36	20.57
From 50 to 59 years old	7	7.53	14	8.00
From 60 to 69 years old	2	2.15	7	4.00
Total	93	100	175	100

* The difference is statistically significant according to χ^2 with Yates correction ($P < 0.0001$)

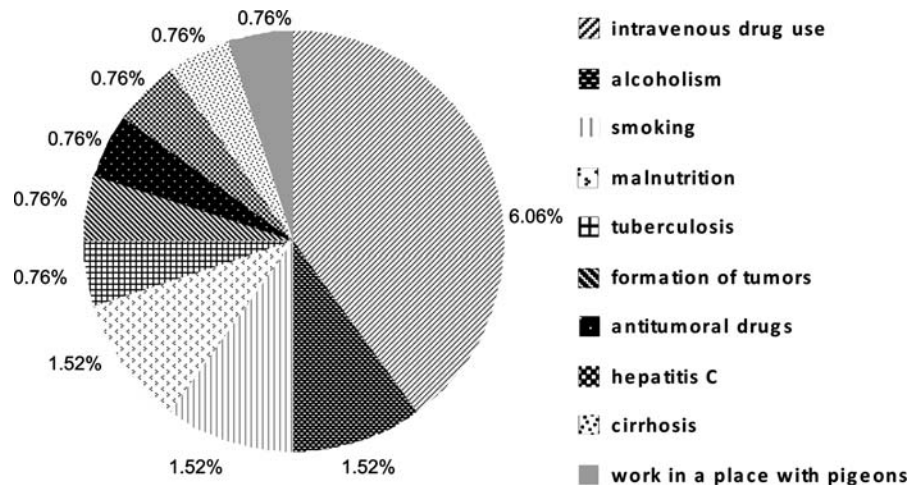
The median age in our study was 36.36 years old, similarly to those found in Africa (34.25 years old) [18] and France (33 years old for females and 36 for males) [12]. In Australia, two independent studies showed differences in the median age between men and women, being 39 years old for men and 46 for women in 18 patients [19] and 36.8 years old for men and 47.7 years old for women in a study of 350 patients [20]. The data in the literature suggest that the median age for cryptococcosis patients is higher in women than in men and higher in HIV-negative patients than in those infected by HIV.

HIV was not the only risk factor for cryptococcal infections reported in our patients. The use of intravenous drugs was reported in eight patients; alcoholism, smoking and malnutrition in two different patients; tuberculosis, formation of tumours, use of antitumoral drugs, hepatitis C, cirrhosis and a workplace with pigeon presence had one patient per factor (Fig. 1). We did not have information about a possible HIV infection in one patient with malnutrition and the one who reported working in a place with pigeon presence. All the other conditions were AIDS associated, except for one patient who was HIV negative and presented malnutrition as a unique predisposing condition.

Chen et al. [20] suggested the need for exploring risk factors not yet studied, such as genetic susceptibility and socio-economic and nutritional status. However, no other reports were found about malnutrition as the only risk factor for infection by *C. neoformans* var. *grubii*. Cancer, cirrhosis, alcoholism, use of antitumoral drugs, tuberculosis, hepatitis C and malnutrition have already been associated with cryptococcosis in patients with or without AIDS [21–23]. Kiertiburanakul et al. [24] stated immunosuppressive therapies as the main predisposing factor (41%) in HIV-negative patients, followed by systemic lupus erythematosus and cancer (16% each).

Analysis concerning race demonstrated that there was an evident Caucasian race predominance, corresponding to 83.5% of patients and being statistically different when compared with the control group ($P = 0.0001$). This statistical difference could reveal the Caucasian race as a risk factor for cryptococcosis, disagreeing with data obtained by Hajjeh et al. [25] that showed a higher ratio for African Americans (31/1,000) than for Caucasians (23/1,000) with AIDS, but the comparison to the control group was not statistically significant. A subsequent study also demonstrated a higher ratio of infection among the

Fig. 1 Risk factors present in the cryptococcal meningitis patients



African American HIV-positive patients than for Caucasian HIV-positive patients. In this work, they suggested that the prevalence of infection in African Americans was not directly related to cryptococcosis, but related to the privation of access to basic care for AIDS treatment, since most of the isolates were obtained from public hospitals [26]. To summarize, no clear relationship was found between race and cryptococcosis.

Concerning the symptoms, only three were statistically dissimilar from those reported by the patients in the control group ($P = 0.0001$). These were headache (80%), sensory loss (14.29%) and stiff neck (11.43%). In another Brazilian study, from Bahia State, 104 patient records of cryptococcosis patients were analysed and the most frequent symptoms reported were headache (92.7%), fever (84.4%) and stiff neck (83.2%) [27].

To our knowledge, this is the first study to assess the epidemiological profile of patients with cryptococcal meningitis in the Brazilian state Rio Grande do Sul. This is an important contribution to the knowledge about this disease because, until now, in this state, there were just a few case reports [28–30] or studies mainly focusing on the epidemiological characteristics of the yeast rather than on the patients themselves.

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