2 Epidemiology of Central Nervous System Fungal Infections

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Abbreviations

CARD9	Caspase recruitment domain-containing protein 9 deficiency
CGD	Chronic granulomatous disease
CNS	Central nervous system
GvHD	Graft-versus-host disease
HCT	Hematopoietic cell transplantation
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
ICU	Intensive care unit
IFI	Invasive fungal infection
SOT	Solid organ transplantation
TNF-α	Tumor necrosis factor-alpha

2.1 Introduction

The burden of invasive fungal infection (IFI) has been increasing in both immunocompetent and the immunocompromised hosts (Vallabhaneni et al. 2016). This phenomenon is due to multiple factors that include increased awareness of fungal infections leading to an increased diagnostic testing, improvements in the diagnostic capabilities, and an ever-increasing pool of at-risk population: cancer, hematopoietic cell transplantation (HCT), solid organ transplantation (SOT), newer immunosuppressive therapies, and neonatal and elderly patients (Powers-Fletcher and Hanson 2016; Vallabhaneni et al. 2016). The spectrum includes fungi that are opportunistic pathogens and true pathogens (latter can lead to fungal infection without any apparent immunodeficiency). This chapter will discuss general considerations of central nervous system (CNS) IFI epidemiology and epidemiology of specific class of fungi: yeasts and molds that are most commonly associated with CNS infection.

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2.2 General Considerations of Epidemiology of CNS Fungal Infection

In the absence of an immunocompromising condition, fungal infection of the CNS is uncommon as the host defense and the anatomy of the CNS (functional and structural) help prevent invasion of their CNS (Chakrabarti 2007; Marra et al. 2014). Although this protects vast majority of mankind, exposures related to diverse environmental/ecological niches of various fungal pathogens can lead to IFI in the context of their endemic distribution: *Coccidioides* (Brown et al. 2013), *Cryptococcus gattii* (Chen et al. 2014; Datta et al. 2009), *Histoplasma* (Chu et al. 2006; Hammerman et al. 1974), and *Blastomyces*

M. Turgut et al. (eds.), *Fungal Infections of the Central Nervous System*,
https://doi.org/10.1007/978-3-030-06088-6_2

(Baumgardner et al. 1992; Dworkin et al. 2005). The sinonasal fungal infection when invasive in nature can extend beyond the extracranial compartment into the brain (Kourkoumpetis et al. 2012; McCarthy et al. 2014) and may manifest as meningitis or space-occupying lesions/abscess. Certain epidemiologic exposures such as drowning have led to infection of the CNS with *Scedosporium apiospermum* (Kantarcioglu et al. 2008) and *Aspergillus* spp. (Kowacs et al. 2004). Diabetic ketoacidosis, steroid use, and iron overload are known risk factors for mucormycosis (Spellberg et al. 2005). Furthermore, iatrogenic fungal infections have occurred in the setting of outbreaks such as with *Exserohilum rostratum* due to contaminated compounded methylprednisolone for spinal injections in 2013 (Chiller et al. 2013), *Exophiala* infection from contaminated injectable steroids (From the Centers for Disease Control and Prevention 2003), and *Aspergillus* meningitis after spinal anesthesia in pregnant women (Gunaratne et al. 2007).

Perhaps, the most significant group that contributes to the burden of IFI is the immunocompromised patient. The high-risk group include, neutropenia in patients undergoing cytotoxic chemotherapy for hematologic malignancy, those who have undergone allogeneic HCT (Kontoyiannis et al. 2010), especially those with graft-versus-host disease (GVHD) requiring immunosuppressive therapy, SOT (Pappas et al. 2010; Singh 2003; Singh and Paterson 2005), use of biologic agents such as TNF-α (Warris et al. 2001), use of Bruton tyrosine kinase inhibitor, ibrutinib (Bercusson et al. 2018; Peri et al. 2018), congenital immunodeficiency such as chronic granulomatous disease (CGD) (Alsultan et al. 2006; Dotis et al. 2007; Henriet et al. 2013), and caspase recruitment domain-containing protein 9 deficiency (CARD9) (Gavino et al. 2014; Lanternier et al. 2015; Rieber et al. 2016). Within the SOT recipients, the type of organ transplant has an impact on the risk of IFI (Munoz et al. 2016). ICU patients are also at high risk for IFI: mainly candida and aspergillus (Denning 2004; Pittet et al. 1994). Patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are at high risk for cryptococcal infection (Rajasingham et al. 2017), and the risk correlates with the status of the cell-mediated immunity.

The CNS IFI can manifest as meningitis, which is the inflammation of the meninges. The symptoms are often protean and can vary from acute onset to subacute and chronic in nature. Patients often present with headaches that are subacute to chronic and may have visual changes, cranial nerve abnormalities, and other symptoms of elevated intracranial pressure. Nuchal rigidity may or may not exist. At times, patients may present with the symptoms/signs of cerebritis suggesting parenchymal involvement. The inflammatory component can result in endarteritis that may result in stroke manifesting with focal neurologic defects. In patients with immunocompromised state, symptoms and signs may be minimal or atypical that often result in delayed diagnosis. Intracranial abscess-/mass-like lesions are mostly encountered with invasive mold infections. Mold infections of the CNS are mostly encountered in the immunocompromised patients and typically present with space-occupying parenchymal lesions/abscesses and less likely to be associated with meningitis.

This chapter will provide an outline of the epidemiology for CNS infections related to common fungal pathogens (true and opportunistic), and the description will be centric to the specific organism.

2.3 Yeast Infections of the CNS

2.3.1 *Cryptococcus neoformans*

This pathogen belongs to basidiomycetous fungi and is the leading cause of CNS fungal infection manifesting as meningitis and may be accompanied by brain abscesses "cryptococcomas." Its distribution is worldwide and is ubiquitously found in soil, bird droppings, and animals. Humans can be colonized with it as well. There are eight genotypes, with the most common being *C. neoformans* var. *neoformans* in the USA and Europe. *C. neoformans* var. *grubii* is most common in the rest of the world. The most significant burden from this pathogen is in the

HIV/AIDS patient population, and the risk of developing this infection is directly correlated with the cell-mediated immunity that increases with the declining CD4 count (most cases occur when CD4 is <100 cells/μl) (Rajasingham et al. 2017). With the availability of HAART, the incidence of cryptococcal CNS infection has decreased in the USA, although it is still a major cause for morbidity and mortality in the developing world (Rajasingham et al. 2017). After HIV/AIDS, SOT recipients have the highest rate of CNS infection (Pappas et al. 2010), but it is rare in recipients of HCT (with more cases observed in autologous than allogeneic) (Kontoyiannis et al. 2010). In the SOT, *Cryptococcus* contributed to 8% of all IFI in a large prospective study (Pappas et al. 2010), and the CNS is the most common extrapulmonary site of infection. Increased risk for CNS involvement was correlated with abnormal mental status, late-onset disease, and high serum cryptococcal antigen titer (Osawa et al. 2010).

C. gattii is an emerging pathogen worldwide that was previously described primarily in tropical and subtropical areas such as Australia, New Guinea, Hawaii, Southern California, Central Africa, and Southeast Asia (Maziarz and Perfect 2016). Originally described with eucalyptus trees, the recent outbreaks noted association with trees such as oaks and firs. There has been an evolving epidemic in the Vancouver Island and Pacific Northwest, USA, and cases have been described in multiple states across the USA (Harris et al. 2011). This pathogen primarily affects the healthy individuals although there is an association with anti-GM-CSF antibodies and *C. gattii* infection (Rosen et al. 2013; Saijo et al. 2014). The disease process is frequently severe with meningitis and cryptococcomas in the immunocompetent patients (Chen et al. 2014).

2.3.2 *Candida*

Candida species are an important cause of healthcare-associated infection presenting as disseminated infection (candidemia). They are found in soil, on inanimate objects, and on hospital surfaces and colonize the respiratory/GI tract of normal and immunocompromised hosts. The risk factors for candidemia include critically ill neonates associated with prematurity, low APGAR score, shock, intubation and congenital malformations, neutropenic host, HCT recipients with mucositis or graft-versus-host disease (GVHD) of the gut, SOT, use of broad-spectrum antibiotics, central venous catheter, intravenous drug use, total parenteral nutrition, gastrointestinal surgery, diabetes, sepsis, pancreatitis, ICU stay, and dialysis (Blumberg et al. 2001). *C. albicans* is the most frequent cause of infection in the USA followed by *C. glabrata* (Matsumoto et al. 2014), and there is variability in the distribution of species based on geography and patient population (Pfaller et al. 2012); *C. glabrata* is more frequently isolated from SOT and elderly patients. Additionally, there has been emergence of drug-resistant *Candida* spp. such as triazole and echinocandin resistance in *C. glabrata* (Pfaller et al. 2010; Pfaller et al. 2011). *Candida auris*, a multidrug-resistant candida species, has gained notoriety in recent years as a cause of outbreaks associated with high morbidity and mortality (Sarma and Upadhyay 2017).

Candida used to be the most common cause of fungal meningitis, but that has been replaced by *C. neoformans*. *Candida* meningitis/brain abscesses occur in the context of disseminated candida infection in premature infants and neonates (Faix 1984; Fernandez et al. 2000) and patients with AIDS (Casado et al. 1997), neutropenia from chemotherapy (Flynn et al. 1993), CGD (Cohen et al. 1981), and SCID (Smego Jr et al. 1984). Direct inoculation may occur with traumatic injuries (Brenier-Pinchart et al. 1999), CNS ventricular shunts (Baradkar et al. 2009; Shapiro et al. 1989) and polymer wafers used in local chemotherapy are additional risk factors (Glick et al. 2010).

2.3.3 *Coccidioides*

The disease caused by *Coccidioides* is commonly referred to as coccidioidomycosis or "valley fever," named after the common occurrence of this endemic fungal infection in the San Joaquin Valley in California. *C. immitis* and *C. posadasii* are the two species that cause disease in humans. It is a dimorphic fungus that is able to survive in dry and arid environment. It is highly infectious and inhalation of even a few arthroconidia can lead to infection (Kong et al. 1964). Endemic areas include California, with particularly high rates in Kern and Fresno counties, Arizona, New Mexico, Nevada, Utah, Washington, Texas, Mexico, Central America, Honduras and Guatemala, and South America: Brazil, Venezuela, Argentina, and Paraguay (Stevens 1995). Changing environmental and human factors in the endemic area, changes in surveillance and definitions, diagnostic methods, and increasing pool of immunocompromised patients may be affecting the increase of rates in California and Arizona (Stockamp and Thompson 3rd 2016). Certain natural disasters such as major earthquakes (Schneider et al. 1997), digging/excavation activities, and dust storms may lead to local epidemics. Coccidioidal meningitis is a dreaded complication that is associated with significant morbidity and mortality. Basilar meningitis with its inflammatory exudate is commonly complicated with obstructive hydrocephalus that requires ventricular shunt. Patients with coccidioidomycosis with headache, visual changes, or any CNS symptom or sign should undergo spinal tap.

In a study of allogeneic HCT recipients living in endemic areas with prior history of exposure/infection, 11/426 (2.6%) were noted to develop active coccidioidomycosis post-HCT (Mendoza et al. 2015). In a study with SOT recipients with prior history of coccidioidomycosis, reactivation was observed in 5% despite antifungal prophylaxis (Keckich et al. 2011). Mortality rates of up to 55% have been reported in allogeneic HCT (Mendoza et al. 2015) and 28% in SOT (Mendoza and Blair 2013). Other risk factors include the use of TNF-α blockers (Bergstrom et al. 2004) and HIV/AIDS (CD4 less than 250) (Masannat and Ampel 2010), pregnant women, and race. It is more frequently observed in African Americans and Filipinos with the propensity to develop CNS involvement.

2.3.4 *Blastomyces*

Blastomyces dermatitidis is a dimorphic fungus that is endemic in the Midwestern states of the USA, Canadian provinces along the great lakes, and the Mississippi and Ohio river valleys (Castillo et al. 2016). Cases have been reported from other states and countries too. Even though surveys from Wisconsin show high rates of endemicity, the true prevalence is unknown, secondary to a lack of mandatory reporting. The infection has been associated with exposure to decaying wood or disturbing the soil. The most common site of infection is the skin and lungs with the propensity to develop disseminated disease. CNS involvement occurs in about a third of all infected patients. In a pediatric study that reviewed 114 children with *Blastomyces* infection, 21% had extrapulmonary disease, and only 2 had CNS involvement. The majority of the infections were due to *B. gilchristii* followed by *B dermatitidis*, and the latter was associated with more extrapulmonary disease (Frost et al. 2017). In a study of 22 patients with CNS involvement, 22.7% had isolated involvement of the CNS (Bariola et al. 2010). Presentation varies from symptoms/signs of acute meningitis to chronic meningitis and brain abscess. AIDS patients have high burden from CNS disease developing in 40% of patients (Grim et al. 2012), while it is of rare occurrence in SOT and HCT recipients (Kauffman et al. 2014). Furthermore, the use of corticosteroids and TNF-α blockers also increases the risk (Pappas et al. 1993; Smith and Kauffman 2009).

Blastomyces helicus is an emerging fungus that has been reported to be associated with disseminated disease with CNS involvement in 20% of the infected patients. The primary route of acquisition is inhalational and skin involvement is rare. In a case series of ten patients, six had underlying immunocompromising condition, and 50% had fungemia which is extremely uncommon with *B. dermatitidis* (Schwartz et al. 2018).

2.3.5 *Histoplasma*

Histoplasma capsulatum leads among the other causes for endemic mycoses (Chu et al. 2006; Hammerman et al. 1974). In the USA, it is most prevalent in the Ohio and Mississippi river valleys. Outside of the USA, it has been reported from Mexico, South American countries, parts of Asia, and Southeast Asia. Exposure to soil rich in bird or bat guano is a risk factor for the acquisition of *Histoplasma* (Wheat et al. 2016). The activities that are mostly reported to be significant exposures include farming, cave exploration, remodeling of old buildings, clearing brushes, or cutting trees at sites that had supported blackbird roosting. The highest numbers were seen in the context of HIV/AIDS epidemic (Assi et al. 2007; Kaur and Myers 1983) and, subsequently, exposure in the immunocompromised patients with T cell dysfunction, exposure to TNF-α blockers, SOT, and HCT (Wheat et al. 2016). It is encountered more commonly in the SOT group, while a lower incidence is observed in HCT recipients (Kauffman et al. 2014). Dissemination to the CNS is infrequent and is mostly observed in the immunocompromised patient with development of meningitis or focal lesions in 5–10% of the cases (Chen et al. 2014). A recent retrospective study reviewing 77 cases noted male predominance with most frequent underlying diagnosis of HIV/AIDS in 44% followed by transplantation in 13%, and 14% had other immunocompromising conditions (Wheat et al. 2018). Morbidity and mortality are high in patients with CNS involvement.

2.3.6 *Sporothrix schenckii*

S. schenckii is a dimorphic fungus that is most commonly found in the tropical and subtropical areas. It has been reported mostly from Japan, India, Mexico, Brazil, Uruguay, and Peru. In the USA, outbreaks related to pine seedlings and manipulation of the moss have been reported from the Mississippi Valley (Barros et al. 2011). The activities associated with risk for acquisition of *Sporothrix* are agriculture, floriculture, wood exploration, mining, and exposure to cats that are infected with this fungus (veterinarians, owners, and caretakers of cats) (Barros et al. 2004; Vilela et al. 2007). The most common site of infection is the skin although it can be acquired via inhalation and has the propensity to disseminate in the immunocompromised patients (Barros et al. 2011). CNS involvement has been reported in patients with underlying immunodeficiency (Gullberg et al. 1987; Hardman et al. 2005) and mostly manifests as meningitis.

2.4 Mold Infections of CNS

2.4.1 *Aspergillus*

The increase in the number of at-risk patients undergoing transplantation, chemotherapy for hematologic malignancies, and use of novel immunosuppressive medications has led to a spurt in invasive aspergillosis. *Aspergillus* spp. have a ubiquitous distribution in the nature and are commonly found in soil, decaying vegetation, and food material. The primary route of acquisition is inhalational, although infection related to skin patch dressing and trauma has been observed.

Risk factors for invasive aspergillosis include neutropenia in patients undergoing induction chemotherapy for hematologic malignancy and HCT especially in the context of GVHD that requires treatment with steroids or agents such as infliximab, and ibrutinib (bruton tyrosine kinase inhibitor) and in SOT (Bercusson et al. 2018; Kourkoumpetis et al. 2012; McCarthy et al. 2014; Pappas et al. 2010; Peri et al. 2018; Singh and Paterson 2005). Inherited conditions such as CGD and CARD9 deficiency are also associated with increased risk of *Aspergillus* infection (Alsultan et al. 2006; Dotis et al. 2007; Henriet et al. 2013; Rieber et al. 2016). Patients with diabetes, recent CNS surgery, lumbar puncture, paranasal sinusitis, chronic steroid use, intravenous drug use, pulmonary tuberculosis, and alcoholic liver disease are also at risk.

Aspergillus is now the most common cause of IFI in the allogeneic HCT patients having surpassed *Candida* as reported in a large prospective database (Kontoyiannis et al. 2010). In SOT, the highest incidence is noted in lung, lung-heart transplant (about 6%), and liver and kidney transplants (Pappas et al. 2010). CNS involvement occurred in 15.4% of cases in the context of disseminated disease from a large study in Europe

(Gavalda et al. 2005). *A. fumigatus*, *A. terreus*, *and A. flavus* are the most common species associated with CNS disease. CNS aspergillosis can manifest as meningitis, infarction, or a brain abscess with the latter two presentations being more common.

2.4.2 Non-*Aspergillus* Mold Infections

2.4.2.1 *Mucormycosis*

Mucormycosis is an infection caused by fungi from the *Mucorales* order (Mendoza et al. 2014), with *Rhizopus* spp. the most common offending agent. The organism is found in the decaying organic matter such as vegetables, seeds, fruits, manure, and compost. It releases spores that when airborne can be inhaled.

The incidence of this devastating illness has been increasing over the last decade, in the HCT and SOT, patients with hematologic malignancy (HM) undergoing cytotoxic chemotherapy, uncontrolled diabetes mellitus with acidosis, burns, and trauma (Roden et al. 2005; Walsh et al. 2012). Voriconazole and echinocandin prophylaxis has been associated with increased risk of mucormycosis, while tacrolimus is protective (Singh et al. 2009).

The spread to CNS is primarily via the hematogenous route, although direct extension from the sinuses to the intracranial compartment is well known. In a large retrospective study of 929 patients, CNS involvement was described in one-third of the patients, and of that 69% were related to sinonasal source (Roden et al. 2005). Injection drug users manifest predominantly with cerebral involvement—abscesses or infarcts (Fong et al. 1990; Stave et al. 1989).

2.4.2.2 *Phaeohyphomycoses* (*Dematiaceous Fungi*)

This is a diverse group of pigmented fungi that are emerging as a cause of CNS fungal infections. Many of the fungi in this group are neurotropic, such as *Cladophialophora bantiana*, *Exophiala dermatitidis*, and *Rhinodadeiella mackenziei* (Chakrabarti 2007).

Although *Cladophialophora* infections are reported worldwide, the majority are in areas that have a warm and humid climate (Kantarcioglu et al. 2017). A systematic review of *C. bantiana* cases reported that the majority of cases are from India, the USA, Brazil, Canada, France, Spain, South Africa, and Italy, with sporadic cases from various other countries. The majority of patients were immunocompetent (58.3%) and 97% had brain abscess. Regardless of the immune status, mortality was high at 65% (Kantarcioglu et al. 2017).

Exophiala dermatitidis notoriously causes brain abscesses and is mostly reported from the Asian countries. CARD9 deficiency has been identified as a risk factor (Lanternier et al. 2015). Other molds such as *Lomentospora prolificans*, *Alternaria* spp., *Exserohilum rostratum*, *Scopulariopsis* spp., *Curvularia* spp., *Bipolaris* spp., *Chaetomium*, and *Ochroconis gallopava* are more often encountered in immunocompromised hosts (Kontoyiannis et al. 2010; Pappas et al. 2010). In a review of 72 cases of phaeohyphomycosis (Revankar et al. 2002), the majority of patients (76%) had underlying immunodeficiency, and CNS involvement was identified in 22/72 (30.5%). Only three of the patients with CNS infection did not have an underlying immunologic deficit (two caused by *Curvularia* spp. and one by *Wangiella dermatitidis*). A case series of 12 SOT patients with *Ochroconis gallopava* infection described high mortality rate in those with CNS involvement that reached 80% (Shoham et al. 2008).

From an iatrogenic standpoint, a large outbreak of fungal meningitis due to *Exserohilum rostratum* in the USA resulted in patients who had received contaminated compounded methylprednisolone used for spinal/epidural injections (Chiller et al. 2013).

2.5 Miscellaneous Fungi

Scedosporium apiospermum is ubiquitously found in the environment, especially polluted environment of high human activity, agricultural soil, and polluted water (Ramirez-Garcia et al. 2018). *Scedosporium* and *Lomentospora* accounted for the majority of non-*Aspergillus* mold infections in both HCT and SOT, 71% and 29%, respectively (Husain et al. 2005).

Paracoccidioides brasiliensis is the main cause for paracoccidioidomycosis that is endemic in South America, and chronic disease is a risk factor for CNS involvement (Shikanai-Yasuda et al. 2017). *Fusarium* spp., *Acremonium* spp., and *Paecilomyces* spp. have also been associated with CNS involvement in patients with disseminated disease. Dermatophytes such as *Trichophyton* and *Microsporum* have also been described in immunocompromised patients leading to CNS infection. *Emmonsia* is another emerging fungus that has the ability to cause disseminated disease.

2.6 Conclusion

Fungi are ubiquitous in the environment and exposure to them is inevitable. The epidemiologic trends of CNS yeast and mold infections demonstrate varying risk based on the host immune status and environmental exposures especially in the context of endemic fungi, as well as non-endemic fungi. With the advancement in the care of very ill patients and neurosurgical interventions, these infections may occur more frequently. Increased awareness coupled with diagnostic advances over time should result in the timely establishment of diagnosis and intervention with a potential improvement in outcomes. The CNS IFI carries high morbidity and mortality and is a challenging medical/surgical condition.

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