International Journal of Biomedical Research
ISSN: 0976-9633 (Online); 2455-0566 (Print)
Journal DOI: https://dx.doi.org/10.7439/ijbr
CODEN: IJBRFA

Original Research Article

Cerebrospinal fluid parameters influencing the outcome of Cryptococcal meningitis: Indian experience

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***Article History:**
Received: 07/02/2017
Revised: 11/02/2017
Accepted: 17/02/2017
DOI: https://dx.doi.org/10.7439/ijbr.v8i2.3931

Abstract

Purpose: Incidence of Cryptococcal meningitis (CM) is increasing as prevalence of HIV, long term steroids use and organ transplant increase. The study was done to analyze demographic, clinical and biochemical parameters and to correlate these parameters with mortality.

Materials and Method: 50 patients of CM, diagnosed on the basis of India ink positivity, Cryptococcal antigen or Culture. Patients were followed up till discharge or death.

Results: Out of the 50 patients, 45 patients were HIV positive. Headache was the most common symptom (100%), followed by vomiting, fever, and altered sensorium, blindness, seizures, diplopia and psychiatric symptoms. The factors associated with a greater risk for mortality were CD4 ≤ 50 cells/ cu.mm (p=0.012), low GCS ≤ 8 (p=0.000011), blindness (p =0.034), papilledema (p=0.0009) and low CSF sugar (p=0.0005). There was an association between high CSF pressure (>30 cm of H_2O) and blindness (p=0.005). Other factors which were associated with a higher trend of mortality but not significant were associated tuberculosis and high CSF pressure.

Conclusions: Mortality associated with CM continues to be high in spite of availability of medications. Factors associated with high mortality were low initial CD4, lower GCS at presentation, blindness, papilledema and low CSF sugar.

Keywords: Cryptococcal, meningitis, mortality, outcome, CSF.

1. Introduction

Cryptococcus neoformans, encapsulated yeast like fungus was discovered in 1894 by two Italian scientists, Francesco and Sanfelice. It grows in pigeon faeces and is spread by aerosolization and inhalation. It is theorized that primary infection is acquired in childhood. A fall in immunity predisposes to the disease. Cryptococcal disease presents in either pulmonary or disseminated forms.

In the pre HIV era, cryptococcal meningitis was seen in 0.15% of apparently normal individuals. An increase in incidence of cryptococcal meningitis has been attributed to the HIV pandemic (6.5% in HIV positive patients) and the increasing use of immunosuppressants in organ transplant patients. The other predisposing factors are diabetes mellitus, lymphoreticular malignancies. A normally functioning host immune system is capable of eliminating this infection, or can sequester *Cryptococcus neoformans* into sites where it can remain controlled via fungistatic and fungicidal host defence mechanisms. A defect in cellular immunity predisposes to cryptococcal meningitis. A CD4 count <50 cells/ µL is known increase the risk.

In cryptococcal meningitis, basal meninges are preferentially involved, with a mucoid thickening of meninges and subsequent involvement of underlying brain. The mucoid material is the excess capsular material that the organism secretes actively and in which the organism grows. The release of this mucoid material is thought to increase intracranial tension and is associated with poor prognosis.

Into the third decade of the HIV and Acquired Immunodeficiency Syndrome (AIDS) epidemic, there are 34 million people worldwide living with HIV, five million of whom are aged between 15 and 24 years [1]. These are the patients who are PLHIV for next decades to come. An estimated 1 million cases of cryptococcal meningitis (CM) among occur among people with HIV/AIDS worldwide each year, resulting in nearly 625,000 deaths [2, 3]. If left untreated CM is fatal. Late presentation as a result of patients remaining stable until later in the disease often delays detection and results in a poor outcome in patients. In immune competent patients unless clinician has high suspicion and good clinical acumen CM can be easily missed. Cryptococcal meningitis can also present as immune reconstitution syndrome (IRIS) at the initiation of Highly Active Anti-Retroviral Therapy (HAART).

Treatment of choice is Amphotericin B in intensive phase and fluconazole or Itraconazole as maintenance therapy. The purpose of this study was to look for factors prognosticating outcome of newly diagnosed patients of cryptococcal meningitis.

2. Methods

2.1 Study design

This was a Prospective and retrospective observational study conducted at KEM Hospital, which is a tertiary care center in Mumbai, India. Total 50 patients fulfilling the requirements of the inclusion and exclusion criteria for the study were included. The study protocol was approved by the institutional review board (IRB). All patients provided written informed consent.

2.2 Subject selection criteria

Newly diagnosed patients with cryptococcal meningitis between 13 to 60 years of age who were willing to give consent were included in the study. Patients were diagnosed as Cryptococcal meningitis by the presence of either positive cryptococcal culture or cryptococcal antigen or India ink positivity in CSF. Pregnant ladies were excluded from the study. Hypertension, Diabetes mellitus and ischemic heart disease patients were excluded from the study.

2.3 Procedure

50 patients were enrolled in the study after fulfilling inclusion and exclusion criteria. Detailed history was recorded. Baseline investigations complete haemogram, Liver function tests and renal function tests were done. Lumbar puncture was performed. CSF parameters which were assessed were opening pressure, sugar level, proteins, leukocyte count, India ink preparation and Cryptococcal antigen with titres. Neuroimaging was done as and when indicated. All investigations were done as per standard protocols of management, as per treating physician's advice. All patients were offered standard therapy with Amphotericin B for two weeks,followed by maintenance phase with Fluconazole. The patients were followed up till discharge or death in ward.

2.4 Statistical analysis

The data was analysed using descriptive statistics. Results are expressed as percentage. Chi square test was used.

3. Results

A total of 50 patients were included in the study. 20 patients (40%) died during hospital stay. Maximum numbers of patients were in the 31 to 40 years age-group, and the average age was 35.74 ± 8.37 years. As shown in Figure 1 maximum mortality (70%) was seen in the 41 – 50 years age group, however the difference in mortality between ≤ 40 years and > 40 years group was not significant. Out of 50 patients 35 (70 %) were males and 15 (30%) were females. In males 21 (60%) were cured, 14(40%) died. Out of 15 female patients 9 (60 %) and 6 (40%) succumbed to the illness.

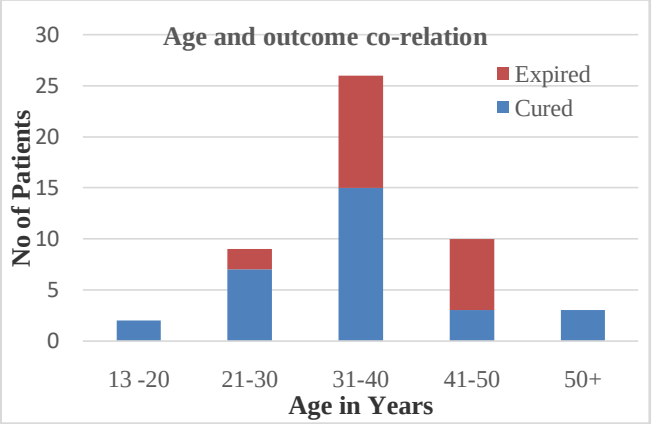

Figure 1: Age of patient and Cryptococcal meningitis outcome

43(86%) patients were married. Out 0f 50, 45(90%) were HIV positive. Out of the 45 HIV positive patients, 16 (35.6%) were newly detected.There was no difference in mortality between the newly detected and known HIV positive patients (p = 0.34). 9 patients (31%) of previously diagnosed HIV positive patients were on HAART prior to diagnosis (Figure 2); however HAART did not confer any survival benefit (p = 0.72).Out of the HIV negative patients, 1 patient had Idiopathic CD4 lymphocytopenia, 1 was a post renal transplant patient on steroids. The remaining 3 did not have any predisposing condition. Out of HIV positive patients 27(60%) were cured of CM and 18 (40%) died. In the Immunocompetent patients survival rate was 33%.

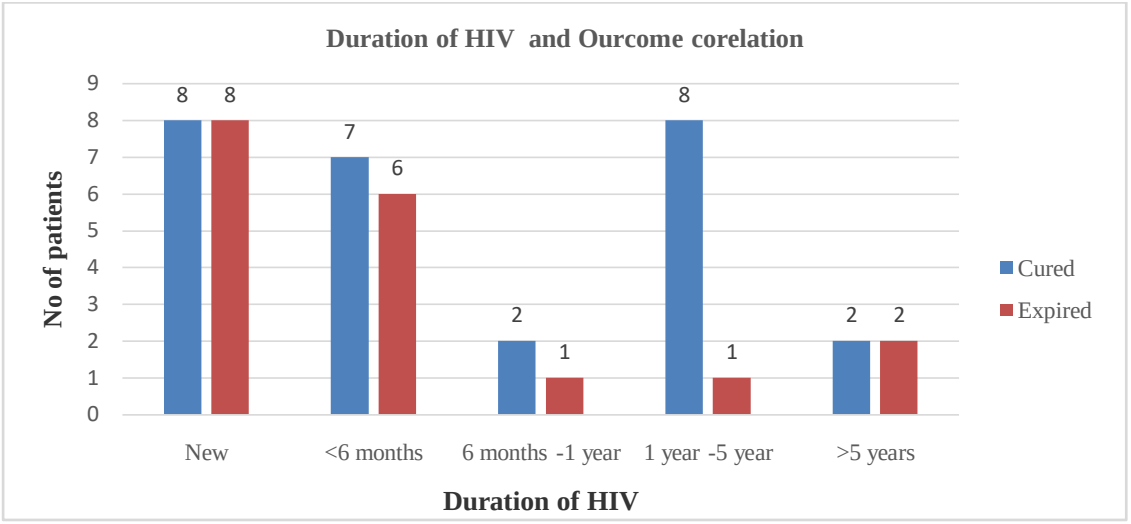

Figure 2: Duration of HIV and outcome of Cryptococcal meningitis

23(48 %) of patients came with a history of 10 days illness, out of which 12(52%) responded to therapy and the rest succumbed to the illness. Patients with symptoms of 11 to 20 days 17(34%) had a cure of 11(65%). There were 10 (20%) patients with more than 21 days of symptoms, they had cure rate of 70%. The mean CD4 in HIV positive patients was 59 ± 31.13 cells/ cu.mm and CD4 ≤ 50 cells/ cu.mm was associated with poor prognosis (p = 0.012).Co-infection with tuberculosis was present in 15 patients (Pulmonary TB - 8, Abdominal TB – 5, TB meningitis – 2) and although there were more deaths with TB co-infection it was not significant (p = 0.088).

The mean duration of presenting illness was 16.86 ± 12.8 days. Headache was the most common symptom and was present in all patients. Figure 3 is a graph depicting the spectrum of symptoms encountered in the study (in percentage). Only blindness was associated with increase in mortality (p = 0.034).

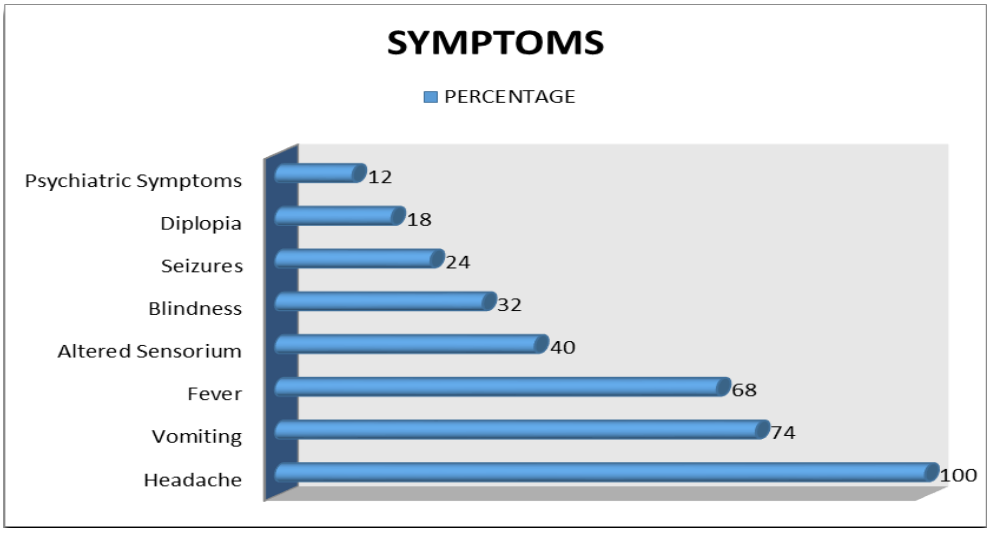

Figure 3: Spectrum of symptoms encountered in the study (in percentage)

Neck stiffness was present in 44 patients (88%) and was associated with greater mortality (p = 0.03). The mean Glasgow Coma Score (GCS) was 11.06 ± 3.24. GCS score of ≤ 8 was significantly associated with mortality (p = 0.000011). Papilledema was present in 20 patients (40%) and was associated with greater mortality (p = 0.0009). Other cranial nerves involved were VI (9 patients), VII (2 patients) and VIII (4 patients). One patient had hemiparesis and one had cervical myeloradiculopathy.

Table 1 shows the CSF parameters of patients included in the study. Low CSF sugars (< 40 mg/dL) were strongly associated with mortality (p = 0.0005). Although there was greater mortality with high CSF opening pressure (> 30 cm of H_2O), it was not significant (p = 0.085). The

association between high opening pressure and blindness was significant (p = 0.005).

Table 1: CSF parameters of study population

CSF parameters	Mean
Opening pressure (cm of H_2O)	29.64 ± 7.55
CSF Lymphocytes (cells/ µL)	40.82 ± 46.02
CSF polymorphs (cells/ µL)	10.24 ± 16.35
Sugars (mg/dL)	32.36 ± 15.06
Proteins (mg/dL)	97.78 ± 60.51
India Ink positivity (%)	72

Neuroimaging was normal in 28 patients (56%), showed cerebral atrophy in 10 patients (20%), hydrocephalus – 5 patients (10%), basal exudates - 3 patients (6%), cerebral edema – 3 patients (6%) and infarcts – 1 patient (2%).

Hypokalemia was the seen in 28 (56%) patients, a complication of Amphotericin B therapy. Patients were not symptomatic for hypokalemia.

Comparison between groups: Patients were divided into two groups i.e. survival group and mortality group. Demographic (table 2), clinical and laboratory parameters (table 3) of both groups are shown.

The parameters which were associated with mortality were blindness, neck stiffness, a low GCS score, Papilledema, low CD4 levels and low CSF sugars (< 40 mg/dl).

Table 2: Demographic parameters of study population

	Survival Group	Mortality Group	p value
Mean Age in years	34.87 ± 9.39	37.05 ± 6.58	0.372
Sex - Male %	21 (70)	14 (70)	1
HIV Positivity %	90	90	1
HIV Newly diagnosed %	29.6	44.4	0.354
Mean HIV duration in months	28.87 ± 29.72	28.8 ± 41.80	0.695
Previously diagnosed HIV on HAART %	22.2	16.67	0.721
TB co-infection %	26.67	35	0.547

Table 3: Clinical and CSF parameters affecting outcome

Parameter		No of patient's (%)	Survival Group (%)	Mortality Group (%)	P value
Mean Glasgow Coma scale		50	13.07 ± 1.98	8.05 ± 2.26	0.00079
Neck Stiffness	Present	43(86)	23(54)	20(46)	0.033
	Absent	7(14)	7 (100)	0	
Papilledema	Present	31(62)	6 (30)	14(70)	0.0009
	Absent	19(38)	13(68.42)	6(31.57)	
CD4 count cells/ cu.mm	< 50	18(41.8)	6 (33.3)	12(66.7)	0.007
	>50	25(58.1)	19 (76)	6 (24)	
	Mean	45	84.67 ± 81.01	45.94 ± 28.85	
CSF Opening pressure mm H_2O	Normal	5(10)	3(60)	2(40)	0.085
	Elevated >20	45(90)	28(62.2)	18(37.7)	
CSF Lymphocytes//mm ^{3}	<25	28(44)	14(50)	14(50)	0.501
	>25	22(56)	16(72.7)	6(27.27)	
	Mean		52.57 ± 58.05	48.8 ± 55.3	
CSF sugar / mg/dL	Normal	13 (26)	13(100)	0	0.00055
	<40 mg/dl	37(74)	17(45.9)	20(54.05)	
CSF Proteins/ mg/dL	Normal	11(22)	9(82)	2(18)	0.235
Cryptococcal Antigen/ titre	>50	39(78)	21(53.84)	18(46.15)	0.05
	1:50	4(8)	0	4(100)	
	>1:100	30(60)	22(73.3)	8(26.7)	
	>1:200	16(32)	8(50)	8(50)	
CSF India Ink	Negative	14(28)	10(71.42)	4(28.6)	0.353
	Positive	36(72)	20(55.6)	16(44.4)	
Total		50	30(60)	20(40)	

4. Discussion

Cryptococcal meningitis is the second most common fungal infection after *Candida albicans* infection in HIV positive patients [4]. However there is marked geographic variation in its prevalence, being greatest in Sub-Saharan Africa and South East Asia (19 % in HIV positive patients in a study in Thailand between 1994 and 1998) and least in Europe and North America [5]. Studies reveal that the prevalence of Cryptococcal meningitis in HIV positive patients in India was 3.1% [6] to 7% [7]. A study over five and a half years concluded that 16.6% of all cases of meningitis admitted in a tertiary care hospital in North India had Cryptococcal meningitis [8].

Cryptococcal meningitis is more common in males [7,8] and in the age group ≤ 40 years [7], with average age ranging from 30 to 40 years [7,9,10] and was reflected in our study. However neither was found to affect cure rates. Cryptococcal meningitis is more common in HIV infected individuals than HIV negative, although incidence in HIV positive patients is decreasing in developed countries due to availability of HAART [11]. The disease can occur with chronic steroid use, diabetes mellitus, solid organ transplant patients, lymphomas and idiopathic CD4+ lymphocytopenia. While some studies have found greater mortality in HIV negative patients [12]; some have found greater mortality in HIV positive patients [13], while others have found that an immunocompromised state (apart from corticosteroid use) is not a factor in determining mortality [14]. Mortality was equal in HIV positive and negative patients in our study. A limiting factor in the analysis was the small sample size in the HIV negative group.

Majority of cases are seen in patients without a previous diagnosis of HIV [15], however in our study only 35.6% were newly diagnosed to have HIV. Duration of HIV disease did not alter mortality. Initiation of HAART is known to reduce the incidence of Cryptococcal meningitis [16]. However, acute (<3 months) mortality rates in cryptococcal meningitis were found to be similar in Anti-retroviral therapy(ART) naïve and ART experienced patients in a study in South Africa [17], which was also evident from our study. The long term (> 1 year) mortality was significantly greater for ART naïve patients in the South African study [17], and in a study from Thailand [18]. We did not look at long term mortality rates.

Cryptococcal meningitis occurs in advanced stages of HIV disease with CD4+ cells counts usually less than 100/cu.mm, with mean CD4+ cell counts between 50 – 100 cells/cu.mm [9, 11]. In our study, the mean CD4+ cell count was 59 ± 31.13 cells/ cu.mm and a CD4 ≤ 50 cells/ cu.mm (indicative of severe immune suppression) was significantly associated with poor prognosis.

Co-infection with tuberculosis is an issue in India especially tuberculous meningitis, which was found in 10.5% of CM patients in a study in South India [11] and 4% in our study. There was a trend towards greater mortality in patients co-infected with tuberculosis in our study but was not statistically significant.

Although Cryptococcal Meningitis is classified as chronic meningitis, as many as 80% of our patients had an acute to sub-acute presentation (< 20 days duration), suggesting the need to investigate for cryptococcal meningitis in all HIV positive patients with features of meningitis regardless of duration of illness. Similar results were found in other studies in PGI, India [19] and in China [12]. The Chinese study found that the duration of symptoms was significantly lower in HIV positive individuals [12], but this was not corroborated in our study. This was probably due to the very low number of HIV negative patients in our study.

The commonest symptoms were headache followed by vomiting, fever, altered sensorium, blindness, diplopia, seizures and psychosis. Focal deficits were very rare like in other studies [7,19]. Similar findings were found in other studies [7-9,11,12,19]. Amongst the clinical features blindness (either due to raised intracranial pressure or direct invasion of the optic nerve [20]), neck stiffness, low GCS and papilledema were associated with a greater risk of mortality. Other studies have found the following poor prognostic factors – Low GCS [9,11,19], Papilledema [9,11], Headache [9], blindness [9] and weight loss [21]. An association was also found between high CSF pressure and blindness in our study.

The only CSF parameter associated with mortality in our study was low CSF sugar level. There was a trend towards greater mortality in patients with high CSF pressure (> 30 cm H_2O), but it was not statistically significant. Other studies have found the following poor prognostic CSF markers – high CSF pressure [9,11,19,21,22], Low CSF sugar [9,22], Low CSF cell count [9, 22], high CSF protein [21], high CSF Cryptococcal antigen titre and initial India Ink positivity [11,22]. Multivariate analysis in our study, however, revealed that only low CSF sugar was associated with mortality.

Neuroimaging was normal in 56% of our patients, and showed generalized atrophy in another 20%. Similar high rates of nonspecific findings on neuroimaging have been observed in other studies as well [23]. We did not find any patient with cryptococcomas.

The overall mortality was 40% in our study. Mortality in studies from India is usually high at around 36% to 50% [3, 4, 6, 10, 21], with the exception of a study from north India where it was 22.2% [8]. Mortality in studies from other developing countries like South Africa [17] and Kenya [25] is also high (~38%). Studies from Denmark – 13.3% [26], Taiwan – 19% [13] and Thailand – 24% [21] have shown lesser mortality rates. Limitation of the study was small sample size.

5. Conclusion

Mortality rates in patients with Cryptococcal meningitis remain high in India. Factors associated with greater mortality in our study were blindness, a low GCS, Papilledema, CD4+ cell counts ≤ 50 cells/ cu.mm and CSF sugars ≤ 40 mg/dl. Co-infection with tuberculosis is a major problem in India.

Acknowledgement: Nil

Conflict of Interest: No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

References

[1] UNICEF. Opportunity in crisis: Preventing HIV from early adolescence to young adulthood. June 2011, available at http://www.unicef.org/media/files/Opportunity_in_Crisis_LoRes_EN_05182011.pdf [accessed 16 Jan 2017].

[2] 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 Feb 20; 23(4):525-30.

[3] Pappas PG. Cryptococcosis in the developing world: An elephant in the parlor. *Clin Infect Dis*. 2010; 50:345–6.

[4] Juhi T, BibhaBati M, Aradhana B, Poonam L, Vinita D, Archana T. Cryptococcal Meningitis in a Tertiary Care Hospital. *Jpn J Med Mycol* 2009; 50(2):95-9.

[5] Chariyalertsak S, Sirisanthana T, Saengwonloey O, Nelson KE. Clinical presentation and risk behaviors of patients with acquired immunodeficiency syndrome in Thailand, 1994--1998: regional variation and temporal trends. *Clin Infect Dis* 2001; 32(6):955-62.

[6] Jaiswal S P, Hemwani N, Sharma N, Athale S, Chitnis D S. Prevalence of fungal meningitis among HIV positive & negative subjects in Indore (MP State). *Indian J Med Sci* 2002; 56:325-9.

[7] Subramanian S, Mathai D. Clinical manifestations and management of cryptococcal infection. *J Postgrad Med* 2005; 51:21-6.

[8] Prasad KN, Agarwal J, Nag VL, Verma AK, Dixit AK, Ayyagari A. Cryptococcal infection in patients with clinically diagnosed meningitis in a tertiary care center. *Neurol India* 2003; 51(3):364-6.

[9] Majumder S, Mandal SK, Bandyopadhyay D. Prognostic markers in AIDS-related cryptococcal meningitis. *J Assoc Physicians India* 2011; 59:152-4.

[10] Shih CC, Chen YC, Chang SC, Luh KT, Hsieh WC. Cryptococcal meningitis in non-HIV-infected patients. *QJM* 2000; 93(4):245-51.

[11] Satishchandra P, Mathew T, Gadre G, Nagarathna S, Chandramukhi A, Mahadevan A et al. Cryptococcal meningitis: clinical, diagnostic and therapeutic overviews. *Neurol India* 2007; 55(3):226-32.

[12] Liao CH, Chi CY, Wang YJ, Tseng SW, Chou CH, Ho CM et al. Different presentations and outcomes between HIV-infected and HIV-uninfected patients with Cryptococcal meningitis. *J Microbiol Immunol Infect* 2012; 45(4):296-304.

[13] Khanna N, Chandramuki A, Desai A, Ravi V. Cryptococcal infections of the central nervous system: an analysis of predisposing factors, laboratory findings and outcome in patients from South India with special reference to HIV infection. *J Med Microbiol* 1996; 45(5):376-9.

[14] Harris JR, Lockhart SR, Debess E, Marsden-Haug N, Goldoft M, Wohrle R et al. Cryptococcus gattii in the United States: clinical aspects of infection with an emerging pathogen. *Clin Infect Dis* 2011; 53(12):1188-95.

[15] Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2010; 50(3):291-322.

[16] Ives NJ, Gazzard BG, Easterbrook PJ. The changing pattern of AIDS-defining illnesses with the introduction of highly active antiretroviral therapy (HAART) in a London clinic. *J Infect* 2001; 42(2):134-9.

[17] Bicanic T, Meintjes G, Wood R, Hayes M, Rebe K, Bekker LG et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with Amphotericin B or Fluconazole. *Clin Infect Dis* 2007; 45(1):76-80.

[18] Chottanapund S, Singhasivanon P, Kaewkungwal J, Chamroonswasdi K, Manosuthi W. Survival time of HIV-infected patients with cryptococcal meningitis. *J Med Assoc Thai* 2007; 90(10):2104-11.

[19] Kumar S, Wanchu A, Chakrabarti A, Sharma A, Bambery P, Singh S. Cryptococcal meningitis in HIV infected: experience from a North Indian tertiary center. *Neurol India* 2008; 56(4):444-9.

[20] Rex JH, Larsen RA, Dismukes WE, Cloud GA, Bennett JE. Catastrophic visual loss due to Cryptococcus neoformans meningitis. *Medicine (Baltimore)* 1993; 72(4):207-24.

[21] Pitisuttithum P, Tansuphasawadikul S, Simpson AJ, Howe PA, White NJ. A prospective study of AIDS-associated cryptococcal meningitis in Thailand treated with high-dose amphotericin *B. J Infect* 2001; 43(4):226-33.

[22] Diamond RD, Bennett JE. Prognostic factors in cryptococcal meningitis. A study in 111 cases. *Ann Intern Med* 1974; 80(2):176-81.

[23] Popovich MJ, Arthur RH, Helmer E. CT of intracranial cryptococcosis. *AJR Am J Roentgenol* 1990; 154(3):603-6.

[24] Sachdeva RK, Randev S, Sharma A, Wanchu A, Chakrabarti A, Singh S et al. A retrospective study of AIDS-associated cryptomeningitis. *AIDS Res Hum Retroviruses* 2012; 28(10):1220-6.

[25] Kendi C, Penner J, Koech J, Nyonda M, Cohen CR, Bukusi EA et al. Predictors of outcome in routine care for Cryptococcal meningitis in Western Kenya: lessons for HIV outpatient care in resource-limited settings. *Postgrad Med J* 2013; 89(1048):73-7.

[26] Mathiesen IH, Knudsen JD, Gerstoft J, Cowan S, Benfield T. Outcome of HIV-1-associated cryptococcal meningitis, Denmark 1988-2008. *Scand J Infect Dis* 2012; 44(3):197-200.