



GLOBAL JOURNAL OF MEDICAL RESEARCH: A  
NEUROLOGY AND NERVOUS SYSTEM  
Volume 14 Issue 2 Version 1.0 Year 2014  
Type: Double Blind Peer Reviewed International Research Journal  
Publisher: Global Journals Inc. (USA)  
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

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**GJMR-A Classification :** *NLMC Code: WW 400, WC 475*



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# Neuromeningeal Cryptococcosis: A Fatal Disease in Tropical Practice

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**Discussion:** NMC remains under estimate with non specific signs. Early diagnostic and rapid therapeutic approaches are the challenges to achieve for all neurologists in tropical setting.

**Conclusion:** We recommend to research cryptococcus in CSF forwards any meningitis in HIV infected patient.

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## I. INTRODUCTION

This paper deals with neuromeningeal location of *Cryptococcus neoformans* which is the most common in HIV/AIDS infection. It caused fatal meningoencephalitis in low income countries.<sup>[1]</sup> Its incidence varied from 5 to 10% in developed countries,<sup>[2,3]</sup> and 15-35% in central Africa.<sup>[1,4,5]</sup> The prevalence varied from 2.24 to 5.1% in Africa.<sup>[6-9]</sup> Clinical data show no specific clinical signs. Laboratory confirmation test is done by highlighting "*Cryptococcus neoformans*" in CSF by India ink.<sup>[8,10,11]</sup> In our developing countries cryptococcal meningitis is under diagnosed despite the high frequency of non-specific signs

encountered in consultation, and the prevalence of HIV/AIDS. We aimed to study the epidemiological and clinical characteristics of neuromeningeal cryptococcosis.

## II. MATERIALS AND METHODS

This retrospective study was conducted in the departments of internal medicine, infectious diseases and neurology, and laboratories of the four major public hospitals of the region (Tokoin university hospital, Campus university hospital, Regional Hospital and District Hospital). These four sites were selected for their important capacity which is a total of 409 beds and the quality of the technical platform of their laboratory. This study focused on the analysis of recorded patients admitted between 1 January 2007 and 31 December 2011, and the positive of *Cryptococcus neoformans* in CSF. The main variables studied were formed by the epidemiological indicators (age, sex, incidence, frequency), clinical features (clinical signs and associated pathologies), routine analyzes (CSF, search of cryptococcus neoformans by staining the India ink and culture on Sabouraud medium, HIV status and CD4 count), therapeutic and progressive (disease duration before the consultation, hospitalization stay and the outcome). Physician in charge of the patient decided to perform or not CSF analysis, depending on clinical symptoms encountered. CSF study consisted of three phases namely cytology examination, direct staining India ink and the quantitative determination of proteins and glucose. The search of soluble antigens was not available. The determination of CD4 lymphocytes was performed by an automatic CD4 counter. HIV serology was considered positive by the detection in serum of specific antibodies by both tests (ELISA I and II) and confirmatory test by Western Blot. The study of viral load was not available. CT scan was done for all patients, and shown diffuse cerebral edema with leptomeningeal contrast. All patients had provided informed consents and the study were approved by the local Ethics Committees.

## III. RESULTS

During the study period, 41,327 patients were hospitalized in all four hospitals involved in this study (table I). Seven thousands six hundred fifty-three patients or 18.52% (7653/41,327) were diagnosed with

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HIV. CSF was analyzed in 1758 with 978 samples from HIV+ subjects. The incidence was highly variable from one year to the next with an average of 1.6 cases. The research of *Cryptococcus* was performed in 19.40% (341 cases). It was positive in 8 cases or 2.34%. The sex ratio was 1.67 (5/3) with an average age of 36 years and extreme of 28 to 45 years. Hospital prevalence of CNM was 0.02% and 0.10% in HIV+ patients. Fever (6/8), headaches (5/8) and impaired consciousness (4/8) were the most frequently encountered clinical signs. The oropharyngeal candidiasis (37.50%) were the main associated pathology. CSF was normal according to macroscopic and cytochemical criteria in 3/8 cases and clear appearance in 6/8 cases. Cytology was almost normal in all cases with 0 and 5 cells/mm<sup>3</sup>. The culture was negative after 5 days for all patients. The average glucose and protein level was respectively 0.36 g / l (range 0.10 to 0.57 g / l) and 3.43 g / l (range 2.44 to 4.45g/ l). The CD4 + lymphocytes count ranged between 21 and 87 cells / mm<sup>3</sup> with an average of 37.4. The white blood cells count was normal in 3/4 cases and anemia with decreased hematocrit was present in all cases. All patients were treated with oral fluconazole or through a nasogastric tube in the event of loss of consciousness or swallowing. The injectable form was difficult to access. The mean duration of symptoms prior to consultation was 5.5 days with a range of 1-14 days. The average length of stay was 12.25 days with a range of 4 to 37 days. The outcome of hospitalization was marked by death for 5 patients and positive for 2 patients. Table II reports the clinical, biological and evolutionary description of cases of CNM observed during the study period.

#### IV. DISCUSSION

The main concern of this paper had been a retrospective study consisted of the analysis of hospital recorded files in four public hospitals in the biggest region of the country. We encountered some difficulties such as patient's financial difficulties and poor access to care, which limited the sample size. In other words, this study is by no means exhaustive and does not allow beforehand to assess the extent of cryptococcal meningitis in the general population in the community or at the national level. The limitation of the study was also that we were unable to assess all patients admitted for brain infection meningitis in the region. Finally, because we only included patients admitted to hospitals, we were unable to collect patients who could not afford hospital care or were more likely to attend basic clinic-type (Level 1) hospitals or traditional healers. These have been the bias in the recruitment of patients encountered in the retrospective studies. These findings may not reflect the real incidence and frequency of that disease. However, the consistency of our results with other studies provides some validity to the data.

Search for cryptococcal antigens soluble in blood and CSF were not made for technical

shortcomings, which would have allowed us to approach the real frequency of further disease. Some studies, however, showed that the use of both tests the India ink and the search of soluble antigens did not reveal a significant difference in observed frequency.<sup>[5,9,12]</sup> The average age was 36 years (range from 28 to 45 years). It is comparable to that reported in Morocco, Mali and Zambia which were respectively 32 years, 34 years (18-60 years) and 33 years (15 to 65).<sup>[13-15]</sup> The age of the young population slice is superimposed on the most affected by HIV /AIDS in our communities and is also the target of death.<sup>[13,16]</sup> We found a male predominance (M/F:1.67), as in most studies,<sup>[6,9,15]</sup> while HIV is feminized. Only 3.82% of patients (1578 /41327) underwent CSF examination and research of *cryptococcus neoformans* by the India ink was performed in 18.54% of cases. This rate of lumbar puncture seems as low as noticed Mbuagbaw et al.<sup>[6]</sup> This low rate may be due to limited technical tray and non-specific clinical signs of cryptococcal meningitis. Hospital frequency of CNM was 0.02% for all patients and 0.10% in HIV + patients. The incidence of cryptococcosis in Africa varies greatly by region, from 1.7% in Gabon to 94.6% in Ivory Coast.<sup>[5, 11, 12, 17, 18]</sup> The number of cases per year is highly variable from year to year and in the same region. The hospital incidence is 1.6 cases / year. This incidence is similar to that reported from Senegal, 2.9 cases/year<sup>[19]</sup> and below than the average from South Africa with 10.48 cases / year (range 1.6 to 230 cases / year).<sup>[13,14,20]</sup> The variable incidence rate are related to the ecological environment favorable or not, and the prevalence of HIV / AIDS in the studied region. The symptoms and signs most frequently encountered were fever (75%), headaches (62.50%) and impaired consciousness (50%), as reported by several studies.<sup>[7,10, 15, 21,22]</sup> These nonspecific signs may explain the low frequency and the lack of attention to asymptomatic neuromeningeal cryptococcosis in our regions. The search of *cryptococcus* in CSF depends on the physician appreciation concerning the patient clinical presentation.

*Cryptococcus* clinical presentation is really vague and no specific signs but in HIV condition the mainly symptoms were marked by fever, severe headaches and confusion or sometimes loss of consciousness. In case of tuberculosis, the evolution is sub acute and fever is fewer than 38.5°C follow by loss of body weight and rarely loss of consciousness. CSF is clear in both cases. CT scan imaging shows a diffuse edema in case of *cryptococcus* and granuloma as an abscess with large edema in case of bacterial or parasitary infection. The differential diagnosis is made by cytology examination of the granuloma.

Up on analyzing aspects, CSF was clear, it came up with 6/8 and troubles in two cases. The cell count was normal. The low glucose and high protein averages level in CSF were respectively 0.36 g / l and 3.43 g / l. Data from the literature confirm this fall in

predominance of low glucose / high protein level.<sup>[6]</sup> Depending on the degree of immunosuppression observed, the average CD4 count was 37.4 with a range of 21-87 cells/mm<sup>3</sup>. The opportunistic nature of cryptococcosis was already known before the era of HIV/AIDS. A severe deficiency in cell-mediated immunity (CD4 count <100 cel/mm<sup>3</sup>) is often involved.<sup>[23]</sup> However, there are studies describing cases of CNM in immunocompetent patients without apparent risk factors.<sup>[24,25]</sup> The mean duration of symptoms prior to consultation was 5.5 days range 1 to 14 days but it was reported longer (22 to 27.24 days) in the literature.<sup>[12]</sup> The hospital stay ranged from 4 to 37 days with an average of 12.25 days. Our patients therefore consulted earlier than the other groups. The therapeutic management is done with fluconazole and amphotericin B. Fluconazole is the drug of choice used solely in almost all cases<sup>[1,26]</sup> or associated with Flucytosin (5-FC).<sup>[26,27]</sup> Amphotericin B injection as flucytosine are difficult to access and use in our regions.<sup>[15,22]</sup> Treatment with fluconazole early undertake help patient to survive. The second condition is the early admission and quiet diagnostic. *These are some difficulties encountered in the treatment of NMC.*

The mortality rate was 62.5% (5/8). In sub-Saharan Africa, the mortality rate varies from 28.5 to 71.1% with an average of 45.9%. The survival median ranged between 10 and 26 days (range 1-164 days) according to several authors.<sup>[9,13,16]</sup> NMC remains a fatal disease in our region in HIV setting.

## V. CONCLUSION

Neuromeningeal cryptococcosis is under diagnosed because of its deceptive symptomatology and lack of technical facilities. It affects a young population, severely immune compromised HIV male with limited income. Then it is a real diagnostic and therapeutic challenge for this disease which remains bonded to a high mortality rate in our region.

## VI. ACKNOWLEDGMENT

No acknowledgment permission form needed to declare. No source of founding or grant to declare.

## REFERENCES RÉFÉRENCES REFERENCIAS

- Laroche R, Deppner M, N'Dabane Z. La cryptococcose à Bujumbura (Burundi) à propos de 80 cas observés en 42 mois. *Med. Afr. Noire* 1990; 37: 588-91.
- Brian P, Currie M, Casadevall A. Estimation of prevalence of cryptococcal infection among patient infected with the HIV in New-York city. *Clin Infect Dis* 1994; 19: 1029-33.
- Bodasing N, Seaton RA, Shankland GS, Kennedy D. *Cryptococcus neoformans* var. *gattii* meningitis in an HIV-positive patient: first observation in the United Kingdom. *J Infect.*2004; 49:253-5.
- Muyembe TJJ, Mupapap KD, Luki N, Ngwala BD, Tondouanda K, Izzia KW et al. Cryptococcose à *Cryptococcus neoformans* var *gattii* : à propos d'1 cas associé au syndrome d'immunodéficience acquise (SIDA) à Kinshasa (Zaire). *Med Trop* 1992;52:435-8.
- Bissangnène E, Ouhon J, Kra O, Kadio A. Aspects actuels de la cryptococcose neuroméningée à Abidjan. *Med Mal Infect.* 1994;24:580-5.
- Mbuagbaw JN, Biholong NP, Njamnshi AK. La cryptococcose neuroméningée et l'infection au VIH dans le service de médecine du centre hospitalier et universitaire de Yaoundé-Cameroun. *AJNS*, 2006;25:13-20.
- Ki-Zerbo G, Sawadogo A, Millogo A, Andonaba JB, Yameogo A, Ouedraogo I et al. La cryptococcose neuroméningée au cours du SIDA: étude préliminaire à l'hôpital de Bobo-Dioulasso (Burkina Faso) *Méd. Afr. Noire* 1996; 43:13-8.
- Sow PS, Diop BM, Dieng Y, Dia NM, Seydi M, Dieng T, Badiane S et al. Cryptococcose neuroméningée au cours de l'infection à VIH à Dakar. *Med. Mal. Infect.*1998; 28: 511-15.
- Bogaerts J, Rouvroy D, Taelman H, Kagame A, Aziz MA, Swinne D et al. AIDS-associated cryptococcal meningitis in Rwanda (1983-1992): epidemiologic and diagnostic features. *J. Infect.*1999;39:32-7.
- Kwon-Chung KJ, Sorrel TC, Dromer F, Fung E, Levitz SM. Cryptococcosis: Clinical and biological aspects. *Med. Mycol.*2000;38:205-13.
- Woldemmanuel Y, Haile T. Cryptococcosis in patients from Tikur Anbessa Hospital, Addis-Abeba, Ethiopia. *Ethiopian Medicine Journal* 2001; 39: 185-92.
- French N, Gray K, Watera C et al. Cryptococcal infection in cohort of HIV-1-infected Ugandan adults. *AIDS* 2002;16:1031-8.
- Mwaba P, Mwansa J, Chintu C. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. *Postgrad. Med. J.*2001;77:769-73.
- Aoufi S, Agoumi A, Seqat M. Cryptococcal neuromeningitis in immunosuppressed subjects at Rabat University Hospital (Morocco). *Ann. Biol. Clin. (Paris)*.2008; 66:79-81.
- Oumar AA, Dao S, Ba M, Poudiougou B, Diallo A. Aspects épidémiologique, clinique et pronostique de la cryptococcose neuroméningée en milieu hospitalier à Bamako, Mali. *Rev. Med. Brux.* 2008;29:149-52.
- Balogou AAK, Volley KA, Belo M, Amouzou MK, Apetse K, Kombate D et al. Mortalité des patients



VIH-positifs dans le service de neurologie du CHU-Campus de Lomé-Togo. AJNS 2007;26:95-101.

17. Bisson GP, Lukes J, Thakur R, Mtoni I, MacGregor RR. Cryptococcus and lymphocytic meningitis in Botswana. S Afr. Med. J. 2008;98:724-5.
18. Okome-Nkoumou M, Mbounja-Lo clo ME, Kombila M. Panorama des infections opportunistes au cours de l'infection par le VIH à Libreville, Gabon. Cahiers Santé 2000;3: 329-37.
19. Soumare M, Seydi M, Ndour CT, Dieng Y, Diouf AM, Diop BM. Aspects actuels de la cryptococcose neuroméningée à Dakar. Med Trop 2005; 65: 559-62.
20. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS. 2009;23:525-30.
21. Soumare M, Seydi M, Ndour CT, Dieng Y, Ngom-Faye NF. Les méningites à liquide clair chez les patients infectés par le VIH à Dakar. Bull. Soc. Pathol. Exot. 2005; 98:104-7.
22. Millogo A, Ki-Zerbo G-A, Andonaba JB, Lankoande D, Sawadogo A, Yameogo I et al. La cryptococcose neuroméningée au cours de l'infection par le VIH au Centre hospitalier de Bobo-Dioulasso (Burkina Faso). Bull. Soc. Pathol. Exot. 2004;97:119-21.
23. Kisenge PR, Hawkins AT, Maro VP, Michele JP, Swai NS, Mueller A et al. Low CD4 count plus coma predicts cryptococcal meningitis in Tanzania. BMC Infect. Dis. 2007;7:39-43.
24. Ndiaye M, Soumaré M, Mapoure YN, Seydi M, Sène-Diouf F, Ngom NF et al. Cryptococcose neuroméningée chez des patients apparemment non-immunodéprimés: à propos de 3 cas à Dakar, Sénégal. Bull. Soc. Pathol. Exot. 2008;101:311-3.
25. Bretaudeau K, Eloy O, Richer A, Bruneel F, Scott-Algara D, Lortholary O et al. Cryptococcose neuroméningée chez un sujet en apparence immunocompétent. Revue neurologique 2006; 162:233-7.
26. Collett G, Parrish A. Fluconazole donation and outcomes assessment in cryptococcal meningitis. S Afr. Med. J. 2007; 97: 175-6.
27. Longley N, Muzoora C, Taseera K., Mwesigye J, Rwebembera J, Chakera A et al. Dose response: effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in southwestern Uganda. Clin. Infect. Dis. 2008;47:1556-61.

TABLES

Table 1 : Recapitulative of data collected from hospitals center

	Number (n) of beds	Patients (n)	HIV+ (n)	CSF tested (n)
TOKOIN - UTH*	281	27605	6174	1253
CAMPUS- UTH	77	7560	743	366
DHB †	36	4872	508	97
RHL‡	15	1290	228	42
Total	409	41327	7653	1758

Legend: \*UTH: University teaching hospital; †DHB: District hospital of Bè; ‡RHL: regional hospital of Lomé

Table 2 : Description of clinical, biological and evolution cases of NMC

N°	Sociodemographic data	Clinical features	CSF analysis	CD4 count (cel/mm <sup>3</sup> )	Evolution (days)
1	42 years Female Saler	Symptoms lasting over 3 days ; headaches, fever, nausea, vomit, unconsciousness, general body state altered	Clear 5 elements Glu <sup>1</sup> =0,13g/l Prot <sup>2</sup> =1,44g/l	40	Deceased after 5 days
2	45 years Male Solder Married	Symptoms lasting over 2 days ; headaches, fever, convulsions or seizures	Trouble 4 elements Glu <sup>1</sup> =0,15g/l Prot <sup>2</sup> =2,65g/l	21	Deceased after 4 days
3	28 ears Female Household wife Married	Symptoms lasting over 5 days; general well being altered, digestive Candidosis, chronic diarrhea, tuberculous	Clear 0 elements Glu <sup>1</sup> =0,20g/l Prot <sup>2</sup> =1,64g/l	12	Deceased after 6 days
4	33 years Male Public employee Married	Symptoms lasting over 1 day ; headaches, altered of conscience, meningeal signs, agitation, Sarcoma of Kaposi	Trouble 0 element Glu <sup>1</sup> =0,25g/l Prot <sup>2</sup> =2,69g/l	87	Improved after 37 days

5	38 years Male SOTOTOL employee Married	Symptoms lasting over 5days; headaches, fever, nausea, vomit, digestive candidiasis, altered of conscience and general well being	Clear 0 element Glu <sup>1</sup> =0,10g/l Prot <sup>2</sup> =4,45g/l	18	Improved after 13 days
6	40 years Male Trader Married	Symptoms lasting over 7days ; violent headaches, fever, vomit, chronic diarrhea, focal deficits	Clear 3elements Glu <sup>1</sup> =0,21g/l Prot <sup>2</sup> =3,25g/l	21	Discharged after 12 days
7	30 years Female housewives Married	Symptoms lasting over 14 days; fever, digestive candidosis, focal deficits, unconsciousness, diffuse cerebral oedema	Clear 5 elements Glu <sup>1</sup> =0,17g/l Prot <sup>2</sup> =4,13g/l	16	Deceased after 10 days
8	32 years Male Police officer Married	Symptoms lasting over 7days; fever, meningeal signs, headache ocular cytomegalovirosis	Clear 0 element Glu <sup>1</sup> = 0,15g/l Prot <sup>2</sup> =2,35g/l	56	Deceased after 11 days

Legend: <sup>1</sup>glucose, <sup>2</sup>total proteins, d = day, cel=cell, CSF= cerebrospinal fluid, NMC= neuromeningeal cryptococcosis, g/l= gramme/liter





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