



PROFILE OF CRYPTOCOCCAL MENINGITIS IN A TERTIARY CARE HOSPITAL FROM NORTHERN INDIA

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ABSTRACT

A retrospective observational study was conducted over a period of 11 years, on the patients suspected to be suffering from chronic meningitis to evaluate the clinical and laboratory manifestations of Cryptococcal meningitis. Cerebrospinal fluid (CSF) samples from these patients were processed by India Ink preparation / antigen detection by latex agglutination test / culture. Patient's demography and clinical profile of the disease were studied. A total of 139 (1.9%) patients were diagnosed with Cryptococcal meningitis. Positivity of microscopy, culture and latex agglutination test in CSF for the diagnosis of cryptococcal meningitis was 48.2%, 73.4% and 100% respectively. Fever, headache, vomiting, altered sensorium and seizures were the frequent clinical presentations. Co-morbidities associated with the disease were - HIV, diabetes mellitus, tuberculosis, renal transplantation etc. Cryptococcal meningitis has been identified as one of the important AIDS defining illnesses in the present study. Early diagnosis of the disease and institution of antifungal therapy well in time may alter the prognosis of these patients.

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INTRODUCTION

Cryptococcus neoformans, an encapsulated yeast causes primarily a chronic infective condition that affects the central nervous system (CNS), although pneumonia, skin and soft tissue infections have also been reported [1-2]. With the increase in incidence of HIV and other immunocompromised conditions; last 20 years have seen the surge in the infections caused by *Cryptococcus neoformans*. [3] It is the leading infectious cause of meningitis/meningoencephalitis in patients with AIDS and is used as a marker for the initial AIDS defining diagnosis, mostly occurring in patients with CD4 counts <100 cells/mm³. [4] The morbidity and mortality in Cryptococcal meningitis is 10-30 % in developed countries and 50-100% in developing countries.[5] The Centers for Disease Control and Prevention (CDC) of the United States estimated that worldwide, nearly 220,000 new cases of cryptococcal meningitis occur each year, resulting in 181,000 deaths. Most of the illnesses and deaths occur in sub-Saharan Africa and South & Southeast Asia. [6] In addition to AIDS, other reported possible risk factors for invasive cryptococcosis, include liver cirrhosis, diabetes mellitus, lymph proliferative malignancy, hematological malignancy, cancer, autoimmune diseases,

and lung diseases [7-9]. Antiretroviral and antifungal therapy has substantially decreased the long-term mortality, but survivors can suffer neurocognitive impairments, though reversible, even after clinical cure, if not diagnosed early and specific treatment instituted.[10-12] Therefore, for management of cryptococcosis early diagnosis is imperative. Cryptococcal meningitis has been relatively understudied in developing countries such as India. Therefore, this retrospective study was undertaken to assess the prevalence and clinical profile of cryptococcal meningitis in a tertiary care centre of north India.

METHODS

A total of 6953 hospitalized patients, over a period of 11 years (Jan 2007 - Dec 2017) suspected to be suffering from chronic meningitis were included in the study. Cerebrospinal fluid (CSF) samples from these patients were tested by India ink preparation / antigen detection by latex agglutination test (CALAS, Meridian Bioscience) / culture.

Direct microscopy from the centrifuged deposit of the CSF sample was performed using India ink preparation. Presence of encapsulated budding yeast cells against the

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dark background was identified as *Cryptococcus neoformans*.

Fungal cultures of all the CSF samples were performed on Sabouraud dextrose agar (SDA) slants and the cultures were incubated at both 37°C and 25°C in BOD incubator for 4 weeks. The cultures were examined at regular intervals for any growth. The growth of *Cryptococcus neoformans* was identified on the basis of colony morphology, India ink preparation and standard biochemical tests.

Patient's demography, clinical signs and symptoms at the time of presentation, underlying disease, HIV status and outcome were analyzed.

Cryptococcal meningitis was defined as - clinical features of meningitis/meningo-encephalitis along with positive CSF cryptococcal antigen test or positive CSF India ink preparation or isolation of Cryptococcus neoformans in the CSF culture.

RESULTS

A total of 6953 hospitalized patients, suspected to be suffering from chronic meningitis were included in the study. Cerebrospinal fluid (CSF) samples from these patients were tested by India Ink preparation, latex agglutination test (CALAS, Meridian Bioscience) for antigen detection and fungal culture. Based upon the above mentioned investigations and clinical suspicion, a total of 139 (1.9%) patients were diagnosed with Cryptococcal meningitis. All the 139 patients have their CSF sample positive for cryptococcal antigen. Comparison of Cryptococcal antigen and India ink was done over a period of 9 years and only 48% of the Antigen positive CSF samples were also positive on India ink preparation. Approximately 73% of the antigen positive specimen showed growth of *Cryptococcus neoformans* on SDA slants.

Demographic, clinical profile and epidemiological data of 62 patients with cryptococcal meningitis was studied and has been depicted in Table 1.

The age of the patients diagnosed with cryptococcal meningitis ranged from 17 to 84 years with an average age of 43.6 years. Male outnumbered female patients (70% males). Approximately 50% of the patients were in the age group of 40-50 years.

Most common clinical features found in patients with cryptococcal meningitis were fever (56.4%), headache (54.8%) and vomiting (17.2%) followed by general weakness (19.3%), altered sensorium (17.7%) and seizures (11.3%). Co-morbidities associated with the disease were - HIV (66.1%), diabetes mellitus (16.1%), tuberculosis (20.9%), renal transplantation (11.3%), Drug addiction (14.5%), alcohol abuse (11.3%), hypertension (8.1%) etc.

After receiving antifungal therapy, 45.2% showed improvement/ recovery, 9.7% expired, while the outcome for 45% cases was not known as they were either discharged on request (DOR) or left against medical advice (LAMA).

Table 1 Clinical profile of patients (n=62) diagnosed with *Cryptococcus neoformans* meningitis

Variables	Number (%)
Demographical Profile:	
Age: Average 43.6 years (Range: 17-84 years)	
Sex (M)	Males: 98 (70%)
Clinical Presentations	
Abnormal behavior/irrelevant talk	3 (4.8%)
Vomiting	17 (27.4%)
Fever	35 (56.4%)
Headache	34 (54.8%)
General Weakness	12 (19.3%)
Seizures	7 (11.3%)
Altered Sensorium	11 (17.7%)
Underlying disease/comorbidities	
HIV Status	41 (66.1%)
Diabetes Mellitus Type 2	10 (16.1%)
Tuberculosis	11 (17.7%)
Alcoholic	13 (20.9%)
Drug Addiction	7 (11.3%)
Hypertension	9 (14.5%)
Renal Transplant	5 (8.1%)
Others	7 (11.3%)
Clinical Outcome	
Improved	28 (45.2%)
DOR	19 (30.6%)
Expire	6 (9.7%)
LAMA	9 (14.5%)

DISCUSSION

Cryptococcus neoformans is known to cause an opportunistic infection in immune-compromised patients, but can also affect healthy individuals.[9] In the present study, out of the 139 patients diagnosed with cryptococcal meningitis, 41 (66.1%) were positive for HIV infection. Cryptococcal meningitis has been reported from people of any age with predominance of males.[13-15]. In addition the various studies published during the last 80 years have documented that most of the patients diagnosed with cryptococcal meningitis were in their fourth decade of life [16]. The present study also supports this observation.

Cryptococcal meningitis is one of the AIDS defining illnesses in patients with late stage HIV infections and other immune-compromised conditions. In the present study 66.1% of the patients with cryptococcal meningitis were HIV positive, whereas a large proportion of the patient had other co-morbid conditions such as diabetes mellitus, tuberculosis, renal transplantation, drug addiction, alcohol abuse etc, directly or indirectly affecting the immune status of the individual. Pappas *et al* (2001) have reported predisposing conditions, responsible for cryptococcal meningitis include steroids (28%), organ transplant (18%), chronic organ failure (liver, lung, kidney) (18%), malignancy (18%), and rheumatological disease (13%). [17] Shih *et al* have documented that 44.6% patients with cryptococcal meningitis in non-HIV-infected status had documented underlying diseases, including lymphoma (12%), rheumatological diseases (11%), diabetes mellitus (9%), transplantation (6%), cancers (6%), cirrhosis of the liver (6%), and chronic renal failure (5%). [18] Lee *et al* have also reported a higher proportion of patients with the above predisposing conditions in these patients. [9] Fever and headache were the most common clinical features found in patients with cryptococcal meningitis followed by vomiting and altered sensorium. Seizures were

observed in 11.3% of the patients. Similar clinical presentations have been documented in earlier studies, in patients with cryptococcal meningitis.[9, 13,19]

In the present study the positivity of microscopy, culture and latex agglutination test in CSF for the diagnosis of cryptococcal meningitis was 48.2%, 73.4% and 100% respectively and is consistent with the earlier reports. [20]. Latex agglutination test for cryptococcal antigen detection was found to be a useful test for early diagnosis of cryptococcal meningitis with very high sensitivity.

In the present study, after receiving antifungal therapy and aggressive medical treatment, in hospital mortality was reported in 9.7% of the patients. However actual mortality might be much higher as outcome for patients who were either discharged on request (DOR) or left against medical advice (LAMA) can't be ascertained. Sun *et al.* has previously reported a mortality rate of 10.3% and 20.7%, within 2- 10 weeks of hospitalization in HIV negative and in HIV-infected patients, respectively.[21] Three month mortality rate of 20% has been reported, during management of acute cryptococcal meningoencephalitis in HIV positive patients.[10, 22]

To conclude cryptococcal meningitis has been identified as one of the important AIDS defining illnesses. Early diagnosis of the disease may alter the prognosis of these patients. Antigen detection by latex agglutination test proved to be both sensitive and specific method for the diagnosis of cryptococcal meningitis, however culture and India ink are specific but lacks sensitivity.

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