Cryptococcal Meningitis in AIDS

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Abstract

A large proportion of people with acquired immune deficiency syndrome contact cryptococcal meningitis. This opportunistic infection is associated with high mortality, particularly in resource-poor developing countries. The causative fungus, Cryptococcal neoformans, has a worldwide distribution. The clinical features of cryptococcal meningitis are not notably different from those of bacterial meningitis. Thus a high index of suspicion is critical for its diagnosis, particularly in areas of the world where standard medical laboratory facilities are difficult to come by. Prompt institution of effective and appropriate systemic antifungal drugs is also essential. This article discusses the mycology, clinical features, diagnosis and treatment of AIDS-associated cryptococcal meningitis.

INTRODUCTION

The current epidemic of acquired immune deficiency syndrome (AIDS) is one of the most destructive in recorded history, being associated with the death of more than 25 million people since the syndrome was recognized in 1981. Despite increasing global efforts to curb this menace, an estimated 39.5 million people now have the human immunodeficiency virus (HIV), with about 4.3 million new infections in 2006. [1] AIDS associated cryptococcal meningitis (CM), caused by Cryptococcus neoformans, is a severe opportunistic infection with a high mortality, even in developed countries. [2] Early mortality rates of 11% to 45% have been reported among cohorts from the United States. [3] In Africa, CM is responsible for 13% to 42% of all deaths among HIV-infected people. [4,5] CM is the AIDS-defining illness in 25% to 30% and 64% to 91% of cases in South-East Asia [6] and sub-Saharan Africa, [4,5,7] respectively.

BIOLOGY AND PATHOGENESIS

C. neoformans is a round-to-oval yeast-like fungus with a polysaccharide capsule. This capsule contains glucuronoxylomannan, which is the primary virulent factor. In its sexual teleomorphic form, the fungus produces mycelia, which bear the basidiospores. [8] C. neoformans is particularly found in soil contaminated with bird droppings. There are four serotypes of C. neoformans, designated A, B, C and D, according to antigenic determinants on the polysaccharide capsule. [9] Serotypes A and D (C. neoformans neoformans) cause most of the infections, with 90% of these occurring in immunocompromised hosts. [10] C. neoformans is a common cause of meningitis in HIV/AIDS. [11] The transmission of infection appears to occur through inhalation of either the basidiospores or the encapsulated form. [12] The fungus has two major aggressive mechanisms by which it invades the central nervous system.

One is the antiphagocytic property of the capsule which contains mainly glucuronoxylomannan. This substance contributes to virulence by suppressing the immune response, inhibiting leucocyte migration and enhancing HIV replication. [13] The second mechanism is exploited by membrane-bound phenoloxidase enzymes which convert phenolic compounds, such as catecholamines, into melanin. [14] There are both cellular and humoral host immune responses to cryptococcal infection, which is characterised by little or no necrosis until late in the disease; organ damage is primarily from tissue distortion due to the expanding fungal burden. Extensive inflammation or fibrosis is rare. The characteristic lesion of C. neoformans comprises a cystic cluster of yeast cells with no well defined inflammation. [14]

CLINICAL FEATURES

Some individuals with CM may have non-specific symptoms at presentation. However, CM commonly presents with headache, fever, neck stiffness and altered mental status, which may include personality changes, confusion, lethargy, obtundation and coma. Nausea and vomiting are also frequent features (Table 1). [14,15] Cutaneous involvement

occurs in about 10% to 15% of cases of AIDS with CM; the lesions include nodules, ulcers and papules. [14] Symptoms such as photophobia and diplopia may be elicited, and can be caused by arachnoiditis, papilloedema, optic neuritis and chorioretinitis. Focal disease is rarely described. [16] Complications such as hydrocephalus, motor deficit, seizures or dementia may also occur.

DIAGNOSIS

The diagnosis of CM requires a high index of suspicion. This is particularly important in sub-Saharan Africa, where there is a dearth of standard medical laboratory facilities and expertise. The role of detailed history and thorough physical examination cannot be over-emphasized. The diagnosis also involves a cerebrospinal fluid (CSF) smear, cryptococcal antigen (CRAG) detection in CSF and/or serum, and culture of C. neoformans in the CSF.

SERUM AND CSF SEROLOGY (CRAG TEST)

Cryptococcal polysaccharide can be detected by latex agglutination technique in the serum and CSF of people with CM. The CRAG test is an extremely important diagnostic procedure; CSF CRAG is locally produced in the subarachnoid space by the invading C. neoformans, not by active or passive diffusion from the serum. [17] Positive CRAG in either serum or CSF has more than 95% sensitivity and more than 95% specificity in the diagnosis of CM. [18] Anticryptococcal antibodies do not have any diagnostic importance in CM.

CSF SMEAR

The Indian ink stain (Figure 1) is commonly used to identify C. neoformans on direct examination of the CSF. [19] This stain outlines the polysaccharide capsule of the organism and is positive in more than 80% of AIDS cases with CM. Other stains include Alcian blue, mucicarmine and methenamine silver, but these are seldom used. [14]

CSF CULTURE

C. neoformans can be isolated using Sabouraud dextrose agar with or without antibiotics for the suppression of bacterial growth. The organism grows at 37°C, assimilates inositol and produces urease; it does not form mycelia on cornmeal agar. It also yields melanin when incubated on agar that contains seeds from the common weed, Guizotia abyssinica. [14] Fungal culture is a rarity in most of the resource-poor settings of sub- Saharan Africa.

OTHER CSF FINDINGS

Abnormal CSF findings, such as pleocytosis and low glucose and high protein concentrations, are seen in 40% of cases of AIDS-related CM; 55% have <10 lymphocytes/l CSF; and the CSF opening pressure is >200 mmH2O in 70% of cases. [20,21]

IMAGING STUDIES

Imaging studies have little or no diagnostic significance in CM. CT or MRI of the brain may reveal diffuse atrophy or evidence of cerebral oedema, with homogenous or contrast medium- enhanced areas.

TREATMENT

Prompt treatment of CM for people with AIDS is essential. Treatment of a first episode of CM is known as primary treatment, and its success is defined as CSF sterilization at the 2 nd and 10 th weeks and/or a patient who is clinically stable at the 2 nd week and asymptomatic at the 10 th week. [22] Primary treatment comprises initial and consolidation phases. Maintenance treatment follows successful primary treatment, and is required to prevent relapse.

PRIMARY TREATMENT

The recommended first-line treatment for people with AIDS and CM is based on the results of the Mycoses Study Group (MSG)/AIDS Clinical Trials Group (ACTG). [22,23,24] It comprises administration of amphotericin B, 0.7 mg/kg/day, plus flucytosine, 100 mg/kg/day (in four divided doses), for 2 weeks of initial treatment, followed by fluconazole, 400 mg/day for 8 weeks of consolidation treatment and 200 mg/day for maintenance treatment. The study also identified absence of flucytosine during the initial treatment as an independent risk factor for relapse. However, flucytosine may be withheld if the patient cannot tolerate it. [22,23,24] Itraconazole may be used during the consolidation treatment for people who are unable to tolerate fluconazole. [22] Some have proposed an alternative guideline for primary treatment, with fluconazole and flucytosine for 6 weeks followed by lifelong fluconazole maintenance treatment. Pilot studies have indicated that initial treatment with fluconazole and flucytosine is not as effective as treatment with amphotericin B and flucytosine; in addition, the combination of fluconazole and flucytosine has significant toxicity. [25] The effectiveness of azole drugs in the initial treatment of CM is rather poor and they should be reserved for cases with absolute contraindication for amphotericin B, such as those with renal disease (excluding end-stage renal

disease) or known hypersensitivity to amphotericin B. [26]

MAINTENANCE TREATMENT

This is also known as secondary prophylaxis. The relapse rate for CM in persons with AIDS is more than 50% within the first year. Studies by the California Collaborative Treatment Group (CCTG) and MSG/ACTG have firmly established that oral fluconazole, 200 mg/day, is the drug of choice for maintenance treatment. [27,28,29] Although the consensus of opinion favours a lifetime of maintenance treatment, the United States Public Health Services (USPHS) /Infectious Disease Society of America (IDSA) guidelines recommend its discontinuation if patients successfully complete a course of primary treatment; remain asymptomatic with respect to symptoms and signs of CM; and have a sustained increase, for more than 6 months, in their CD4+ counts to more than 100 to 200 cells/mm ^{3} on antiretroviral treatment (ART). [30] The treatment can, however, be restarted if the CD4+ counts declines to less than 100 to 200 cells/mm ^{3} .

MANAGEMENT OF INCREASED INTRACRANIAL PRESSURE

Aggressive management of increased intracranial pressure is as important as antifungal drugs in the treatment of CM, and plays a major role in clinical outcome. The majority of deaths in CM have been associated with acute cerebral oedema with raised intracranial pressure. [22,23,31] It is important to measure intracranial pressure at the time of initial lumbar puncture, and this should be repeated after 2 weeks of initial treatment for individuals with normal baseline opening pressures (<200 mmH_2O). [31] Patients with elevated opening CSF pressures of >250 mmH_2O should have serial daily lumbar punctures to remove about 30 ml of CSF each time, until the pressures are normal. Lumbar drains or ventriculoperitoneal shunts may be considered when opening pressures are >400 mmH_2O. Although acetazolamide has been used to treat intracranial hypertension in these cases, its effectiveness is yet to be well established. The roles of manitol and corticosteroids also remain controversial. [32,33]

PREVENTION

The prevention of first-time CM is termed primary prophylaxis, taking into account that the risk of CM is considerably higher in those with advanced HIV disease with CD+ counts <50 cells/mm ^{3} . Fluconazole is effective in preventing CM in those at risk, but there is concern about the potentials for development of acquired resistance from prolonged use, drug-related adverse reactions and drug-drug interactions. Primary prophylaxis is likely to be significantly beneficial in resource-poor countries with scarce access to ART and high prevalence of CM. Studies are continuing to evaluate the effectiveness of primary prevention in Africa.

SHORT NOTES ON COMMONLY USED ANTIFUNGAL DRUGS

AMPHOTERICIN B

Amphotericin B is the drug of choice for initial treatment of cryptococcal meningitis. This compound has a faster onset of action than fluconazole (even when fluconazole is administered intravenously), and crosses the blood-brain barrier more reliably than the azoles. Its antifungal activity results from two mechanisms. First, it attaches to the sterol sites of the fungal cytoplasmic membrane, causing increased permeability to monovalent ions. Second, it brings about auto-oxidation of the fungal cytoplasmic membrane and release of lethal free radicals. Some people cannot tolerate amphotericin B because of severe side effects such as renal damage, anaemia, leucopenia and hypotension; this has generated much interest in the development of intralipid or liposomal formulations of the drug. [34] Currently, there is no clear, strong evidence of improved clinical outcome with the use of these formulations, so that their role in cases of AIDS with intolerance to amphotericin B remains uncertain. [6,35]

FLUCYTOSINE

Flucytosine is deaminated within the fungal cells into 5-fluorouracil, which inhibits fungal protein synthesis by replacing uracil with 5-fluorouracil in fungal RNA. It also interferes with fungal DNA. [36,37] Flucytosine is always used with another active antifungal drug, such as amphotericin B. It may cause nausea, abdominal discomfort, diarrhoea, seizures, photosensitivity and bone marrow suppression.

FLUCONAZOLE

This is an oral triazole agent active against many yeasts and dimorphic fungi. It selectively inhibits fungal cytochrome P 450 and sterol C-14 demethylation. The drug may cause hepatitis, cholestasis or fulminant hepatic failure among people receiving ART for AIDS. Pregnant women are advised not to use fluconazole or any of the azole drugs, as these may result to severe birth defects.

CONCLUSION

Although CM is a treatable cause of death in AIDS, it is

often undiagnosed in most resource-poor settings. A consciously high index of suspicion coupled with improved human, laboratory and research capacity is critical to effective management of this infection. Also the need for availability of cheap and effective antifungal drugs can not be overemphasized. Timely institution of combination antiretroviral therapy (cART) for those who require them is also essential. While the tempo of global preventive programs on HIV/AIDS should be sustained, there is also the urgent and crucial need to scale up efforts to make ART drugs universally available, accessible and affordable.

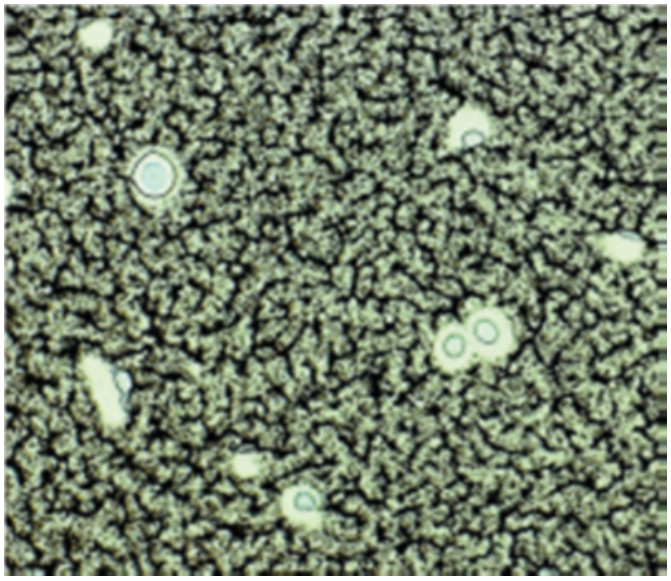
Figure 1

PRACTICAL POINTS

- Cryptococcal meningitis is caused by a yeast-like fungus known as *Cryptococcus neoformans*
- This meningitis is common among people with AIDS and has a high mortality
- Frequent clinical features are headache, fever, neck stiffness and altered mental status. Focal disease rarely occurs
- A high index of suspicion is critical for diagnosis, particularly in resource-poor countries where adequate medical laboratories are rare
- Cryptococcal meningitis can be misdiagnosed as tuberculous meningitis
- Prompt treatment with appropriate antifungal drugs is essential. Maintenance treatment is always needed to prevent relapse

Figure 2

Figure 1: Indian ink stain of



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