

Review article

Central nervous system fungal infections; a review article

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Abstract

Central nervous system (CNS) fungal infections have a high rate of morbidity and mortality that increased during last three decades. CNS fungal infections present a diagnostic and therapeutic challenge. High numbers of organ transplants, chemotherapy patients, intensive care unit hospitalizations, immunocompromised patients and haematological malignancies increase morbidity and mortality. Several fungi including, saprophytic fungi, melanized fungi, dimorphic fungi, yeast and yeasts-like cause CNS fungal infections. New antifungal, posaconazole, voriconazole and echinocandins as well as traditionally antifungal, amphotericin B, flucytosine and itraconazole were used for CNS fungal infection therapy.

Keywords: CNS fungal infection, *Candida*, *Cryptococcus*, Saprophytic fungi, Dimorphic fungi

Introduction

Infections of the central nervous system (CNS) with fungi can cause devastating consequences. Although several fungi may cause infection in normal humans, most of them are opportunistic and influence immunocompromised hosts. With the exception of *Candida albicans*, that is a normal flora of the human mucus, most fungal elements get into the body through breathing or skin scrapes. Invasion of the CNS with fungi can cause one or more the symptoms such as acute or chronic meningitis, abscesses or granuloma,

encephalitis, stroke, parenchymal brain, or myelopathy [1-2]. A diversity of fungi lead to CNS infection which can be a meningitis or space-occupying lesion.

Acute or neutrophilic meningitis has been most frequently seen in *Candida* meningitis, whereas *Cryptococcus neoformans* typically causes the chronic lymphocytic meningitis and *Coccidioides immitis* causes the granulomatous meningitis. Although meningitis is the most frequent symptom of CNS fungal infections, the filamentous fungi cause granuloma or brain abscess more often than

meningitis. Haematogenous dissemination could follow the primary fungal infection, with following involvement of CNS. Seldom, trauma or local injuries pare the way to CNS infection [3]. A mechanical barrier protects the CNS from fungal invasion. Though, in proper conditions the CNS is infected by a haematogenous route. In addition, the CNS infection can occur after the anatomic barrier is infringed with a trauma, surgery or by spreading to paranasal sinus or canal of ear.

Causative Fungi

Cryptococcus neoformans

There are two varieties of *C. neoformans* var. *neoformans* (Serotype A and D) and var. *gatti* (Serotype B and C). Serotype A is distributed worldwide and is most associated with pigeon droppings [4]. Serotype D is isolated in Europe with heterogeneous distribution and serotype B is originally associated with vicinity of Eucalyptus trees [5]. The etiological place of serotype C has not been identified. Molecular epidemiology of *C. neoformans* reveals genetic variation among different isolates.

The most prevalent agent which caused chronic fungal meningitis is *C. neoformans* var. *neoformans* and 90% of infections happen in immunocompromised patients [6]. Moreover in places where *C. neoformans* var. *gatti* is endemic, the commonest isolate from AIDS patients is *C. neoformans* var. *neoformans*. There is not any report of transmission from animal to human and human transmission is rarely reported. *C. neoformans* make a capsular antigen, glycoronoxylomannan, in huge quantities, that is stable to heat, resistant to pronase and has 24 hours half life [7].

Cryptococcus has higher incidence among AIDS patients in Africa and Southeast Asia than in the USA [8]. In the developed countries, the beginning of strong antiretroviral treatments has resulted

the reducing of the cryptococcosis incidence related to AIDS. Cryptococcoma or brain mass lesions because of *C. neoformans* are very less frequent in comparison to meningitis caused by serotype A and D. In contrast, serotype B, common in non-immunocompromise hosts, frequently causes a pseudotumor mass in brain. Rarely, a mass lesion could occur without meningitis [9]. The majority of cryptococcoses begin as a primary pulmonary infection. Approximately 5-10% of HIV infected hosts develop the cryptococcal meningitis as an AIDS important disease and approximately 40% of cases first manifest the disease [10-11].

Candida species

Candida species live as normal flora of the mucous membrane and skin. *C. albicans* is the most frequent cause of meningitis and abscess of brain among *Candida* species. Other less common pathogens species are *C. tropicalis*, *C. parapsilosis*, *C. lusitaniae*, *C. glabrata* and *C. krusei*. In infants meningitis is more common than in older patients. Occasionally, *Candida* meningitis could happen in a healthy human [12]. Autopsies of disseminated candidiasis patients revealed a high occurrence of brain abscesses (50% of patients) [13]. The progress of mass lesion or meningitis in brain caused by *Candida* is related to factors which control the local proliferation and facilitate *Candida* access to the CNS.

In newborns, candidiasis of CNS is an infection of the compromised or premature child. *Candida* meningitis associated to neurosurgery was also described. Direct inoculation into the CNS throughout surgery happened in 72% patients [14]. After IV therapeutic management or throughout open heart surgery, *Candida* colonizing in the muco-cutaneous as normal flora can invade the CNS by infection of blood stream [15]. Broad different conditions such as long term antibiotics,

steroids, immunosuppressive and chemotherapeutic agents, neutropenia and AIDS promote haematogenous dissemination [15-17].

Aspergillus species

Aspergillus is ubiquitous saprophyte organism in soil, water and decaying vegetation. This fungus enters the body through the respiratory tract and paranasal sinuses [18]. The invasion to CNS is followed by direct inoculation into a region anatomically near to the brain or by the haematogenous seeding. In addition to primary infection of lungs, haematogenous dissemination is also initiated by direct inoculation into bloodstream via the middle ear, paranasal sinuses, eye, and mastoid or as a result of open-heart operation [19]. Occurrence of *Aspergillus* infection can spread to infant CNS [20].

Aspergillus fumigatus is recognized as the most frequent species to cause invasive infection. *A. flavus* is considered as the agent of a great part of infections in paranasal sinus [21]. Although *A. terreus* is an unusual cause of CNS invasion, it is amphotericin B resistance and consequently related with high death [22]. Meningitis is rare in aspergillosis. Abscesses of brain are common in disseminated aspergillosis [13]. Extended neutropenia and use of high-dose of corticosteroids are the main predisposing factors in patients with solid organ transplant and cancers [13,23]. Though, the infection could happen in an immunocompetent human [24].

Zygomycetes

CNS zygomycosis is a worldwide fungal infection caused by class Zygomycetes such as the Genera *Rhizopus*, *Rhizomucor*, *Absidia*, *Mucor*, *Cunninghamella*, *Apophysomyces* and *Saksenaes*. Zygomycosis is an opportunistic fungal infection and the distribution of its different clinical types is more according to

predisposing factors than on gender, race, age or geography. Zygomycetes thrive in a highly acid condition that has rich carbohydrate. Therefore a diabetic ketoacidosis person has a more risk of defective phagocyte function and offers an environment for quick invasion [25]. In addition, Zygomycetes proliferate in neutropenic patients whose serum iron concentration is increased by deferoxamine [26]. Although these fungi have been considered opportunistic, the cerebral forms of the disease has been recorded in previously healthy individuals [27].

Melanized fungi

Infections of CNS with pigmented fungi are dramatically reported in recent years [28]. *Exophiala dermatitidis*, *Ramichloridium mackenzie* and *Cladosporium bantiana*, mainly cause the primary cerebral infections. Secondary cerebral phaeohyphomycosis arises from extension of an infected site and haematogenously spreads to brain [29]. *E. dermatitidis* has been described as the major neurotropic fungi of East Asia though it is isolated worldwide in environment.

Melanin has been recognized as a virulence factor in several fungi and widely researched in *C. neoformans* and *Wangiella dermatitidis* [30-31]. An uncommon symptom of brain involvement is formation of abscess without meningitis. Otherwise, meningitis can be the only symptom [32]. The infections are frequently reported in apparently immunocompetent hosts [28]. Clinical managing of patients with primary CNS caused melanized fungi is difficult because of their weak response to antifungals and death rates is high despite of immune response.

Other fungi

Among dimorphic fungi *C. immitis* and *Histoplasma capulatum* are the frequent organisms causing infections of the CNS. A

frequent cause of meningitis is *C. immitis* which is geographically limited to Southwest United States and South America countries [13,33]. Coccidial meningitis happens in 30-50% of patients with disseminated infection. The infection can occur in an immunocompetent human. Patients with HIV positive, solid organ transplant, treated by steroids and pregnancy are at a high risk of dissemination [13].

Histoplasmosis caused by *H. capsulatum* is endemic in the United States, South America, Southeast Asia and Africa [13]. This dimorphic fungus can cause meningitis in 5-25% of AIDS patients which is similar to non-AIDS patients [34]. CNS infections may involve the patients who have solid organ transplantation and patients treated with steroids. CNS histoplasmosis has been identified in 10-20% of disseminated hosts [34]. Occasionally, brain abscesses are presented [35].

CNS localization in blastomycosis can occur in 5% of immunocompetent humans and 40% of cases who suffers from progressive HIV. Meninges are infrequent sites and abscesses of brain are also rare [36]. CNS infections in paracoccidioidomycosis, penicilliosis because of *Penicillium marneffei* are very unusual. Cerebral infections by *Pseudoallesheria boydii* are very rare. This fungus causes meningoencephalitis and microabscesses. *Maduralla mycetomatis* involves the CNS rarely. The fungus infects the brain after local trauma. There are a few reports of brain abscesses because of *Fusarium* [37].

Diagnostic tests

CNS clinical manifestations, neuroimaging (CT or MRI) and CSF cytochemical characteristics are main criteria of diagnosis. In addition, diagnosis is also made by fungal tests including direct and

culture examination of CNS biopsy and CSF. Grocott's methenamine silver (GMS) staining is usually used for biopsy staining. Causative agents have several morphology and size based on disease type. Branched septate hyphae indicate *Aspergillus*, *Cephalosporium* and *Penicillium* whereas non-septate hyphae were seen in CNS infection due to Zygomycetes. Melanized fungi including; *Cladosporium*, *Exophiala*, *Wangiella* are presented as dematiaceous elements [38,39]. Yeast forms (up to 20µm in diameter) were usually seen in CNS caused by *Blastomyces dermatitidis*, *Candida species*, *C. neoformans*, *H. capsulatum*, *Sporotrichum* and *Paracoccidioides*. The presence of spherule indicates CNS infection with *C. immitis* [40].

Treatment

A high rate of morbidity and mortality of patients with fungal infections of CNS are caused by several factors, such as organ transplant, chemotherapy, ICU hospitalization, immunocompromised patients and haematological malignancies. The treatment of fungal CNS infection is influenced by multiple factors including, the host, the pathogen and its drug susceptibility, drug delivery across the blood-brain barrier and drug activity in the CNS, brain and spinal cord [39]. Amphotericin B is a polyene antibiotic that binds to ergosterols in the cell wall of fungi and increased cell permeability. K⁺ leakage due to this permeability causes cell death [41]. Amphotericin B and/or flucytosine in combination are recommended for CNS infections especially caused by *Candida* and *C. neoformans* [42-44].

Fluconazole as intravenous or oral preparations has more activity against yeasts (*Candida* and *Cryptococcus*) than filamentous fungi and is widely distributed throughout body tissues, including the CSF.

Itraconazole has a wider spectrum activity against fungi than fluconazole. It has been used successfully to treat CNS infections due to *Aspergillus* species however its penetration into CSF is poor. High CSF levels of voriconazole (0.08-3.93 µg/ml) in fungal meningitis patients have been reported to achieve rapidly. CSF levels from 0.08 to 3.93 µg/ml are reported (CSF: serum ratios of 0.22-1) [39]. In addition, posaconazole as an oral medication is also presented as valuable alternative for CNS fungal infection therapy [45]. Echinocandins as intravenous infusion significantly bound to fungal proteins with half-live compatible. Clinical studies have shown that echinocandins are used to treat *Candida* and *Aspergillus* infections.

Conclusion

The CNS fungal infections were previously regarded as rare diseases. The extensive uses of corticosteroids and cytotoxic drugs and AIDS epidemic have increased the frequency of CNS mycoses. Progress of effective antifungal agents has improved the prognosis of the CNS fungal infections.

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