Review Article

Microbiology & Infectious Diseases

Prevalence and Associated Factors to Cryptococcosis in the Infectious Diseases Department of the National University Hospital Center of Fann in Dakar (Senegal)

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Received: 11 June 2018; **Accepted:** 04 July 2018

Citation: Ossibi Ibara BR, Manga NM, Daye Ka, et al. Prevalence and associated factors to Cryptococcosis in the Infectious Diseases Department of the National University Hospital Center of Fann in Dakar (Senegal). Microbiol Infect Dis. 2018; 2(3): 1-3.

ABSTRACT

Objective: *To describe the profile and evolution of patients admitted for cryptococcosis.*

Methodology: *This study was cross-sectional, retrospective, descriptive and analytical. It was carried out in the Infectious Diseases Department of the Fann National University Hospital in Dakar from January 1, 2008 to July 31, 2012, including patients admitted for cryptococcosis.*

Results: *Fifty-seven patients, including 53 men (68%), were included (1.2% of overall admissions). The average age was 40.9 ± 9.1 years. HIV infection (52 cases) was the main associated factor and the average TCD4 + cell was 101.3 ± 123.58 / mm³. The average patient consultation time was 44 days. There were 22 case of meningeal stiffness, 7 cases of focal signs, and 23 cases in coma. Cryptococcosis was neuromeningeal in 47 cases (82%). There were 13 cases of positive Cryptococcal antigenemia (25%). The lethality was 61.4%. It was higher in patients aged 30 to 49 years or with a deep coma (p <0.0001).*

Conclusion: *The lethality associated with cryptococcosis remains high in our series. Prevention, early HIV infection management, and wider accessibility to antifungal therapies would improve its management.*

Keywords

Cryptococcosis, HIV, lethality, sub-Saharan Africa.

Introduction

Cryptococcosis is a deep mycosis caused by Cryptococcus neoformans, an encapsulated fungus [1]. It mainly affects immunocompromised individuals (human immunodeficiency virus, immunosuppressive therapy). It is one of the leading causes of death in HIV patients [1,2]. It mostly causes meningoencephalitis, but the infection can also be pulmonary [2,3]. Cryptococcosis is the inaugural stage of HIV infection in 29% of patients and defines the stage of Acquired Immunodeficiency Syndrome in 58% of patients [3]. Since the advent of antiretroviral therapy (ARVs), the incidence of cryptococcosis has dropped in France by 46% between 1997 and 2002. 75% of cryptococcal infections occur in patients infected with HIV. In Africa, however, this disease remains the second most fatal opportunistic infection after tuberculosis in HIV-infected individuals, affecting in some countries up to 30% of them in the absence of antiretroviral (ARVs) access [1,4,5]. In Senegal, cryptococcosis is the leading cause of meningitis for adults [6].

The main goal of this study is to describe the profile and evolution of patients admitted for cryptococcosis. As secondary goals, the study aims to describe the epidemiological characteristics of

these patients; the clinical, paraclinical and evolutionary aspects of cryptococcosis, and to determine factors associated with the prognosis of patients treated for cryptococcosis.

Patients and Method

Type, period, setting: This cross-sectional study was carried out from January 1, 2008 to July 31, 2012, in the infectious diseases department of the Fann National University Hospital (CHNU) in Dakar, Senegal.

Patients

Patients over 15 years diagnosed with cryptococcosis by cerebrospinal fluid (CSF), bonchoalveolar fluid (BAL) or cryptococcal antigenemia were included.

Study variables

This study variables were epidemiological (age, sex, socio-professional status, marital status, antecedents, risk factors for HIV infection); clinical (reason for consultation or admission, consultation period, WHO classification); paraclinical (CSF analysis (cytochemistry, direct examination after staining with Indian ink, cryptococcal antigen test, culture), cryptococcal antigenemia, blood count, serum creatinine, HIV serology, TCD4 lymphocyte level, plasma viral load and brain CT scan). A compendium of the therapies used (antifungal and antiretroviral treatment) and patient outcomes (healing, sequelae, death) supplemented these data.

Statistical Analysis

The data was processed with the software EPI Info 3.3.2 (CDC Atlanta, USA). Quantitative variables were expressed as means ± standard deviation, and extremes in square brackets. Qualitative variables were reported in numbers and percentages. Comparisons of the qualitative variables used the chi-2 test, while the quantitative variables used the Student's test. The significance level for comparisons was $p < 0.05$.

Results

Descriptive study

Fifty-seven patients were included (1.2% of admissions in the infectious diseases department), including 33 men (58%). The sex ratio (H/F) was 1.4. The mean age was 40.9 ± 9.1 years [23-65]. Thirty-three of them (57.9%) were married, including 17 polygamous and 16 monogamous; 11 patients (19.3%) were single. 25 patients were unemployed (43.9%), 15 workers or artisans (26.3%), 14 merchants (24.6%), 2 civil servants (3.5%) and 1 retired (n=1).

Table 1 shows medical history, reasons for consultation, and general signs. There were 52 cases of patients with positive HIV (91.2%). The average consultation time was 44 ± 57.2 days [3-60]. Table 2 is about the distribution of patients according to clinical signs. The associated pathologies were oral candidiasis (n=30, 52.6%), pleuropulmonary tuberculosis (n=13, 22.8%), chronic diarrhea (n=9; 21%), isosporosis (n=2), cryptosporidiosis (n=1) and pneumocystosis (n=1).

		n	%
Medical antecedents	Pulmonary tuberculosis	10	47,6
	Cryptococcosis	4	19
	Shingles	4	19
	Delusional psychosis	2	9,5
	Pneumopathy with common germs	1	4,8
Consultation reasons	Fever	47	82,5
	Headaches	33	57,9
	Vomiting	28	49,1
	Chills	16	28,1
	Profuse sweats	13	22,8
	Consciousness disorders	10	17,5
	Seizures	7	12,3
General signs	Fever	47	82,5
	Dehydration	23	40,4
	Pallor	23	40,4
	Undernutrition	19	33,3
	Icterus	4	7
	Edema lower limbs	4	7
	Collapse	1	1,7

Table 1: Distribution of antecedents, reasons for consultation and general signs (n=57).

		n	%
Neuropsychiatric signs	Coma	23	40,4
	Psychomotor retardation	13	22,8
	Agitation	9	15,8
	Confusion	6	10,5
	Paralysis of a cranial nerve	7	12,3
	Motor deficiency	6	10,5
	AV weakening	4	7
	Deafness	3	5,3
Meningeal signs	Headaches	33	57,9
	Neck stiffness	22	35,6
	Kernig sign	12	21
	Brudzinski sign	10	17,5
	Cutaneous hyperesthesia	9	15,8
Respiratory signs	Cough	23	40,4
	Pulmonary condensation	21	36,8
	Chest pains	11	19,3
	Hemoptysis	4	7
	Dyspnea	4	7
Immunodepression signs	Smooth trichopathy	14	24,6
	Prurigo	10	17,6
	Onyxis	1	1,8
Others	Lymphadenopathy	3	5,3
	Papular rash	2	3,5
	Hepatomegaly	2	3,5
	Splenomegaly	1	1,8

Table 2: Distribution of clinical signs. AV: Visual Acuity.

The average CD4 was 101.29 ± 123.58 / mm³ [1-459]. This rate was less than 100 / mm³ in 32 cases (56.1%) and between 100 and 299/mm³ in 18 cases (31.5%). Neuromeningeal cryptococcosis was the main site (47 cases). The other locations were cutaneous (1 case) and disseminated (9 cases). In 23 cases (40.4%), a cough was associated with pulmonary condensation syndrome.

All patients were treated with oral fluconazole and no adverse effects were reported. The mean duration of treatment was 24 ± 17 days [2-65]. The minimum delay between the date of diagnosis and the start of anticryptococcal treatment was 31 days. A lumbar puncture evacuator was performed in 2 cases (4%). ARV treatment was started in 20 cases (35%). Only 4 patients had received ARV treatment prior to admission. Four patients (2.3%) presented with immune reconstitution syndrome (IRIS). The delay between antifungal therapy and initiation of ARV treatment in these patients was 33 days with baseline CD4 averaging 85 ± 19/mm³.The mean duration of hospitalization was 23.9 ± 20.3 days [2-80].

The evolution was favorable in 22 cases (38.6%). Complications were sequelae (n=9) including blindness (n=5; 9%) and deafness (n=4; 7%); and death in 35 cases (61.4%). The causes of death were: cardiovascular collapse (26 cases), cardiorespiratory arrest (4 cases), acute respiratory distress (4 cases) and cerebral involvement (3 cases).

Analytical study (univariate analysis)

The recovery rate was statistically associated with ART use after admission and Glasgow score > 8 on admission (Table 3).

Parameters		Recovery n (%)	Death n (%)	P-value
Sex	Male	13 (39,4)	20 (60,6)	0,896
	Female	9 (37,5)	15 (62,5)	0,896
Age (years)	20-29	3 (60,0)	2 (40,0)	0,360
	30-39	6 (31,6)	13 (68,4)	0,630
	40-49	10 (37,0)	17 (63,0)	0,960
	50-65	3 (50,0)	3 (50,0)	0,660
Serology	Positive	21 (40,4)	31 (59,6)	0,679
	Negative	1 (20,0)	4 (80,0)	0,679
TARV	Yes	12 (60,0)	8 (40,0)	0,031
	No	10 (27,0)	27 (73,0)	0,031
Fluconazole	Fluconazole 400 mg	12 (40,0)	18 (60,0)	0,965
	Fluconazole 800-1600 mg	10 (37,0)	17 (63,0)	0,965
Score de Glasgow	< 8	0 (0,0)	20 (100)	0,000039
	≥ 8	22 (59,5)	15 (40,5)	0,000039
Consultation time	< 48 h	15 (35,7)	27 (64,3)	0,660
	≥ 48 h	7 (46,7)	8 (53,3)	0,660
LCR Cytology	< 10/mm³	10 (29,4)	24 (70,6)	0,145
	≥ 10/mm³	12 (52,2)	11 (47,8)	0,145
LTCD4 rate	< 100/mm³	9 (39,1)	14 (60,9)	0,834
	≥ 100/mm³	13 (38,2)	21 (61,8)	0,834

Table 3: Comparison of Different Study Parameters by Healing and Death. VIH: Acquired immunodeficiency virus, TARV: Antiretroviral theurapy, LTCD4: T CD4 lymphocytes.

Discussion

The frequency of cryptococcosis is high in our series (1.2% of in-service admissions of infectious diseases). It is similar to that of other African authors [1,5-8]. Male predominance is common in sub-Saharan Africa as reported by E.Gbangba et al. in Bangui, Soumaré et al. in Dakar, Millogo et al. in Burkina Faso, [1,7,8]. This male predominance contrasts with the feminization of HIV infection.

Young adults are the most concerned [6,8]. This population is the most affected by HIV infection which is the main field of cryptococcosis occurrence in our countries. Our service is only specialised for adults. However, according to data from the literature, the number of children making cryptococcosis is very low [9]. This relative resistance to infection is poorly explained since the fungus is present in the environment and children are, like adults, able to produce anti-cryptococcal antibodies. Differences in lifestyle, occupation or exposure cannot explain differences by age and sex alone. It is possible that hormonal or genetic factors come into play.

Patients with low standards of living and working in low-income occupations are the most affected in our study. This finding, often reported in Africa, reflects the socio-economic environment that is the bedrock of HIV-AIDS [1,8].

Neuromeningeal cryptococcosis was associated with other pathologies including tuberculosis in 13 patients. These results are consistent with those of Sow and Cameron in Dakar [6,10]. Oral fluconazole was the only antifungal used in our study. This molecule was used in the series of Soumaré [8] and Milongo [7], respectively in 93% of cases in perfusion and 100% in bones. Numerous studies in recent years have noted a superiority of amphotericin B and 5-fluorocytosine over fluconazole or amphotericin monotherapy [11-13].

The mean duration of induction therapy in our fluconazole patients was 24 days. This longer or shorter duration could be justified by the persistence of the clinical picture in our patients and the absence of CSF negativization taken after 15 days. Also, it should be noted that the difference was not significant regarding the doses of fluconazole administered in our patients.

In our series, two patients (4%) had lumbar puncture evacuation. These were patients who were suspected of persistent intracranial hypertension manifested by atrocious headache. This low rate can be justified by the weakness of our technical platform for the diagnosis of intracranial hypertension.

Twenty patients (35%) had received antiretroviral therapy. The initiation of highly active ART after the diagnosis of cryptococcosis should be early to avoid the occurrence of other opportunistic infections. Nevertheless, it must take into account the risk of IRIS

[14-17]. In our study, the delay between the start of antifungal therapy and antiretroviral treatment was thirty-one days. This long delay can be explained in part by the scarcity of the molecule on the market, the financial difficulties of the patient who deals with the opportunistic infection himself.

The average length of stay was 23.87 days in our series. This result corroborates that obtained by Milongo in Burkina Faso [7]. This can be explained by the fact that patients go to hospital at a fairly advanced stage of the disease, thus prolonging the duration of the treatment. Lethality was 61.4% in our series. This rate is lower than that obtained by Sow et al. in Dakar (71%), Bissagnene in Cote d'Ivoire (64.8%), [6.18]. These studies were conducted before the advent of highly active ART. In fact, Aoussi, in Abidjan, had a lower lethality (41.2%) in a study on neuromeningeal cryptococcosis and HIV in the era of ART in Cote d'Ivoire. This study was also characterized by a greater frequency of evacuation puncture [19]. Most authors emphasize that clinical improvement during cryptococcal meningitis treatment is usually slow (1 to 2 weeks). Sterility of CSF is obtained after 15 days up to 2 months [6 18]. Also, the average duration of CSF sterilization is shorter with amphotericin B (.15 days) + flucytsin than with fluconazole (approximately 40 days) [20]. The low standard of living of our patients for whom the cost of care is out of reach, the delayed diagnosis, our working conditions characterized by the limitation of the therapeutic means would largely explain this high mortality rate (61.4%). %) [21].

Conclusion

Cryptococcosis remains the second most fatal opportunistic infection in HIV patients and profoundly immunocompromised. It remains a real public health problem in Africa, associated with a high lethality. Prevention, early management of HIV infection, and wider accessibility to antifungal therapies would improve management and limit the impact.

References

1. Gbangha Ngai E, Fikouma V, MossoroKpinde CD, et al. La cryptococcose neuromeningée au cours de l'infection à VIH à Bangui, à l'ère du traitement antiretroviral. 2014; 107: 106-109.
2. Aberg JA, Mundy LM, Powderly WA. Pulmonary cryptococcosis in patients without HIV infection. Chest. 1999; 115: 734-740.
3. Dromer F, Mathoulinpelissier S, Fontanet A, et al. Epidemiology of HIV- Associated cryptococcosis in France (1985-2001): comparison of the pre- and post-HAART era. AIDS. 2004; 18: 555-562.
4. Dromer F, MathoulinPélissier, Launay O, et al. The French Cryptococcosis study Group. Determinants of diseases presentation and outcome during cryptococcosis: the crypto A/D study. PLoS Med. 2007; 4: e21.
5. Kadjo K, Ouattara B, Adoubryn KD, et al. Aspects actuels de la cryptococcose neuroméningée des sujets adultes infectés par le VIH dans le service de médecine interne du CHU de Treichville d'Abidjan (Côte d'Ivoire). Journal de mycologie médicale. 2011; 21: 6-9.
6. Sow PS, Diop BM, Dieng Y, et al. Cryptococcose neuro-méningée au cours de l'infection à VIH à Dakar. Med Mal Infect. 1998; 28: 511-515.
7. Millogo A, Ki-Zerbo G, Andonaba JB, et al. La cryptococcose neuro-méningée au cours de l'infection par le VIH au Centre Hospitalier de Bobo-Dioulasso (Burkina Faso). Bull Soc Pathol Exot. 2004; 97: 119-121.
8. Soumare M, Seydi M, Ndour CT, et al. Aspects actuels de la cryptococcose neuro-méningée à Dakar. Med Trop. 2005; 65: 559-562.
9. Abadi J, Nachman S, Kressed AB, et al. Cryptococcosis in children with AIDS. Clin infect Dis. 1999; 28: 309-313.
10. Cameron ML, Bartlett JA, Gallis HA, et al. Manifestattion of pulmonary cryptococosis in patient with the acquired immunodeficiency syndrome. Rev Infect Dis. 1991; 13: 64-67.
11. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2010; 50: 291-322.
12. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet. 2004; 363: 1764-1767.
13. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. The New England Journal of Medicine. 2013; 368: 1291-1302.
14. Lortholary O, Fontanet A, Memain N, et al. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV associated cryptococcosis in France. AIDS. 2005; 19: 1043-1049.
15. Lawn SD, Meintjes G. Pathogenesis and prevention of immune reconstitution disease during antiretroviral therapy. Expert Rev Anti Infect Ther. 2011: 9: 415-430.
16. Shelburne SA, Darcourt J, White AC, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. Clin Infect Dis. 2005; 40: 1049-1052.
17. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. The New England Journal of Medicine. 2014; 370: 2487-2498.
18. Bissagnené E, Ouhon J, Kra O, et al. Aspects actuels de la cryptococcose neuro-méningée à Abidjan. Med Mal Infect. 1994; 24: S580-S585.
19. Aoussi EF, Ehui E, Dembélé JP, et al. Cryptococcose neuro-méningée et VIH l'ère des antirétroviraux en Côte d'Ivoire. Med Mal. 2012; 33: 1-6.
20. Dromer F, Bernede-Bauduin C, Guillemot D, et al. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. PloS one. 2008; 3: e2870.
21. Loyse A, Thangaraj H, Easterbrook P, et al. Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries. The Lancet Infectious diseases. 2013; 13: 629-637.