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**BURDEN OF CRYPTOCOCCAL MENINGITIS AND UNUSUAL  
FINDINGS IN PATIENTS WITH HIV INFECTION ADMITTED IN A  
TERTIARY CARE SUPER SPECIALTY HOSPITAL IN NORTHERN  
INDIA**

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Received 17<sup>th</sup> Aug. 2020; Revised 16<sup>th</sup> Sept. 2020; Accepted 7<sup>th</sup> Oct. 2020; Available online 1<sup>st</sup> July 2021

<https://doi.org/10.31032/IJBPAS/2021/10.7.5520>

**ABSTRACT**

**Background:** Meningitis is a leading causes of early mortality in HIV infected patients. But the findings, characteristics and clinical outcome is still in their infancy. There are still some unusual findings that need to be documented.

**Methods:** Patients were recruited who were admitted to Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, with confirmed diagnosis of meningitis. A total of 55 patients of meningitis were available for this study from June 2016 – June 2019. Lumbar puncture was performed in all cases and Cerebrospinal Fluid (CSF) was sent for analysis. Cerebrospinal Fluid (CSF) from all cases was tested to rule out the cause of infection. CSF analysis was done by India ink, Cryptococcal Antigen Latex Agglutination test, followed by fungal culture. CD4 count, CSF cell count, biochemical analysis, corresponding CSF sugar and protein levels.

**Results:** Out of 55 patients, 40 were diagnosed with Cryptococcal meningitis and 8 were having tubercular meningitis. Mean age of patients was 40.43±12.64 years. Fever (92.5%)

and Headache (85%) was the most prominent clinical feature in CM patients. We also observed some unusual features such as one patient with stroke, one with diplopia, one with nystagmus, one with petechias and one with invasive disease of bone marrow. The CSF India ink was positive in 14 (87.5%) a rural area and 19 (79.2%). urban area patient.

**Conclusion:** Cryptococcal meningitis is the most common laboratory confirmed aetiology in HIV infected patients in northern India region. Some unusual findings are also there which may lead to miss the diagnosis. So a clear evaluation is very important.

**Keywords:** Meningitis, Cryptococcal meningitis, HIV

## INTRODUCTION

Meningitis is a major opportunistic infection seen in immuno-compromised patients and is particularly common in those infected with HIV [1]. It is an important fungal infection causing an estimated 1 million cases and 625,000 deaths per year due to central nervous system (CNS) disease among patients with HIV worldwide [2]. Differences in geographical distribution, epidemiology and clinical presentation have been observed among all HIV patients. The incidence of Cryptococcal meningitis (CM) remains a major opportunistic infection and leading cause of mortality in patients infected with HIV [3]. The global burden of CM is estimated to be 9,57,900 cases resulting in an estimated 6,24,700 deaths within 3 months of Cryptococcal infection [4]. Even with the availability of ART, CM related mortality remains high (20% -30%) [5]. Among AIDS patients, the rate of infection ranges from 23% to 48.6%, and approximately 70% to 90% of patients have signs and symptoms of subacute meningitis

or meningo-encephalitis with high mortality rates [6]. The mortality rate may be as high as 30%, particularly with delay in diagnosis and definitive treatment [7]. The mortality rate of Cryptococcal Meningitis varies regionally [8-10]. Common clinical picture comprises fever, headache, meningeal signs altered mental status, with cerebrospinal fluid (CSF) pleocytosis, and those with a Cryptococcal antigen (CALAS; Cryptococcal latex agglutination system) titre of more than 1:8 and/or positive India Ink preparation for encapsulated yeast cells and/or a positive CSF culture yielding *Cryptococcus neoformans* was suggestive of CM [11]. In case of blood samples, Cr-Ag latex test reported high with confusion, seizures, visual loss due to papilloedema and rarely, focal neurological deficit [13]. There are still some unusual findings which need to be documented. In this study we also tried to find out the most common causative agent of meningitis in northern India population.

## METHODOLOGY

The present study was conducted between June 2016 to June 2019 in the Deptt. of Microbiology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India. It is a tertiary care superspeciality hospital where patients from all over Uttar Pradesh are admitted. A total of 55 subjects diagnosed with meningitis along with HIV infection were enrolled in the study. Patients' demographical details, medical history, microbiological investigations were documented. Demographic details such as age, gender, occupation, area of residence and clinical characteristics [Human immunodeficiency virus (HIV) co-infection, previous use of ART and clinical outcomes during the hospitalization period were also obtained (Table 1). Clinical, radiological, microbiological, and other laboratory data were evaluated and the diagnosis of meningitis was made based on a combination of clinical and CSF findings (Table 2).

## ASSESSMENT

### 1: Lumbar puncture

CSF samples were collected under aseptic conditions by lumbar puncture by expert doctors. Before collection of CSF samples, the informed written consent of all subjects was obtained. The median lumbar puncture pressure was 19.2 cm of H<sub>2</sub>O and 18 patients had elevated opening CSF pressure (>20cm of H<sub>2</sub>O). CSF was clear in majority

of patients and turbid in 10 patients. CSF was sent for further analysis. One patient with opening pressure 30.8cm H<sub>2</sub>O was also noted.

### 2: Microbiological Investigations

#### 2(a) Bacterial meningitis

Patients were diagnosed with the Bacterial (Pyogenic) meningitis on the basis of clinical findings such as sudden onset of fever, headache, altered mental status, or other meningeal signs, a positive CSF Gram stain and bacterial culture was performed on Blood Agar, MacConkey Agar, Chocolate Agar plates and Brain Heart Infusion Broth and typical CSF findings (CSF pleocytosis with polymorphonuclear cell predominance, low glucose, and elevated protein.

#### 2(b) Cryptococcal meningitis

A diagnosis of cryptococcal meningitis was made in the presence of a positive CSF India ink stain or CSF cryptococcal antigen test using latest agglutination test kit (CALAS, Meridian Bioscience Europe, Nice, France) according to the manufacturer's instructions, Cryptococcal Latex Agglutination Test (LAT) was performed with CALAS (Bio-Rad, PastorexTMCrypto plus). On the other hand, cases of Cryptococcal meningitis (n=40) were also tested for HIV antigen/antibodies (as per the NACO HIV testing guidelines. A new technique of

Cryptococcal Antigen Lateral Flow Assay test in urine was also done. Its significance of this technique is that it is a non-invasive technique, easy to use and hence less chances for infection. This technique was used first time in department to validate the result. After the completion of the study this technique was found to be valid, reliable and standardized.

### 2(c) Tubercular meningitis

Patients were diagnosed with the TB meningitis on the basis of clinical features of meningitis, brain CT findings suggestive of Tubercular meningitis such as basal meningeal enhancement or hydrocephalus, with negative CSF Gram stain and cultures for bacteria, negative CSF cryptococcal antigen test, and at least one of the following: (i) characteristic CSF findings (CSF pleocytosis with lymphocytic predominance, low glucose, and elevated protein); (ii) evidence of active tuberculosis at another site (e.g chest X-ray suggestive of TB); d) Positive AFB smear using Ziehl-Neelsen stain; e) Lowenstein Jensen medium (for Mycobacterial species).

Data was analysed by SPSS software (version 20.0). Categorical variables were analysed by Chi-Square test. A P-value < .05 was considered statistically significant. Graph pad PRISM was used to plot the figures.

## RESULTS

### A. Baseline characteristics

55 patients were diagnosed with meningitis who were having HIV infection. Out of 55 patients, five patients expired during the study due to multiple organ involvement, 2 were lost to follow-up while study. The study subjects comprised 48 individuals, 28 were males and 20 females with HIV infection. Mean age of the patients was  $40.43 \pm 12.64$  years. Out of 48 patients, 40 were diagnosed with Cryptococcal infection, 8 were having tubercular meningitis, (Table 1). About 50% of the patients had unknown HIV status on admission. 92% patients presented with fever and 85% were having Headache. Nausea & vomiting were reported in 30% patients while focal convulsions were present in 17.5% patients only. 17.5% patients had altered sensorium, 25% had Hallucinations, 15% had neck stiffness and sensitivity to light was reported by 20% patients.

### B. Prevalence of Cryptococcal meningitis

Cryptococcal antigen was positive in both serum and CSF of 30 patients (75%) and India ink showed encapsulated yeast cells in 33 patients (82.5%) (Figure 1, 2). No patient had a positive India ink with a negative CSF Cr Ag test. CD4 count was performed at nodal centres after they were referred by ART centres. The value of CD4 count was < 200 cells/mm<sup>3</sup>. In our study, we carried out CD4 counts of all 48

patients. HIV patients had non-significant number of leukocytes in their blood. A non-significant increase was observed in CSF protein content, however, there was no significant difference in CSF glucose levels. At least one CSF culture was done in all the patients for detection of Cryptococcal meningitis. The CSF India ink was positive in 14 patients (87.5%) from rural and 19 (79.2%) patients from urban area. Cryptococcal antigen was also tested by urine analysis. It is a new technique which is non invasive and easy to do.

### C. Unusual findings

Petechias were noted in one patient. One patient with diplopia and one with nystagmus were also noticed. One patient had stroke and one patient with bone marrow invasion was also documented (Figure 3 and 4).

### D. Outcome

All 40 patients in our study responded to induction therapy using Amphotericine B (1mg/kg daily) for 2 weeks, followed by Fluconazole 400 mg daily for 2months. Out of 20 HIV positive patients, 4 (20%) were on ART for the past 3 months, 6 (30%) patients were on ART for the past 6 months and 10 (50%) were on ART for more than 1 year. Out of 40 patients who were given induction therapy, 10 patients survived, 4 expired, and there remaining 6 patients were lost to follow up.

In rest of patients relapse of the disease was observed. One patient had stroke. All patients were managed by medical and rehabilitation management.

### E. Length of hospital stay

The mean length of hospital stay was 2.5 months (Range 1- 5 months). Patients with turbid CSF were also observed to have longer hospital stay (Table 3).

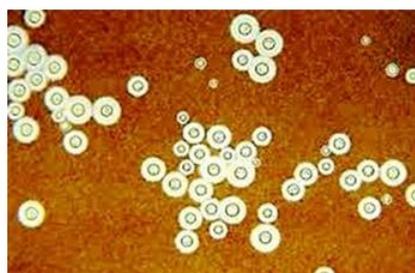


Fig 1



Fig 2

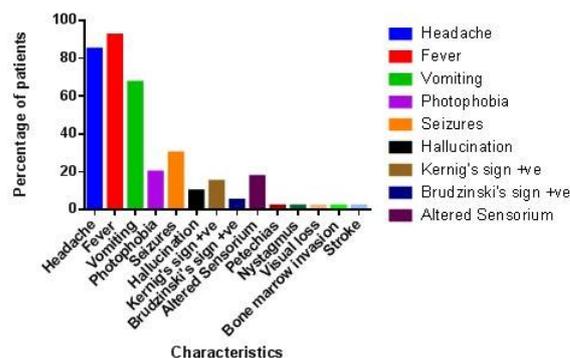


Fig 3

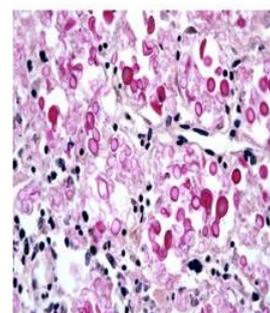


Fig 4

Figure 1: India Ink Preparation showing encapsulated budding yeast cells of *Cryptococcal neoformans* (Narrow based budding yeast cells variable sized measuring in 5-25µ)

Figure 2: Creamy color colonies on Sabouraud Dextrose Agar

Figure 3: Clinical characteristics of patients of meningitis with HIV infection

Figure 4: Mucicarmine stain in bone marrow seen in *Cryptococcus neoformans*

Table 1: Demographic details of subjects with meningitis	
Characteristics	Values Number (%)
Age (Years)	40.43±12.64
Gender Male/ Female	10 /10
Merital status	
Unmarried	4
Married	36
Occupation	
Job	6
Without job	34
Residence	
Rural	16
Urban	24
Symptoms and signs on admission	
Fever (%)	92.5
Headache (%)	85
Convulsions ( generalized) (%)	30
Nausea and Vomiting (%)	20
Convulsions focal (%)	67.5
Altered sensorium (%)	10
Neck stiffness (%)	17.5
Photophobia (%)	15
Kernig's sign positive (%)	20
Brudzinski's sign positive (%)	15
Nystagmus	2
Stroke	2
Petechias	2
Bone marrow invasion	2
HIV status on admission	
New	10 (25)
Known	30 (75)
Baseline CD4 count	< 200 cells/mm <sup>3</sup>
CD4 count in known patients (cells/µl) [median (Maximum)]	28(46)
CD4 count in newly diagnosed (cells/µl) [median (Maximum)]	19.5(34)

Characteristics	Value
Lumbar puncture opening pressure Normal (<20 cm of H <sub>2</sub> O) Elevated (>20 cm of H <sub>2</sub> O)[Median(Range)]	32 (-35)
CSF appearance Clear Turbid	20 10
CSF sugar [Median(IQ Range)]	37.5(- 95)
CSF protein [Median(IQ Range)]	72.405(-61.85)
CSF WBC count (cells/ $\mu$ l) [Median(IQ Range)]	8.5(-3.125)
India ink positive (%)	35 (87.5%)
CALAS positive (%)	40 (100%)
Crypto AG LFA positive (%)	40 (100%)
CSF routine Culture positive (%)	30 (75%)
CSF: Cerebro spinal fluid, IQ: Inter quartile	

No. of Patients	Length of hospital stay	Symptoms	No. of patients	Percentage (%)
10	5 months	Fever	5	50
		Headache	10	100
		Nausea & Vomiting	3	30
15	2 months	Fever	6	40
		Headache	7	46.6
		Neck	2	13.3
		Stiffness		
10	1 month	Headache	5	50

## DISCUSSION

The symptoms of meningitis among HIV-infected individuals may vary depending on the cause. In our study we found that CM was the most common infection followed by tubercular infection in HIV infected patients. The most common combination of presenting clinical features for patients suspected to have meningitis was headache and neck stiffness. Clinical manifestations of Cryptococcal meningitis include acute or sub acute fever, headache, meningeal signs (positive Kernig's sign and Brudzinski's sign) or altered mental status, with a cerebrospinal fluid (CSF) abnormal biochemistry and/ or pleocytosis. Hallucination was also observed in some

patients. Petechia was observed in one patient only. One patient had stroke. According to Ellis *et al.* (2018) [12] stroke is a complication of Cryptococcal meningitis and is a result of inflammatory response of body. According to Oberman *et al.* (2018) [13] stroke may be a complication of CM due to central nervous system vasculitis. In this study our aim was to find out the most common opportunistic infection, clinical characteristics and outcome in Cryptococcal meningitis in patients with HIV infection. We also found some unusual findings along with such as diplopia, nystagmus, stroke and bone marrow invasion which may make the physician to miss the actual diagnosis. This

study to determine different etiologies of meningitis among HIV infected patients. Amongst 40 HIV-infected patients with CM infection, 62.5% were males in rural region and 58.3% males prominent in urban region. In same way, 37.5% females in rural region and 41.7% in urban region. Male to female ratio in urban region was 1.4:1 and in rural region was 1.6:1. In previous study, a greater involvement of men (76.7%) than women was there in infection by *Cryptococcus spp.* [14-16]. The underlying causes for this is increased susceptibility may be related to the following factors:

- 1) Occupational exposure,
- 2) Behavioural aspects,
- 3) Alcoholism, smoking and
- 4) HIV infection [17, 18]

In previous studied urban population of Cryptococcosis higher than the rural population [19, 20]. This yeast was observed in the excreta of captive birds and domestic pigeon like (*C. livia*) in public areas that are commonly used by human [21-23]. Vidal *et al* [24] showed those person who live in poverty and affected by opportunistic diseases have limited access medical care. In other study observed socioeconomic status of cryptococcosis ranges from several days to several months [25, 26]. If delays in the diagnosis of Cryptococcal meningitis patients facing difficulties in health services as well as limited diagnostic resources (serological

tests, microscopic findings and associated with Cryptococcosis seems to be decreasing<sup>28</sup> but the disease has a high mortality rate where the occurrence of AIDS is high if not diagnosed and treated. In our study symptoms of headache, fever and vomiting were predominant in all the cases of Cryptococcal meningitis, which is similar to those reported earlier in the literature [29-32]. Although less typical clinical manifestations of Cryptococcal meningitis in HIV- infected patients) (such as headache, altered mental status and neck stiffness) were reported previously. In our study, Headache is the most significant symptom showed clinically. No significant difference in the other mentioned clinical features between two areas was seen in our study. In our study, smear by India ink preparation was positive in 87.5% in rural area and 79.2% in urban area, while in a study conducted by Satishchandra *et al.*, >90% of patients had India Ink test positive [33]. This simple test can be done in the primary care setting. In view of the high prevalence of Cryptococcal meningitis in HIV cases, India Ink smear should be routinely done in every CSF examination. Cryptococcal Latex Agglutination test, Cryptococcal Antigen Lateral Flow Assay and culture are the specific and sensitive tests for the diagnosis of CM. The World Health Organization recommended the

early diagnosis and treatment of HIV (HAART) as one of the most important and cost-effective preventive strategies for reducing the incidence and mortality associated with cryptococcal meningitis [24]. When available, screening tests, including investigations of the presence of cryptococcal capsular antigen in asymptomatic and symptomatic patients, also contribute to the optimization of the diagnosis and treatment of cryptococcosis [34].

Our study also demonstrates the potential value of testing urine samples against Cryptococcal Antigen. Therefore, this diagnostic strategy may help to screen out patients presenting with symptoms of Cryptococcal meningitis in preliminary stage or rural clinics where Lumbar Puncture may also be avoided. So, the Cryptococcal Antigen Lateral Flow Assay test in urine samples could be promising and reliable diagnostic method against Cryptococcal meningitis. Therefore, urine screening would be ideal.

## CONCLUSION

Cryptococcal meningitis is the most common laboratory findings among HIV infected patients. This study presented the high mortality associated with Cryptococcal meningitis in routine care setting and supports. On the basis of our clinical findings we can also suggest that all patients who are immune compromised,

should be screened for CM. The unusual finding may lead to misdiagnosis or missed evaluation.

**Conflict of interest:** The authors have no potential conflict of interest. The disclosure of potential conflict of interest in the prescribed format has been obtained from all the authors.

**Ethical approval:** The study was approved and the work was performed in accordance with the guidelines of Institutional Ethics Committee of Dr. Ram Manohar Lohia Institute of Medical Sciences.

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