Review Article

# Epidemiology of central nervous system mycoses

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Fungal infections of the central nervous system (CNS) were considered rare until the 1970s. This is no longer true in recent years due to widespread use of corticosteroids, cytotoxic drugs and antibiotics. Immunocompromised patients with underlying malignancy, organ transplantations and acquired immune deficiency syndrome are all candidates for acquiring fungal infections either in meninges or brain. A considerable number of cases of CNS fungal infections even in immunocompetent hosts have been reported. A vast array of fungi may cause infection in the CNS, but barring a few, most of them are anecdotal case reports. *Cryptococcus neoformans*, *Candida albicans, Coccidioides immitis*. *Histoplasma capsulatum* are common causes of fungal meningitis; *Aspergillus* spp., *Candida* spp., Zygomycetes and some of the melanized fungi are known to cause mass lesions in brain. Few fungi like *C. neoformans, Cladophialophora bantiana, Exophiala dermatitidis, Ramichloridium mackenzie, Ochroconis gallopava* are considered as true neurotropic fungi. Most of the fungi causing CNS infection are saprobes with worldwide distribution; a few are geographically restricted like *Coccidioides immitis*. The infections reach the CNS either by the hematogenous route or by direct extension from colonized sinuses or ear canal or by direct inoculation during neurosurgical procedures.

**Key words:** *Aspergillus, Candida*, central nervous system, *Cryptococcus,* epidemiology, fungi, melanized fungi, mycoses



**Table 1: Fungi causing central nervous system infection**

| Meningitis | Space-occupying lesions |
|---|---|
| Common agents | |
| *Cryptococcus neoformans* | *Aspergillus* spp. |
| *Coccidioides immitis* | Zygomycetes |
| *Candida albicans* | *Candida* spp. |
| *Histoplasma capsulatum* | Melanized fungi |
| Uncommon or rare agents | |
| *Blastomyces dermatitidis* | *Histoplasma capsulatum* |
| *Paracoccidioides brasiliensis* | *Coccidioides immitis* |
| Melanized fungi | *Pseudallescheria boydii* |
| *Aspergillus* spp. | *Fusarium* spp. |
| Zygomycetes | *Blastomyces dermatitidis* |
| *Sporothrix schenckii* | *Sporothrix schenckii* |
| | *Paracoccidioides brasiliensis* |
| | *Pencillium* spp. |
| | *Ustilgo* spp. |
| Very rare agents | |
| *Rhodotorula rubra* | *Trichosporon* spp. |
| *Blastoschizomyces capitatus* | *Trichoderma longibrachiatum* |
| | *Chaetomium strumarium* |
| | *Chaetomium atrobrunneum* |
| | *Schizophyllum commune* |
| | *Paecilomyces* spp. |
| | *Metarrhizium anisopliae* |
| | *Microascus cinereus* |
| | *Curvularia clavata* |
| | *Ramichloridium obovoideum* |
| | *Trichophyton* spp. |
| | *Acrophialophora fusispora* |

Fungal infection of the central nervous system (CNS) is a life-threatening disease. A variety of fungi cause infection of CNS – either an acute or chronic meningitis or space-occupying lesion [Table 1]. Acute or neutrophilic meningitis is most commonly seen in *Candida* meningitis, while *Cryptococcus neoformans* classically cause chronic lymphocytic meningitis and *Coccidioides immitis* cause granulomatous meningitis. Though meningitis is the most common presentation of CNS mycoses, some of the filamentous fungi cause brain abscess or granuloma more commonly than meningitis. The increased occurrence of CNS mycoses is parallel to the increasing number and the diversity of fungal infections of other sites.[1-7] A similar increase in frequency of CNS mycoses is reflected in multiple series from India as well.[7-14]

The CNS is protected by a mechanical barrier from colonization or invasion of fungi. However, in suitable conditions fungi can reach the CNS by a hematogenous route or when the anatomic barrier is breached by trauma, surgery or by direct extension from paranasal sinus or ear canal.

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## Predisposing Factors

Predisposing factors in fungal meningitis vary with individual fungal pathogen [Table 2]. The development of fungal meningitis requires both exposure to offending pathogen and often some deficiency of host defenses that permit the fungus to access and replicate in the meninges. Pathogenic fungi *Coccidioides immitis*, *Histoplasma capsulatum* and even *Cryptococcus neoformans* may affect immunocompetent hosts but may occur more often in those with depressed cell-mediated immunity, such as AIDS. *C. neoformans* most strongly characterizes this group.[13,14] Uncommon agents like melanized fungi rarely cause meningitis in immunocompetent hosts.

The mass lesion of brain due to fungi occurs by either direct extension or hematogenous spread. Direct extension occurs commonly from colonized paranasal sinuses or ear canal. The lesion is increasingly being reported over the last two decades and is attributable to an increasing number of immunocompromised patients who are surviving longer periods because of advances in medical management, a larger aging population, increased number of malignancies and transplant recipients.[15-17] Recipients of hematopoietic stem cell transplants (HSCTs) were far more likely to have fungal brain abscess (5.2%) than solid organ transplant recipients (0.4%) ($P<0.001$).[15] Infection is also facilitated by exposure to dank environments, rotting vegetable material or nearby construction, all of which fill the air with infectious conidia or spores. Colonization with these fungal propagules must occur many times daily, but development of disease usually occurs in the host with impaired polymorphonuclear leukocyte and macrophage function. In those patients who develop cerebral mass lesions, infections appear to be more frequent by colonization and then invasion of paranasal sinuses rather than by metastasis from a remote lung lesion or percutaneous inoculation.[12,17-21] In India, Sudan, Saudi Arabia, such cases were reported in many immunocompetent hosts. With the increase of diabetic patients worldwide, uncontrolled diabetes or diabetic ketoacidosis is an important predisposing factor for CNS mycoses.[22,23]

## Causative Fungi

A few fungi were considered as neurotropic as they tend to localize in the CNS after invading the human body [Table 3]. However, most cases of CNS mycoses are part of dissemination due to candidiasis, aspergillosis or zygomycosis. Until recently, *Candida* species have been considered a very common cause of fungal meningitis and brain abscess. A postmortem survey of 1,752 consecutive complete autopsies done at the University of Kentucky Medical Centre from 1964 through 1973 revealed that candidiasis was the most common (43%) fungal infection in the brain even in the endemic fungal area.[24] Over the years, the spectrum of fungal agents causing CNS mycoses has changed [Table 4]. *Aspergillus* spp. is the most common agent in intracerebral granuloma or abscess [7,12,17] and *C. neoformans* is the most common agent causing fungal meningitis, especially in the AIDS era.[13,14,25] The ecology and distribution of some of the causative fungi is elaborated further.

### *Cryptococcus neoformans*

*C. neoformans* has two varieties: var. *neoformans* (Serotype A and D), var. *gattii* (Serotype B and C). Serotype A is ubiquitous and associated with bird droppings and Serotype D is found in Europe with heterogeneous distribution.[26] B serotype had initially been found in the vicinity of *Eucalyptus* trees (*E. camaldulensis, E. teriticornis*) in Australia, California and elsewhere.[27-29] Since 1993, the Serotype B has been isolated occasionally in India from patients with chronic meningitis though Serotype A is the common isolate[14,30] and the agent was isolated from *E. camaldulensis* trees of

**Table 3: Neurotropic fungi**

| True | Relatively common to affect central nervous system |
|---|---|
| *Cryptococcus neoformnas* | *Coccidiodes immitis* |
| *Cladophialophora bantiana* | *Chaetomium atrobrunneum* |
| *Exophiala dermatitidis* | *Chaetomium strumarium* |
| *Ramichloridum mackenziei* | *Bipolaris hawaiiensis* |
| *Ochroconis gallopova* | *Bipolaris spicifera* |
| | *Curvularia pallescens* |

**Table 2: Predisposing factors in fungal meningitis**

| Predisposing factors | *Candida* | *Cryptococcus* | *Coccidioides* | *Histoplasma* |
|---|---|---|---|---|
| Hematological malignancy | ++ | ++ | + | + |
| Solid tumors | + | + | ± | ± |
| Transplantation | +++ | ++ | + | + |
| Acquired immunodeficiency syndrome | ± | +++ | + | ++ |
| Steroids | ++ | ++ | + | ++ |
| Trauma/burns | +++ | - | - | - |
| Antibiotics | +++ | - | - | - |
| Catheter (intravenous/urinary) | +++ | - | - | - |

**Table 4: Causative agents of intracerebral granuloma/abscess in different series**

| Series | Parker *et al*, 1978[1] | Sharma *et al*, 1997[12] | Dubey *et al*, 2005[17] | Sundaram *et al*, 2006[7] |
|---|---|---|---|---|
| Years of study | 1964-1976 [13y*] | 1980-93 [14y] | 1980-2003 [23y] | 1988-2004 [17y] |
| No. of cases | 39 | 95 | 40 | 130 |
| Causative fungi | 19 (49)** | 11 (12) | 1 (3) | 5 (4) |
| *Candida* spp. | | | | |
| *C. neoformans* | 9 (23) | 12 (13) | 3 (7) | 2 (2) |
| *Aspergillus* spp. | 2 (5) | 66 (69) | 25(63) | 73 (56) |
| Zygomycetes | 5 (13) | NK | 7 (18) | 40 (30) |
| *H. capsulatum* | 2 (5) | NK | - | - |
| *B. dermatitidis* | 1 (3) | NK | - | - |
| Melanized fungi | 1 (3) | NK | 4 (10) | 3 (2) |
| Others | - | 6 (6) | - | 7 (6) |

NK – not known; *y=years; **Figures in parenthesis indicate percentage

north India.[31] However, in recent years 22 tree species belonging to diverse genera and families have so far been reported to harbor one or both varieties. Decayed wood in trunk hollows of *Syzygium cumini* (Indian blackberry) was shown as the main well-documented primary environmental niche of both varieties in northwestern India.[32,33] The ecological niche of Serotype C is unknown. Though *C. neoformans* has been isolated from several environmental sources, there has been no outbreak attributable to the environment.

*C. neoformans* var. *neoformans* is the commonest cause of chronic fungal meningitis and 90% of these infections occur in immunocompromised hosts.[34] The majority of AIDS isolates are var. *neoformans*, even in areas where var. *gattii* is endemic. Despite having a high exposure rate to all hosts, *C. neoformans* var. *neoformans* is considered an opportunistic pathogen because it predominantly affects immunocompromised hosts. In contrast, var. *gattii* has a limited geographical distribution and affects predominantly immunocompetent male hosts in their second decade of life. There is no report of animal to human transmission and human to human transmission is rare.

The overall incidence of cryptococcosis is not known. However, it is higher among patients with AIDS in Southeast Asia and Africa than in the United States. The disease appears to be less frequent in Europe.[35] A population-based active surveillance for cryptococcosis in Houston, Atlanta, San Francisco and Alabama in USA from 1992 to 1994 found the majority of patients to be male, consistent with demographics of HIV infection and 89% of patients had CD4 counts <100 cells/μL. The analysis of all four areas found decreased incidence of cryptococcosis in Atlanta and San Francisco from 1992 to 1994, which was attributed to the increased use of azoles.[36] In the developed world, the introduction of potent antiretroviral therapies resulted in a decrease in the incidence of cryptococcosis associated with AIDS.

Brain mass lesions or cryptococcoma due to *C. neoformans* are much less common than meningitis for Serotypes A and D. On the contrary, Serotype B, frequent in non-immunocompromised patients, often produces a pseudotumor mass in the brain. Occasionally, a mass lesion may be present without meningitis.[37]

### *Candida spp.*

*Candida* species are commensal of the skin and mucous membrane. Among *Candida* spp., *C. albicans* is the most common agent causing meningitis and brain abscess. Other species, such as *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae* or *C. glabrata* are less common pathogens. Meningitis is more frequent in infants than in older patients. Rarely, *Candida* meningitis may occur in an otherwise healthy person.[38] Autopsies of patients who died with disseminated candidiasis showed a high frequency of brain abscesses (in up to 50% of cases).[2,6]

The development of meningitis or mass lesion in the brain due to *Candida* spp. depends on factors controlling local proliferation and the access of *Candida* to the CNS. The predisposing factors listed in Table 2, favor the overgrowth of *Candida* and then dissemination or direct inoculation to the CNS. One example is pregnancy, when *Candida* vaginal populations flourish. When a mother with dense candidal vaginal overgrowth delivers a premature infant, especially with defects in neural tube, such as meningomyelocele, rapid infection of the meninges may result.[19] In newborns, CNS candidiasis is a disease of the premature or compromised infant.[2] *Candida* meningitis related to neurosurgery was also reported.[39,40] In a series of 18 patients, direct inoculation into the CNS during surgery by way of an infected wound or ventriculostomy occurred in 72% patients. The time between insertion of ventriculostomy devices and infection was 13 to 36 days.[39] In another series of 21 patients, 86% had ventricular shunt.[40]

### *Aspergillus spp.*

*Aspergillus* spp., ubiquitous organisms in soil and decaying vegetation, enter the body by way of the respiratory tract including the paranasal sinuses.[41] Invasion of the CNS occurs either by direct extension

from an area anatomically adjacent to the brain or by the hematogenous route. Besides primary focus in the lung, hematogenous dissemination has also originated from direct bloodstream inoculation in illicit-drug user[42] or as a consequence of open-heart surgery.[43] Direct extension of the brain may occur from the external ear, nose, paranasal sinuses, eye and following head injury or via the spinal canal secondary to lumbar puncture or following intracranial surgery. Intrauterine *Aspergillus* infection with the spread of the disease to CNS of infant may also occur.[2,44,45]

*Aspergillus fumigatus* is the most prevalent species followed by *A. flavus* and *A. terreus*. However, *A. flavus* is the commonest agent when the disease is extended from paranasal sinuses to CNS, especially in countries like India, Sudan, Pakistan, Saudi Arabia.[20,21,44,45] Isolated meningitis in aspergillosis is rare. Brain abscesses are frequent in disseminated invasive aspergillosis.[6] Bone marrow transplant patients, particularly allogenic transplant with graft versus host disease treated with large dose of steroids or who have CMV infection, represent a major risk of CNS aspergillosis.[46,47] Prolonged severe neutropenia and high-dose corticosteroids are the major predisposing factors in cancer and solid organ-transplant patients.[6,46] However, the disease may occur even in an apparently immunocompetent host.[3,7,12,17]

### *Zygomycetes*

CNS zygomycosis is due to species under the Genera *Rhizopus*, *Rhizomucor*, *Absidia*, *Mucor*, *Cunninghamella*, *Apophysomyces* and *Saksenaea*. Environmental reservoirs and the mechanism of transmission of these agents is similar to the *Aspergillus* spp.[48] Zygomycetes rely on a preconditioned host. These fungi thrive in a highly acid environment, which is rich in carbohydrate. Thus a diabetic patient with ketoacidosis has a double threat of defective phagocyte function (from acidosis) and provides an environment for rapid invasion.[22] Zygomycetes also proliferate in a neutropenic host and in patients where serum iron concentration is raised by deferoxamine.[49,50] Intravenous drug addicts can also infect themselves with contaminated material and a brain abscess will develop.[51,52] A skin portal of entry has also been described, particularly associated with elasticized surgical bandages.[52] *Absidia corymbifera* was isolated in one case after a penetrating head injury.[53] A few patients may develop zygomycosis without underlying immune defect.[22,52] Isolated cerebral zygomycosis has also been described.[54]

### *Dimorphic fungi*

Of all dimorphic fungi *Coccidioides immitis* and *Histoplasma capsulatum* are the common agents causing CNS infections. *C. immitis*, a common cause of meningitis, is environmentally restricted in Southwest United States, Guatemala, Honduras, Nicaragua, Argentina, Paraguay and Venezuela.[6,55,56] Coccidioidal meningitis occurs in one-third to half of patients with disseminated disease. The disease may occur in an immunocompetent host. The patients usually have meningitis within a few months of their primary pulmonary infection. In HIV positive patients of Arizona 11-27% had coccidioidal meningitis.[55,56] Patients with solid organ transplant, treated with corticosteroids and pregnant women are at higher risk of dissemination after primary infection.[6] *C. immitis* is a rare cause of brain abscess. Miliary granulomas have been reported.[57] The disease can be the result of a primary infection, a re-infection or a reactivation after a previous primary infection.[55]

Histoplasmosis caused by *Histoplasma capsulatum* is endemic in the Ohio River and Mississippi river valleys in North America, Mexico, Argentina, Brazil, Colombia, Venezuela, other tropical countries in Southeast Asia and sub-Saharan Africa. The fungus is found in soil enriched with bird droppings or guano of bats, particularly in caves. Outbreaks may occur in highly endemic areas.[6,58] *H. capsulatum* may cause meningitis in 5-25% of its victims who have AIDS. This is similar to estimates in non-AIDS patients with disseminated disease.[58,59] Primary infection, re-infection or reactivation of a previous contamination can occur. Besides HIV infection, CNS histoplasmosis may occur in patients undergoing solid organ transplantation or patients treated with conrticosteroids.[58] Histoplasmosis will develop as a result of reactivation of a latent infection in less than 1% of patients with AIDS in non-endemic areas.[58] Central nervous system histoplasmosis was observed in 10-20% of all disseminated cases.[58,59] Brain abscesses are infrequent, present as miliary non-caseating granulomas, sometimes with a larger size called histoplasmoma.[60]

In blastomycosis, CNS localization may occur in 5% of immunocompetent persons and 40% of the patients with advanced HIV infection. Meninges are rare locations. Brain abscesses are also uncommon with half of them being solitary lesions.[61,62] In paracoccidioidomycosis, penicilliosis due to *Penicillium marneffei* and sporotrichosis CNS infections are very rare.

### *Melanized fungi*

CNS infections by melanized fungi have increasingly been reported in recent years.[9,63,64] Primary cerebral infections are predominantly caused by *Exophiala dermatitidis*, *Cladophialophora bantiana*, *Ramichloridium mackenzie* under the order *Chaetothyriales*. Occasionally, *Ochroconis gallopava* is encountered. Secondary cerebral infections are usually an extension from chronic sinusitis and are due to grass-inhabiting species under the Genera *Bipolaris*, *Dissitimurus*, *Exserohilum* (order *Pleosporales*).

*Exophiala dermatitidis* is the main neurotropic agent of East Asia although it is found worldwide as saprobes. Since CNS infection is found exclusively in Asian patients, the possibility of race-dependent virulence has been suggested.[63] The agent seems to affect an apparently immunocompetent young population.[65] In the US a pseudo-epidemic involving five (four CNS infections) cases as a result of contaminated injected steroid solution has been reported.[66]

*Cladophialophora bantiana,* a neurotropic fungus, has rarely been isolated from sources other than living mammal tissue. Central nervous system infection due to *C. bantiana* is reported worldwide, though a general preference for warmer climate with high humidity is apparent.[63,64] Cases from arid climatic zones are rare. The infection is often found in immunocompetent young males. Around 40% of the infections are reported in solid organ transplant recipients, intravenous drug abusers or those on steroid therapy.[64,67-69]

CNS infection due to *Ramichloridium mackenzie* is found in patients living in or originating from the Middle East although the fungus has never been isolated from the environment or air of the same region. Still, restriction of human infections to the Middle East suggests a preference of the saprobic phase. Most of the patients had a history of previous major surgery. Otherwise, often the patients were immunocompetent.[64,70,71]

The agents causing secondary cerebral infection include *Bipolaris spicifera, Curvularia lunata, Cladosporium cladosporioides, Nodulisporium* species etc. The infection is encountered in apparently immunocompetent hosts with chronic sinusitis and the agents are commonly airborne saprobes.[64]

### *Other fungi*

*Scedosporium apiospermum,* a saprobe isolated worldwide from soil, manure, sewage, polluted water has emerged among the newly recognized pathogens of CNS.[72,73] It has the same epidemiology as *Aspergillus* spp. and has been found to cause pneumopathy in near-drowning people, because it is present in large numbers in polluted water. In some cases the fungus can even disseminate hematogenously to the CNS of near-drowning victims, causing abscesses in the brain.[73] The victims were little children and young adults with the mean age of 23.8 years. The ratio of males to females was 12:5,[73] which is in concordance with higher prevalence of drowning in males. Direct inoculation of pathogen through orbital trauma or lumbar puncture can also be a factor for CNS infection.[74]

A limited number of brain abscesses due to *Fusarium* species has been reported. *Fusarium* spp. are common in soil and are plant pathogens. Disease can be seen in severely immunocompromised hosts.[75] There are a number of anecdotal case reports of CNS fungal infections due to a variety of rare species [Table 1].

## Conclusion

Fungal infections of the central nervous system are increasingly being recognized all over the world. The infection is generally seen in immunocompromised patients but some fungi are known to affect the apparently immunocompetent host. Though the involvement of the central nervous system in most cases occurs as a part of disseminated infection, few fungi are predominantly neurotropic. An increased awareness among physicians and a high level of suspicion help in establishing the diagnosis. Yeasts predominantly cause meningitis and mycelial fungi cause mass lesion of brain. Other than fungi causing endemic mycoses, these fungi are prevalent worldwide and are found as saprobes in the environment.

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