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Prevalence of Cryptococcaemia in HIV Infected Patients with CD4 Counts of ≤100 Cells/mm^3-A Cross Sectional Study in a Tertiary Care Hospital

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ABSTRACT

Backgrounds: This study aimed to investigate the prevalence of cryptococcaemia in HIV infected patients with CD4 counts of ≤100 cells/mm^3 in a tertiary care hospital.

Materials & Methods: The present cross sectional study was conducted at the Sri Guru Ram Das Institute of Health Sciences and Research, India, as a tertiary care hospital. All HIV infected patients with CD4 counts of ≤100 cells/mm^3, referring to the hospital during May 2020 to May 2021 were enrolled in this study. Blood samples taken from patients were processed for wet mounting, negative staining with India ink, gram staining, fungal culture, and cryptococcal antigen (CrAg) lateral flow assay (LFA). Statistical analysis was done using SPSS software Version 20.0 (SPSS Inc. Chicago, IL, USA) by employing Chi-square and Fisher's exact tests to compare categorical variables.

Findings: Out of 100 patients enrolled, 28 (28%) cases had CD4 counts below 50, while 72 (84.7%) patients had CD4 counts in the range of 51-100. Also, 55 patients (55%) received antiretroviral therapy (ART), and 45 (45%) cases were ART naïve. About 56% of patients had no opportunistic infections, and 37% had pulmonary tuberculosis. Three samples were positive in LFA, showing a prevalence of 3%, while only one of the culture samples was positive for *Cryptococcus* species. However, low CD4 count was found to be strongly correlated with positive serum cryptococcal antigenemia.

Conclusion: The present study reveals that cryptococcal antigenemia is a health problem, and that cryptococcal antigen screening and treatment policy recommended by WHO should be performed routinely for HIV patients registered in ART centres in the current setting, especially for those who are ART naïve and have CD4 counts of ≤100 cells/mm^3.

Keywords: HIV, Lateral flow assay, Crytococcaemia, India.

CITATION LINKS

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Introduction

According to a report released by the United Nations Programme on AIDS (UNAIDS) in 2019, 37.5 million persons worldwide were living with HIV in 2018. In the same year, around 1.8 million people were newly infected with AIDS, and about 700,000 people died due to AIDS-related illnesses around the world [1]. Cryptococcosis is a common opportunistic illness in persons with advanced AIDS and a weakened cellular immune system, which significantly contributes to AIDS-related mortality worldwide [2]. Despite the increased availability of antiretroviral therapy (ART), cryptococcal illness remains as the top cause of death among HIV-positive patients in resource-constrained settings [3-5].

There are still many HIV-positive patients diagnosed with late presentation of cryptococcal infection and severe HIV illness [6, 7]. *Cryptococcus neoformans* and *C. gattii* are the most common causes of opportunistic infections in these patients. *C. neoformans* is an encapsulated yeast found in pigeon droppings, which could cause mild to severe illnesses such as meningitis or disseminated disease in people with weakened immune systems. The yeast exhibits a variety of virulence factors that cause infection. Tolerance to mammalian body temperature of 37 °C, a polysaccharide capsule that protects the yeast from phagocytosis, and a thick cell wall containing phenolic melanin that protects the yeast from oxidation are just a few of them.

The total number of individuals living with HIV (PLHIV) in India in 2015 was around 21.5 lakhs (17.11-26.49 lakhs) [8]. Cryptococcal meningitis (CM) is the third most common opportunistic infection in HIV affected patients [9] and one of the leading causes of death in resource-poor nations [10-12]. High incidence of cryptococcaemia and mortality could be reduced by starting ART. Thus, to decrease the mortality rate related to cryptococcosis in HIV positive patients, it is necessary to detect *Cryptococcus* at early stages of infection. In HIV positive patients, cryptococcal antigen (CrAg) is used as an early biomarker for detecting disseminated disease. It could be detected 250 days before the onset of meningitis symptoms [10]. The presence of CrAg in the serum is an indicator of high probability of disease progression to CM in a year [13]. Serum CrAg is detected by the rapid test kit, yielding high-sensitivity and -specificity results [14-16].

However, the question that whether it is cost-effective in resource-limited settings to routinely perform this rapid test for all HIV positive patients with decreased CD4 count remains as a problem (3%) [19]. According to WHO guidelines, early initiation of ART is the most important preventive strategy to lower down the incidence of cryptococcal infection [20]. However, in some recent studies, it has been suggested that screening is cost-effective in environments where the prevalence of cryptococcal infection is higher than 0.6% [13, 17-19, 21]. There is a lack of literature discussing about the prevalence of cryptococcal antigenemia in India. Therefore, it is important to detect the prevalence of cryptococcaemia in the present setting, and there is a need for routine CrAg screening of all patients.

Objectives: This study was conducted to determine the prevalence of cryptococcaemia in HIV positive patients in India.

Materials and Methods

This cross-sectional study was conducted with a sample size of 100 patients in the Department of Microbiology of Sri Guru Ram Das Institute of Health Sciences, Amritsar, India, as a tertiary level teaching hospital after obtaining institutional review board permission. All HIV positive patients referring to the hospital for routine CD4 testing during May 2020 to May 2021 were enrolled for participation in this study. A

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written informed consent was taken from all participants with CD4 counts of ≤100 cells/mm^3. All patients receiving primary prophylaxis for cryptococcosis or having a past history or current cryptococcal infection were excluded from the study as the aim of this study was to find out the prevalence of cryptococcaemia by removing all confounding factors.

A detailed clinical history, consisting of complaints, personal history, HIV serotype (HIV I/II), type of antiretroviral therapy, CD4 count, and opportunistic infections, if any, was taken from all patients. Blood samples were then processed for fungal culture after preliminary microscopic examinations, composing of wet mount, negative staining with India ink, and gram staining. The cultures were then visually examined daily for fungal growth.

Any growth noticed was stained to observe yeast cell morphology and sub-cultured onto appropriate media for identification. On gram staining, round budding yeast cells appeared gram-positive. The colony morphology was noted. *Cryptococcus* species was identified based on yeast-like mucoid colony on SDA (sabouraud dextrose agar) and urease test [37]. One of the culture samples was positive. The IMMY CrAg LFA kit (Immuno-Mycologics, Inc., Norman, OK) is a dipstick method which employs sandwich Immunochromatography to detect the antigen.

Findings

The mean age of 100 HIV-infected patients included in this study was 36.3 years. The majority of patients (76%) were in the age group of 21-40 years. Except for 16 patients who were asymptomatic, 84 patients (84%) had some symptoms. Fever was the most common symptom among patients (72%). Out of 100 patients, 28 (28%) cases had CD4 counts below 50, while 72 (72%) patients had CD4 counts in the range of 51-100. The median CD4 count was 68.

A total of 3 out of 100 serum samples tested were positive in LFA test, showing a prevalence of 3% in HIV seropositive patients with CD4 counts of ≤100 cells/µL. One of the 100 samples in fungal culture was positive for cryptococci, and no other fungal elements were appreciated on microscopy in any of the 100 samples. All patients positive for serum cryptococcal antigen were in the age group of 21-40 years. No statistically significant association was found between age and serum cryptococcal antigenemia. Two patients with CD4 counts of ≤50 cells/µL and one patient with a CD4 count in the range of 51-100 cells/µL were positive for serum cryptococcal antigen. A total of 3 out of 45 cases (6.67%) in the ART naïve group were positive for serum cryptococcal antigen. Serum cryptococcal antigenemia was not detected in the ART-receiving group. All 3 patients positive for serum cryptococcal antigen were positive for HIV-1 antibodies.

Discussion

Cryptococcal Meningitis (CM) is a late manifestation of the disseminated form of cryptococcal infection, which causes significant morbidity and mortality in HIV-infected individuals [8, 10]. Severely immunocompromised HIV-infected individuals with a CD4+T-lymphocyte (CD4) count of ≤100 cells/mL are at higher risk of developing meningitis [10]. Treatment in resource-limited settings is usually difficult and requires expensive intravenous antifungal treatment and monitoring. Patients who survive usually suffer from long-term severe neurological deficits owing to uncontrolled increased intracranial pressure as the disease progresses [22]. Therefore, early detection of cryptococcal infection through routine screening of cryptococcal antigenemia is of primary importance. The prevalence of serum CrAg in patients with advanced HIV infection in Southeast Asian countries varies from 3-18% [23, 24]. In the present study, the

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prevalence of cryptococcal antigenemia was 3.67%. The difference in the prevalence rate may be due to seasonal variations or variable intensity of the presence of *Cryptococcus* in local environments.

Inhalation of spores or dehydrated yeast cells from the environment causes *Cryptococcus* infection. Spores are then deposited in the alveoli, causing an infection that is either eliminated or managed by a strong cell-mediated immune response, resulting in a dormant latent infection. As a result of which, granuloma develops in the hilar lymph nodes and lungs. The fungus could migrate from the lungs to the central nervous system in vulnerable people and cause meningoencephalitis, which is lethal if left untreated.

C. neoformans must survive when reaching the circulatory system in order to spread. The macrophage could be used as a vehicle for the virus transmission and dissemination within the host. It subsequently passes through the blood-brain barrier (BBB), which is most likely mediated via transcytosis, there is evidence that the fungal capsule is also involved in this process [25]. Macrophages may play a key role in *C. neoformans* crossing the BBB via the "Trojan horse" mechanism, which has been shown in vitro to activate macrophage phagosomal extrusion and is a putative escape route allowing infection to spread further.

At present, the WHO recommends CrAg screening in ART naïve individuals with CD4 counts below 100 cells/μL [19]. In the present study, 108 cases received ART, and 48 cases (28%) were ART naïve. However, all four cases positive for serum cryptococcal antigenemia were ART naïve, and the difference was found to be statistically significant (p=.01). The prevalence of serum CrAg in ART naïve patients was 9.52%, which is much higher than the 3% recommended by WHO [20]. Therefore, CrAg screening may be considered for patients in the present setting, especially for ART naive patients with lowered CD4 counts on a priority basis as it has been shown to reduce the mortality and morbidity in patients and is also cost-effective. Recent studies have shown that screening is cost-effective even with a low prevalence of 0.6% [21]. Since the total prevalence found in the present study was 3.0%, routine screening of all patients regardless of ART status might be considered later.

Regarding the possible risk factors of cryptococcal antigenemia, body mass index of less than 18.5 kg/m^2, CD4 count of < 100 cells, patients with a history of headache or neck stiffness, and male gender are considered as important risk factors of cryptococcal meningitis, which could be utilized for public health welfare. Several studies have reported similar findings [26]. Thomsen et al. (2018) reported that headache and fever were predictors of a positive CrAg test [27].

Ocular involvement in the form of visual changes is observed in nearly one-third of HIV-infected patients. It could occur in the form of oculomotor palsies, retinal haemorrhages, and ophthalmitis. Yeasts infiltration into the optic nerve and increased intracranial pressure could cause blindness in these patients. This permanent blindness is associated with decreased vision in the first week of hospitalization [28].

In HIV-positive people with CM, elevated intracranial pressure (ICP) is a common consequence. The aetiology of elevated ICP in CM patients is unknown, but it is thought to be caused by a number of convergent variables. One of the causes of ICP is outflow pathway obstruction caused by the aggregation of fungal polysaccharide in arachnoid villi and subarachnoid spaces, which blocks the routes of CSF (cerebrospinal fluid) drainage. This image fits the description of communicative hydrocephalus. Other major factors could be cerebral oedema caused by cytokine-driven inflammation as well as the impact of an osmotic stress created by fungal mannitol [29].

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At present, culture is considered as the gold standard method for diagnosing infections, and its associated problems include poor sensitivity and the need for a large number of specimens and laboratory infrastructures [30]. Studies have shown that blood culture sensitivity in detecting cryptococcal meningitis is 49-72% [31]. Blood culture was used in this study to detect the presence of *Cryptococcus* in the study population. However, none of the blood cultures in the present study were positive for *Cryptococcus*, except for one sample, thereby limiting its use for routine *Cryptococcus* screening.

The lateral flow assay (LFA) used in the current study is operator friendly. In resource limited settings, LFA is widely accessible as it does not require refrigeration of test materials, cold chain transport, or any other specimen pre-treatment. The median age of patients registered in the present study was 33 years (ranging from 21-66 years). In HIV positive individuals, the rate of hospitalisation per million in total population peaks in the age range of 31-40 years [32]. The present study also revealed that the age group of 21-40 years was the most commonly affected age group, though not significantly, which might be due to more exposure and outdoor activities rather than susceptibility in this age group as observed earlier [33].

There was a significant association between CD4 count of ≤50 cells/μL and serum cryptococcal antigenemia (p ≤.05) in the present study. Out of 100 cases included in the present study, HIV-1 serotype was found in 93 cases (93%) and HIV-2 serotype in only seven cases (7%). All the three cases found to be positive for serum cryptococcal antigen were also found to be positive for HIV-1 antibodies; nonetheless, no significant statistical association was found between cryptococcal antigenemia and HIV serotype. This study subjects were severely immune-deficient and more vulnerable to AIDS related diseases and other opportunistic infections. The symptoms were observed in 84 out of 100 patients in the present study. In this study, a significant association was detected between headache and positive cryptococcal antigenemia (p=.01). Micol et al. (2010) also reported this significant association but stated that headache must not be considered as a specific symptom for cryptococcal meningitis [34]. These findings suggest that symptoms should not be considered as the sole indicators for the identification of patients with cryptococcal antigenemia, and that systematic screening might yield better results. Tuberculosis is the manifestation of AIDS in more than 50% of cases in developing nations [35]. In the current study, 37% of patients had tuberculosis. Also, 2 out of 3 cases had concurrent cryptococcal antigenemia and tuberculosis in the present study (66.67%). The present study findings are consistent with those of Pongsai et al. (2010) [17] and Andama et al. (2013) [36]. These findings suggest that in a developing country like ours, tuberculosis still remains as the most common co-infection in PLHIV. In a review study by Derbie et al. (2020), a total of 8338 HIV positive individuals were reported in 22 studies conducted in ten different countries during 2007–2018. Most articles reported the mean CD4 count of participants below 100 cells/μL. The pooled prevalence of cryptococcal antigenemia in patients with different CD4 counts and ART status was 8% (95%CI: 6–10%) (ranging from 1.7 to 33%). Body mass index (BMI) < 18.5 kg/m^2, CD4 count < 100 cells, headache, and male gender were reported by two or more articles as important predictors of cryptococcal antigenemia [37].

In another study by Imwidthaya and Poungvarin (2000) in Thailand, *C. neoformans* strains isolated from each patient (17 females and 70 males) with cryptococcal meningitis were cultured. The age ranges of patients were

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17–70 years (mean=30.8, SD=13.8) in females and 14–60 years (mean=32.4, SD=8.5) in males. HIV infection was the underlying disease in all patients. The risk of exposure to HIV infection was heterosexual contact for all patients, except for one case (a 14-year-old boy). CD4 lymphocyte counts for female and male patients ranged from 9–205 cells/mm^3 (mean= 59.0, SD=73.4) and 4–212 cells/mm^3 (mean=41.8, SD=50.8), respectively [38].

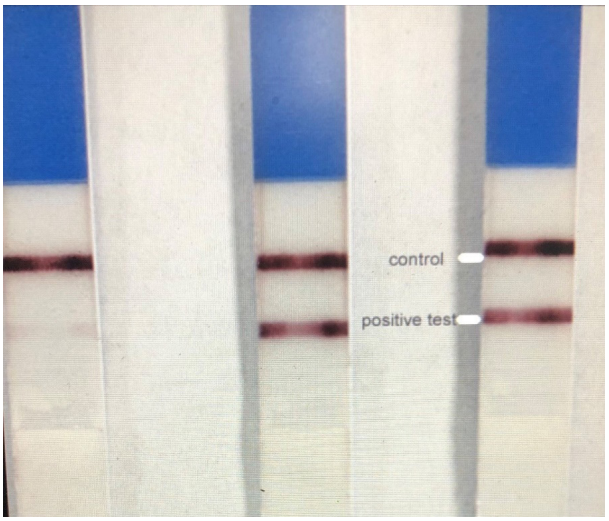

Figure 1) Positive LFA test with positive and negative controls

Figure 2) Sabouraud dextrose agar showing cryptococcal growth

Limitation

In the present study, cryptococcal antigen titter was not performed, and no selective culture media were used. A prospective study is required to know these parameters.

Conclusion

The current study reveals that cryptococcal antigenemia is a public health issue, and that the WHO-recommended cryptococcal antigen screening and treatment policy should be routinely performed for HIV positive patients registered in ART centres in the current setting, particularly for those who are ART naive and have CD4 counts of less than 100 cells/mm^3 measured by rapid point-of-care assays.

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