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Fungal Infections of the Central Nervous System

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Abstract Fungal infections of the central nervous system have manifold presentations and courses that depend largely on both host and organism characteristics. Although subjects with impaired immunity are generally at higher risk for severe disease, several fungal organisms are considered primary pathogens and can also cause disease in otherwise immunocompetent individuals. Herein, we describe the epidemiology, presentation, diagnosis, and management of central nervous system complications of several fungal pathogens.

Keywords Meningitis · Cryptococcus · Cryptococcal meningitis · Endemic Fungi · Yeast · CNS infection

Introduction

The prevalence of CNS fungal infections is increasing [1]. In large part, this can be attributed to the growing numbers of chronically immunosuppressed individuals [2–4], who account for 80 % of all cases, with HIV-positive individuals representing the majority [5]. Other individuals with chronic immunosuppression and solid organ and hematopoietic stem cell transplants are at increased risk. However, immune competence is not entirely protective from fungal CNS infections, and otherwise, healthy individuals are increasingly recognized as being afflicted.

The complexity of managing CNS mycoses is also epitomized by the heterogeneous presentation of these pathogens, which can include meningitis, encephalitis, hydrocephalus, mass lesions, stroke syndromes, and occasionally infections of the spinal cord [2, 3]. Additionally, fungal culture is notoriously low in sensitivity, making diagnostics challenging. This has prompted a search for alternative methods for diagnosis. Specific antigen detection can be helpful, especially in cryptococcal disease, but there is also growing interest in fungal identification via sequencing methods, particularly of the internal transcribed spacer (ITS) region, which are compared to a taxonomic database [6]. Updated epidemiology, clinical manifestations, and diagnostic considerations are considered herein of several fungi capable of inducing CNS disease. An overview can be found in Table 1.

Cryptococcus spp.

Cryptococcosis is the most common systemic and CNS fungal infection in immuncompromised populations and is due to *Cryptococcus neoformans or Cryptococcus gattii*. In fact, approximately 600,000 deaths per year are attributed to cryptococcal meningitis (CM) [7]. Primary infection is pulmonary, and CNS seeding is likely mediated either by macrophage chaperone across the blood-brain barrier or by transcellular migration through endothelial cells [8].

C. neoformans is further divided into subtypes on the basis of capsular agglutination assays, and this seems to affect their endemicity. *C. neoformans* var. *grubii* (capsular serotype D) is responsible for the majority of cases of cryptococcosis worldwide, while var. *neoformans* (capsular serotype A) is more prevalent in Europe [9]. The most common risk factor by far for cryptococcosis secondary to *C. neoformans* is HIV/AIDS.

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Table 1 Primary fungal pathogens of the CNS and their locations of highest endemicity

Organism	Type of fungus	Regions of highest endemicity	Other reported locations
C. neoformans	Yeast	Ubiquitous	
C. gattii	Yeast	Tropics and subtropics, esp Australia, South America, California	Vancouver Island, US Pacific Northwest
H. capsulatum	Dimorphic fungus	Ohio River Valley	Central America, Africa, Asia, Southern USA, Montana
B. dermatitidis	Dimorphic fungus	Great Lakes/Saint Lawrence River, Ohio River Valley	Central and South America
C. immitis	Dimorphic fungus	Southwestern USA, Central and South America	Washington state
P. brasiliensis	Dimorphic fungus	Subtropical Central and South America	
Penicillium spp.	Dimorphic fungus	Southeast Asia	
S. schenckii	Dimorphic fungus	Southeast Asia, India, Central and South America, Mississippi Valley	Australia

However, immunosuppression is not always necessary. A recent study evaluating 120 cases of *C. neoformans* and 9 cases of *C. gattii* showed that 71 % of the isolated strains were from patients without any apparent risk factors while only 8.5 % were from AIDS patients [10].

C. gattii has historically been found in Australia, South America, and California and is traditionally thought to infect immunocompetent individuals, manifesting as CNS disease [11], but recent studies of *C. gattii* infections have demonstrated a great deal of variability in hosts and clinical manifestations, in some part dictated by differences in molecular types (termed "VG" type). Australian isolates, which are frequently VGI, typically infect immunocompetent hosts; one study showed that 72 % of patients were not immunocompromised, with 85 % had some element of CNS involvement [12]. Emergence of a novel VGII-type *C. gattii* that caused an outbreak in the Pacific Northwest in the late 1990s has provided unique insights into microbial evolution, pathogenicity, and risks [13••]. Genotypic analysis of these strains showed that they most resembled the South American strains but, via multiple dispersal events, were more virulent and presented with a distinct pattern of clinical disease of severe pulmonary infections rather than neurologic disease [13••]. Approximately half of patients who had infection with the outbreak strain have an underlying immunologic risk, while many more had other pre-existing conditions, such as lung disease [14]. Other *C. gattii* types, such as VGI and VGIII, are seen in "non-outbreak" situations in the USA, frequently in people with HIV [9, 14, 15]. As few centers have performed routine identification to the species level, our understanding of species distinctions and clinical manifestations remains incomplete.

A consequence of the epidemiologic data on *C. gattii* infections and immune status has led some to hypothesize that there may be unidentified immunodeficiencies in infected individuals that predisposes them to the fungus. One study screened serum from 30 individuals with CM compared to healthy controls and found anti-granulocyte macrophage-colony-stimulating factor (anti-GM-CSF) antibodies in seven patients infected by *C. gattii*, one healthy volunteer, and in no patients infected by *C. neoformans* [16], leading to the theory that anti-GM-CSF autoantibodies are a risk factor for CNS infection by *C. gattii* but not *C. neoformans*.

The most common manifestation of CNS infection by *Cryptococcus* is CM [17], but mass lesions (cryptococcomas) can also occur and are more commonly seen with *C. gattii* than *C. neoformans* [9]. CM typically presents as development of headache, meningismus, and cranial nerve palsies over several weeks. The sensitivity of serum and CSF cryptococcal antigen detection is high but does not distinguish between *C. gattii* and *C. neoformans*. As (1,3)-β-*d*-glucan is not a substantial component of cryptococcal cell walls, this assay is much less sensitive and specific than cryptococcal antigen detection in diagnosis of cryptococcosis [18]. CSF studies typically reveal low glucose, normal or elevated protein levels, and a lymphocytic leukocytosis, but in HIV patients, the CSF may appear not to be consistent with an inflammatory process [19].

Radiologic findings are neither sensitive nor specific for the diagnosis of CM, but common findings on CT or MRI studies include leptomeningeal enhancement secondary to meningeal disease, dilated peri-vascular spaces, hydrocephalus, and/or cerebral edema [18] (Fig. 1a). Extension of the infection into the brain parenchyma can result in the formation of cryptococcomas and gelatinous pseudocysts, most commonly in the midbrain and basal ganglia. These typically present as focal, ovoid lesions with post-contrast sequences ranging from non-enhancing to nodular enhancement around the periphery. Gelatinous pseudocysts have been described as having a "soap

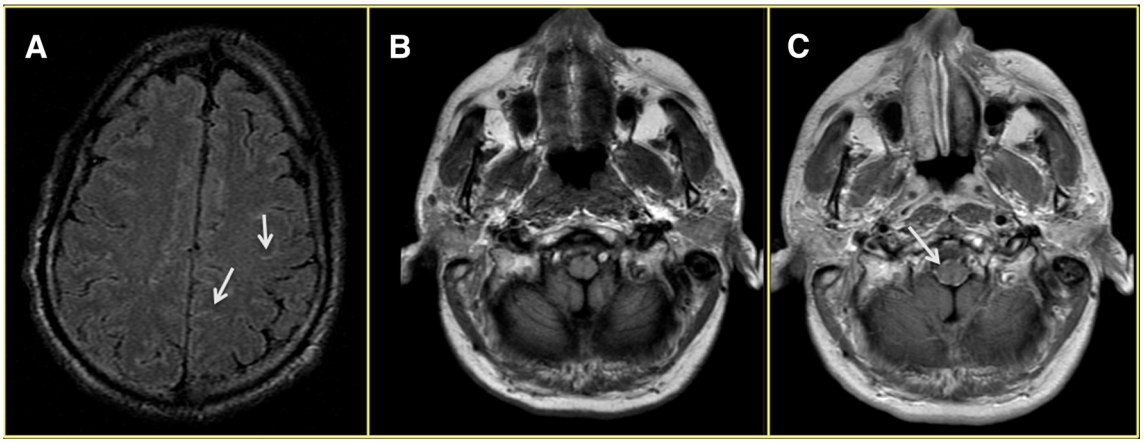

Fig. 1 Imaging findings in CNS fungal infection. **a** Axial T2-weighted fluid-attenuated inversion recovery magnetic resonance imaging of the frontal lobes in a patient with cryptococcal meningitis demonstrates subtle sulcal hyperintensities (*arrows*). **b**, **c** Axial T1-weighted imaging at the level of the cerebellar tonsils before (**b**) and after (**c**) the administration of gadolinium in a patient with *Histoplasma* meningitis demonstrates abnormal leptomeningeal enhancement of the cervicomedullary junction (*arrow*)

bubble" appearance with a decreased T1 signal attributed to mucin production.

There has been much research evaluating the different approaches to antifungals for the three phases of treatment for CM. The Infectious Diseases Society of America treatment guidelines call for induction preferably with amphotericin B (0.7 to 1 mg/kg/day) and 5-flucytosine (100 mg/kg/day) for at least 2 weeks, followed by consolidation therapy preferably with fluconazole (400 mg/day) for a minimum of 8 weeks and maintenance therapy with fluconazole 200 mg/day for 6 to 12 months for organ transplant recipients and at least until the CD4 count has been greater than 100 cells/μL and viral load is undetectable or very low for at least 3 months in HIV-infected individuals. Relapse is treated with repeat induction therapy followed by consolidation with an agent to which the isolate has been deemed susceptible. A direct comparison of different induction therapies confirmed the IDSA recommendations when a 2 week course of amphotericin B (1 mg/kg/day) and fluctyosine (100 mg/kg/day) had fewer mortalities at days 14 and 70 compared to either a 4-week course of amphotericin monotherapy (1 mg/kg/day) or a 2-week course of amphotericin B and fluconazole 400 mg BID [20••]. Timing of combination antiretroviral therapy (cART) initiation is controversial. The 2010 IDSA guidelines suggest deferring 2 to 10 weeks after initiation of treatment for CM given the risk of immune reconstitution inflammatory syndrome (IRIS) [19], but a recent study of Ugandan and South African patients makes the argument that starting at 1 or 2 weeks is associated with increased mortality when compared to waiting for 5 weeks [21]. However, population and treatment regimen differences may limit generalizability of this finding.

Elevated ICP occurs in 40–50 % of CM cases and is associated with a significant increase in mortality [22]: at days 3 and 5, sustained elevations in ICP increase the risk of mortality four and seven times, respectively [22]. Serial CSF drainage is a common approach, targeting pressure reduction by 50 % or less than 20 cm H2O, if opening pressure exceed 25 cm H2O or symptoms of increased ICP are present [19]. In refractory cases, placement of a lumbar drain, ventriculostomy, or ventriculoperitoneal shunt has also proven safe and effective. There is generally no role for hyperosmolar therapy (mannitol or 23 % NaCl), acetazolamide, or corticosteroids in the management of increased ICP in CM secondary to *C. neoformans*. In the relatively more immunocompetent population affected by *C. gattii*, however, there are reports of benefits from corticosteroids [23]. Additionally, there is some evidence supporting the use of corticosteroids in cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) [24].

C-IRIS is common in HIV-associated CM, occurring in approximately 10–30 % of patients after starting antiretroviral therapy [24–26], more frequently as paradoxical worsening than unmasking of disease. Exact mechanisms of pathogenesis are unknown. Profound immune suppression at the time of cART initiation is a risk factor for IRIS in general, and yet since the condition is inflammatory and occurs several weeks later, dysregulation of a reconstituting immune system comes into play. High cryptococcal antigen burden and low rates of CSF clearance at 2 weeks have previously been reported as risk factors, as well [27]. More recent work has shown that patients with C-IRIS tend to have lower *Cryptococcus*-specific CD4 cell responses at the time of and 4 weeks after cART initiation, suggesting that these cells play a role in controlled clearance of the infection [28••]. CM patients who go on to develop C-IRIS also appear to have reduced CSF levels of IFN-γ, TNF-α, IL-6, and IL-8 at the time of initial diagnosis [29], and there is evidence of a strong association between interferon-γ levels and rate of clearance of cryptococcal infection [30]. However, with subsequent T cell expansion of a recovering immune system, immune dysregulation precipitates IRIS. This is evidenced by increased levels of cytokines

such as IL-6 [31] and TNF-α, the latter of which is supported by a solitary report of administration of the TNF-α-blocking agent adalimumab to a patient with intractable IRIS-associated cryptococcoma who subsequently clinically improved [32]. Since currently, no specific preventive strategies exist, the general management approach once C-IRIS manifests typically consists of antigen load reduction with antifungal therapy with or without concomitant corticosteroids; surgical intervention and other experimental immune modulation are considered on a case by case basis, but antiretroviral therapy interruption should generally be avoided.

Histoplasma capsulatum

H. capsulatum is endemic primarily to the Ohio and Mississippi River basins as well as the St. Lawrence River valley and Great Lakes [33]. Outside of the USA, *Histoplasma* is also prevalent in southeastern Mexico and Southeast Asia (e.g. Taiwan). Cases have also been reported in Central America, the Caribbean [34], and recently in Montana [35]. CNS involvement can occur either as an isolated syndrome or in 10 to 20 % of patients with progressive disseminated histoplasmosis [33]. In immune competent individuals, inhalation of the microconidia is predominately asymptomatic. The majority of HIV-positive individuals diagnosed with histoplasmosis, on the other hand, will present with disseminated disease [36].

The most common CNS manifestation is acute or chronic meningitis (Fig. 1b, c), reported in 60 % of cases of CNS disease [36], which can result secondarily in stroke [36, 37]. Meningitis most commonly presents in immunocompromised patients, with advanced HIV infection being the most typical but not required [37]. Less commonly, intracranial mass lesions, cerebral embolism secondary to endocarditis, encephalitis, and an isolated myelopathy can occur. The mass lesions most often present as miliary granulomas but can also, in rare instances, present as the larger-sized histoplasmomas [36]. The MRI characteristics of these mass lesions typically involve a contrast-enhancing lesion, which is usually a non-caseating granuloma.

In meningitis, the CSF profile typically demonstrates a lymphocytic pleocytosis and protein elevation [37]. A positive fungal culture of the CSF is the gold standard but is insensitive. *Histoplasma* antigen has been shown to be detected in >90 % of blood or urine samples from patients with progressive disseminated histoplasmosis [33], but in isolated CNS disease, this is often not the case. Elevated levels of (1,3)-β-*d*-glucan from the CSF may provide a diagnostic clue [38], and/or ITS sequencing methods may identify the fungus. Following urine *Histoplasma* antigen levels is additionally used to monitor antifungal response during maintenance therapy. Treatment is often with liposomal amphotericin B followed by itraconazole for at least 1 year and until CSF abnormalities have resolved [39], but alternative therapeutic regimens have had success.

Blastomyces dermatitidis

B. dermatitidis is a dimorphic fungus endemic to the Great Lakes and the St. Lawrence, Mississippi, and Ohio River basins. Of those infected, 5–10 % will develop CNS involvement [40], and isolated CNS cases have been reported [41]. Presentation varies and includes leptomeningitis, encephalitis, abscesses, infarcts, or mass lesions (blastocytomas) involving the cerebrum, cerebellum, spinal cord, and epidural space [42, 43]. CSF in meningitis cases usually shows lymphocytic pleocytosis (teens to a few hundred cells/μL), elevated protein, and relatively normal CSF glucose [43]. Mass lesions tend to show a predilection for the posterior fossa [42, 43], raising potential for obstructive hydrocephalus. Diagnosis is difficult, with culture being of very low sensitivity. Therefore, *B. dermatitidis* antigen detection has been emphasized in suspected cases. Treatment is typically with liposomal amphotericin B followed by azole monotherapy for at least 12 months [44].

Coccidioides immitis

C. immitis or *Coccidioides posadasii*, endemic to the American Southwest, western Texas, and southern California as well as northern Mexico and Central and South America cause coccidioidomycosis usually following inhalation of aerosolized arthroconidia but occasionally after organ transplant or mother-to-child. Recently, Washington state, whose climate is disparate to the hot and dry Southwest, has been implicated as well, suggesting that an arid environment is not essential for this organism [45, 46•]. Infection is more likely to be severe in those with immune compromise.

Coccidioidal meningitis occurs in one third to one half of cases of disseminated infection [47, 48] and classically involves the basilar leptomeninges. Given this predilection, communicating hydrocephalus is a common complication, reported to develop in 20–50 % of patients and carrying a 12-fold mortality risk increase [49]. Basal meningeal involvement is also thought to lead to vascular obstruction, endarteritis obliterans, and vasculitis affecting the small and medium blood vessels, with subsequent infarction involving the cerebral white matter, basal ganglia, and/or thalamus [48, 49]. Of the three recent Washington state cases, one was complicated by meningitis. Although details of CSF studies for this patient were not included in the report, the usual findings are lymphocytic pleocytosis with an early neutrophilic predominance; up to 70 % will also have CSF eosinophilia [50]. Complement-fixation antibody detection of CSF

antibodies to *C. immitis* in the CSF is the most sensitive assay to confirm CNS infection (95 % sensitivity); however, the antibodies may not be detectable early in the infection and repeated CSF sampling may be required [48]. Magnetic resonance imaging is recommended; this may show basilar or diffuse leptomeningeal enhancement, multifocal infarcts, or be completely normal; when normal, prognosis may be more favorable. Fluconazole is typically the treatment of choice.

Paracoccidioides brasiliensis

Neuroparacoccidioidomycosis is thought to occur in 9–25 % of cases of disseminated disease and can manifest as meningitis or a pseudotumoral process secondary to granuloma formation obstructing CSF outflow [51, 52]. Patients most often have evidence of involvement of other organ systems, but isolated central nervous system involvement has been reported [51]. The most common clinical manifestations reported are seizures in 33 %, hemiparesis or cerebellar signs in 25 %, and headache or hydrocephalus in 21 %, while less commonly reported are sensory changes, confusion, or cranial nerve deficits [51, 52].

CNS infection is usually presumptive, based on the patient's symptoms and neurological signs in conjunction with confirmation of systemic paracoccidioidomycosis [52]. ELISA studies to identify the anti-gp43 antigen antibody in the CSF have been promising, with the caveat that there is cross-reactivity with *Histoplasma* and *Aspergillus* [51, 53]. MRI or CT studies may reveal single or multiple mass lesions, most often in the cerebral hemispheres, less often cerebellum or brainstem, and only rarely in the spinal cord [51, 54]. First-line treatment is generally with trimethoprim/sulfamethoxazole.

Penicillium spp.

Several species of the *Penicillium* genus are known to cause CNS infection, and >80 % are in immunocompromised individuals [55]. With the spread of HIV, *Penicillium marneffei* has become one of the most common opportunistic infections in advanced HIV patients in Southeast Asia [55]. CNS infection manifests as altered mental status, and death frequently occurs within days. Treatment is with amphotericin B followed by azole therapy; recent mortality evidence for systemic disease is reported at 24 % for those receiving antifungal therapy and 50 % for those who do not [56].

Sporothrix schenckii

Fungi belonging to the *S. schenckii* complex usually cause a cutaneous infection but can in rare instances disseminate to the CNS and cause meningitis or, less commonly, ventriculitis, CNS vasculitis, or thrombotic endarteritis and stroke [57, 58]. Immune suppression is typical but not required. Diagnosis is typically by fungal culture, but recent elucidation of the *S. schenckii* genome opens up the potential for molecular diagnostics [59]. Treatment is with amphotericin followed by itraconazole [60], although recent studies have shown genetic variability in susceptibilities [61].

Conclusions

Fungal CNS infections are gaining recognition in both immune compromised and competent individuals, but diagnosis can be difficult in non-cryptococcal cases. Additionally, there is increasing recognition of these pathogens outside of areas traditionally considered endemic, and knowledge of their changing epidemiology and alternative methods of diagnosis can potentially lead to more successful treatment early in the course of disease.

Compliance with Ethics Guidelines

Conflict of Interest Jennifer Lyons, Mark Etherton, and Claire Jacobs have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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