Neuro-Infections Caused By Candida Species

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Abstract

There has recently been a 6 to 17% rise in candida species infections in the central nervous system. Although *Candida* can cause infections in both immunocompetent and immunosuppressed individuals, disseminated candidiasis is mostly seen in patients with impaired immunity due to AIDS, diabetes, neutropenia, underlying malignancy, and extensive wounds (burns and operations). Patients with disseminated candidiasis or with any neurosurgical procedure like ventricular shunts are observed with central nervous system (CNS) involvement. Another high-risk group for invasive candidiasis consists of newborns and infants, particularly those with low birth weight (<1.5 kg). *Candida* crosses the blood–brain barriers by three proposed mechanisms namely the Trojan horse mechanism, paracellular migration, and transcellular migration. Clinical manifestations of neuro-candidiasis are usually variable; however, meningoencephalitis is the most common. Invasive candidiasis mortality is thought to vary from 10 to 70%, rising to 90% in cases when the central nervous system is affected. Analysis of cerebral spinal fluid plus cultures exhibiting growth of budding, yeast-like cells, is used to make laboratory-based diagnoses. The positive serum beta-D-glucan assay aids in the diagnosis but may be positive in patients with various other invasive fungal infections. Liposomal amphotericin B with better CNS concentrations followed by fluconazole as a step-down therapy is considered an effective treatment strategy.

Keywords

Central nervous system · *Candida albicans* · Meningoencephalitis · Disseminated candidiasis

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12.1 Pathogen

Candida neurological infections are almost always due to *C. albicans* (Sánchez et al. 2000). However, the world has seen a gradual rise in the frequency of non-*C. albicans* species over *Candida albicans* over the past decade (Table 12.1). *Candida* infects both immunocompetent and immunosuppressed individuals but disseminated disease mostly occurs in the latter (Cesaro et al. 2017). A remarkable surge from 6 to 17% has been noted in the incidence of CNS infection from *Candida* spp. (Brumble et al. 2017). *Candida albicans* was the cause of 33% of CNS infections among individuals with underlying malignant illnesses or among those with hematopoietic stem cell transplantations. Non-*Candida albicans*, however, accounted for 77% of neuro-infections in such patients; the most common strain found was C. parapsilosis, while isolates of Candida glabrata, guilliermondii, krusei, and tropicalis were also found occasionally. Additionally, multispecies involvements were also reported (Cesaro et al. 2017; McCullers et al. 2000; Murthy and Sundaram 2014).

12.2 Pathogenesis

Although the exact pathogenic mechanisms involved in certain neuro-mycological infections are not entirely known, it is a well-established fact that the fungi must first get past the host defenses in cross the blood–brain barrier (BBB) in order to commence CNS infection. The fungi adhere to the microvasculature of the brain, after which transmigration happens into the brain parenchyma. Trojan horse mechanism, transcellular migration, and paracellular migration are the three mechanisms proposed for crossing the BBB by the fungus (Liu et al. 2011). The building block of BBB is the brain endothelial cells connected with tight junctions; foot process of astrocytes surrounds these cells maintaining its integrity. Fibronectin, vitronectin, and laminin facilitate adhesion of *C. albicans* to the extracellular matrix. Als3 (agglutinin-like sequence 3) and Ssa1 (stress seventy subfamily A 1) are the fungal invasins that mediate invasion of brain endothelial cells by *C. albicans* (Shi and Mody 2016). Als3's affinity for the heat shock protein 96 (gp96), which is expressed on endothelial cells that line the cerebral vessels, promotes the transcytosis of *Candida albicans*. *C. albicans* gets engulfed by the phagocyte in the peripheral blood circulation from where the Trojan horse pathway begins. The fungus inside the phagocyte maneuvers its movement toward the brain, where it adheres on the luminal side of the brain capillaries finally crossing the BBB transcellularly and paracellularly *(*Koutsouras et al. 2016; Liu et al. 2011; Santiago-Tirado and Doering 2017).

Factors that facilitate the penetration of fungi across the blood–brain barrier are downregulation of immunity by various immunosuppressant conditions which lead to increased permeability of the BBB, direct disruption of the BBB by any neurosurgical procedure, colonization of the foreign devices placed in the ventricles of the brain, or activation of microglia and cytokines: Tumor necrosis factor alpha (TNF-α)

Table 12.1 Overview of clinically relevant Candida species

Order: Saccharomycetales ⇒ Family: Debaryomycetaceae ⇒ Genus: Candida	
Species	Remarks
C. albicans	• The most common *Candida* species identified (50–60%) Pappas et al. (2018) • About 70–80% of the *Candida* species found in candidemia/invasive candidiasis are *C glabrata* and *C albicans* Pappas et al. (2018)
C. auris	• Linked to high mortality rates and outbreaks related to healthcare • Frequently resistant to several antifungal agents • Difficult to distinguish in a routine laboratory • Internationally emerging invasive yeast species Ahmad and Alfouzan (2021) • From the time of initial discovery and February 2019, 587 *C auris* cases were documented in USA • 2377 cases have been documented in 2022 alone Egger et al. (2022)
C. Dubliniensis	• Primarily recovered from patients infected with HIV
C. glabrata	• Formerly recognized as *Torulopsis glabrata* (15–20%) • Due to its rising prevalence around the globe, its link to fluconazole resistance in as many as 20% of clinical samples, and its general decreased sensitivity to various azoles and polyenes, *C. glabrata* has recently gained medical significance Lee et al. (2021)
C. guilliermondii	• (< 5%)
C. haemulonii	• Emerging species • Closely related to *C. auris* • Occasionally been implicated in the development of disseminated/invasive candida infections Ben-Ami et al. (2017)
C. Kefyr	• (< 5%)
C. krusei	• (1–3%) • Intrinsically resistant to ketoconazole and fluconazole • Less susceptible to various other antifungal drugs such as itraconazole and amphotericin B Badiee and Alborzi (2011)
C. lusitaniae	• (< 5%) • *C. lusitaniae*, albeit less frequent than other species of *Candida*, is significant clinically as it may be inherently resistant to amphotericin B while still being susceptible to the azoles and echinocandins Mendoza-Reyes et al. (2022)
C. parapsilosis	• (10–20%) • Another crucial species to take into account when treating hospitalized individuals • Occurs in infections linked to prosthetic vascular catheters • Echinocandins have a greater in vitro minimum inhibitory concentration against *C parapsilosis* versus other *Candida* species Trofa et al. (2008)
C. tropicalis	• (6–12%) • Repeatedly been cited as a significant contributor to candidemia in malignancies (leukemia) and bone marrow transplant recipients Sendid et al. (2003)

disrupts the tight junctions of the barrier. After the crossing of the BBB, cerebral and subarachnoid space proliferation of the fungus in the brain parenchyma causes inflammation. Invasion of the brain tissue/meninges by the fungal pathogen after surpassing all the effective barriers surrounding the brain facilitated by the immunosuppressive conditions occurs; subsequently, there is release of immune-enhancing and immune-suppressing chemokines and cytokines by the activated nerve cells occurs. The interplay between these cytokines and chemokines determines the pathogenesis of fungal CNS infections (Koutsouras et al. 2016; Sharma et al. 2012).

The rate and severity of neuro-infection are determined by the fungus' pathogenicity and the host's immunological responsiveness (Koutsouras et al. 2016). Host immune defense against the pathogen in the CNS comprises microglia, endothelial cells, astrocytes, and T cells. They inhibit the fungal infection, thereby limiting the infection by interferon-γ, interleukin (IL)1β, IL6, IL12, TNF-α (i.e., chemokines) production, nitric oxide generation, superoxide anion production, major histocompatibility complex class I (MHC I), and MHC II molecular expression (Koutsouras et al. 2016; Sharma et al. 2012). In invasive cerebral candidiasis, microglial cells are the principle effector cells, and it has been reported that on intracerebral administration; it can limit infection and tissue damage (Blasi et al. 1991; Lionakis et al. 2011). Disruption of tight junction of BBB by cytokine such as TNF-α released by microglial activation has been noted The toll-like receptors (TLR) 2, 4, and 9 are able to identify fungal antigens, including *C. albicans*' pseudohyphae. TLR-2, Dectin-1, and CR-3 all recognize mannose and β-glucans, which are present on the surface of *C. albicans*, as well as on Aspergillus fumigatus, respectively (Koutsouras et al. 2016). The ability of microglia to generate pro-inflammatory cytokines when exposed to the pathogen, however, may be diminished by these carbohydrates attenuating TLR-mediated NF-κB activation (Shah et al. 2009). *Candida* spp. produces biofilm which is protective, as it helps to evade the host defense such as phagocytosis, cytokines, and nitric oxide by microglial cells (Koutsouras et al. 2016).

Numerous single-nucleotide polymorphisms, known as SNPs, in immune-associated genes, appear to be linked to an increased vulnerability to invasive candidiasis. Independent risk factor for the development of systemic risk factor was homozygosity for the dysfunctional CX3CR1-M280 allele that resulted in dysfunctional monocyte signaling and survival (Collar et al. 2018; Lionakis et al. 2013). Additional variables that are linked to an increased likelihood of invasive yeast infections include a malfunctioning CXCR1-T276 allele, which impairs degranulation of neutrophils, SNPs inCD58, TAGAP genes, LCE4A-C1orf68 locus, and also SNP mutations in mannose-binding lectin genes. Nevertheless, not all of the aforementioned variables particularly raise the likelihood of candidiasis of the central nervous system (Kumar et al. 2014; Swamydas et al. 2016; van Till et al. 2008). The molecule whose deficiency leads to profound susceptibility to neurocandidiasis is CARD9, a myeloid-expressed signaling adaptor protein (Lionakis et al. 2017). These conclusions are supported by numerous cases that authors have described (Drewniak et al. 2013; Gavino et al. 2014; Glocker et al. 2009; Herbst et al. 2015; Jones et al. 2016).

12.3 Pathology, Risk Factors, and Clinical Manifestations of Neuro-Candidiasis

Primary candidiasis of central nervous system although uncommon is reported to be around 18–52% of disseminated candidiasis (Jain et al. 2007). Susceptibility rate further increases in neonates, where 66% of the newborns with disseminated candidiasis and 80% with *Candida* endocarditis have CNS involvement (Drummond and Lionakis 2018; Góralska et al. 2018). Unrecognized infection of CNS has been estimated in 6% of patients with disseminated candidiasis (Shankar et al. 2007). Risk factors for CNS invasion by *Candida* (Table 12.2) include neonates [LBW/premature] or recent neurosurgery, patients with CNS shunts or catheters, other devices, neutropenia associated with AIDS/diabetes/hematological

Table 12.2 Spectrum of neuro-candidiasis

Neuro-candidiasis	Remarks
Epidemiological distribution	• Human commensal • Worldwide, global
Risk factors/clinical setting	• Abdominal surgery/post-op • Children • Elderly • Hospital setting • Intravenous (IV) catheters/prolonged IV therapy • IV drug abusers • Neutropenic • Preterm neonates • Prolonged broad-spectrum antimicrobial therapy • Total parenteral nutrition
Transmission	• Blood–brain barrier crossing—Transcellular • Direct access—Intracranial devices • Hematogenous—Disseminated candidiasis • Nosocomial—Neurosurgery, neurological devices • Oropharynx/urogenital
Clinical spectrum	• Aseptic meningitis • Chronic meningitis • Diffuse cerebritis along with microabscesses • Fever that is unresponsive to broad-spectrum drugs • Granulomatous vasculitis • Meningoencephalitis • Mental status alterations • Mycotic aneurysms • Ventriculitis
Microbiological analysis	• Budding-yeast-like-cells with or without pseudohyphae • Cerebrospinal fluid culture, analysis
Primary treatment	• Amphotericin B lipid formulation
Secondary treatment	• Amphotericin B deoxycholate • Echinocandins • Fluconazole • Flucytosine • Voriconazole

malignancies/extensive wounds like burns, prolonged use of steroids in high doses, and graft vs. host disease after bone marrow transplantation (Barton et al. 2014).

Candida has predilection for microcirculation particularly in the middle cerebral artery facilitated by its small size results in multiple cerebral microabscesses and leptomeningitis; however, it can also cause aneurysms and thrombosis of microvessels, cerebral vasculitis, and intracerebral or subarachnoid hemorrhage (Sánchez et al. 2000). Primary focus of infection in disseminated candidiasis is mostly lung/respiratory system or gastrointestinal system [GIT] from where it spreads (Kullberg and Arendrup 2015). Dissemination is favored either when impairment of immune system in conditions like AIDS, newborns, organ transplants, hematological malignancies, prolonged corticosteroids therapy, or after interventions like neurosurgical procedures, placement of shunts, catheters surgery (Barton et al. 2014; Cesaro et al. 2017; Katragkou et al. 2017; Kullberg and Arendrup 2015; Neves et al. 2014; O'Brien et al. 2011).

CNS candidiasis often has varied clinical presentations, meningoencephalitis being the most common others being meningitis, brain abscesses, and ventriculitis. Some more infrequent clinical presentation reported are endophthalmitis, intraventricular fungus balls, hydrocephalus, vasculitis, calcifications, cranial neuropathies, numerous cerebral abscesses accompanied by nodular enhancing lesions, or by ring enhancements, and stroke sequelae in a small number of cases (Huang et al. 1998; Katragkou et al. 2017; McCarthy et al. 2017; Pappas et al. 2016; Shankar et al. 2007).

The symptoms of *Candida* meningitis are neck rigidity, fever, and headache-altered mental status which are also similar to acute or chronic bacterial meningitis. However, signs and symptoms may be subtle in neonates and severely neutropenic/immunosuppressed individuals. Neonates particularly preterm neonates are considered a very high-risk group for developing invasive candidiasis and subsequently neuro-candidiasis. It is reported that 25% of newborn with birth weight < 1.5 kg develop systemic candidiasis and CNS invasion is seen in 50% of the neonates with disseminated candidiasis with a fatality rate of 70% (Baradkar et al. 2009; Faix and Chapman 2003; Lewis et al. 2015; Murthy and Sundaram 2014; Sánchez et al. 2000; Yoshida et al. 2022). Overall mortality from neuro-candidiasis varies between 10 and 30% (Sánchez et al. 2000). Disseminated candidiasis risk factors include certain surgical procedures, extended hospital stay, intubation (endotracheal), neonates with Apgar scores of below 5, parental lipids, prolonged catheterization, and total parental feeding (Lewis et al. 2015). Additionally, as a result the commensal *Candida* species' receptive translocation from the GIT into the bloodstream during necrotizing enterocolitis of newborns is a significant determinant of subsequent disseminated candidiasis occurrence (Barton et al. 2014; Huang et al. 1998).

12.4 Diagnosis

Patients experiencing CNS manifestations involving any or all of the signs/symptoms listed below should have neurological candida infection suspected (Sánchez et al. 2000):

- A *Candida* species isolated in the cerebrospinal fluid (CSF).
- *Candida* isolation from a different, typically sterile location among patients with pleocytosis as detected by CSF biochemistries (Table 12.3). Finding *Candida* species in blood cultures is helpful, but candidemia may not be documented in patients with *Candida* meningitis.
- Inadequate response to treatment for suspected mycobacterial or bacterial meningitis.

12.4.1 CSF Analysis

For establishing a confirmatory diagnosis of CNS candidiasis, obtaining CSF for analysis and culture by lumbar puncture is essential. Around 80% of cases reveal positive cultures. Regardless of whether other microorganisms are found, a positive cerebrospinal fluid culture should not be regarded as a contamination, especially in patients with compromised immunity (Sánchez et al. 2000).

The CSF findings are also variable in patients with neurosurgery-related *Candida* meningitis. Some have a neutrophilic pleocytosis similar to that seen in bacterial meningitis (Nguyen and Yu 1995), whereas others have a lymphocytic predominance (Sánchez et al. 2000).

Those with chronic meningitis have a harder time being diagnosed since there is only a minimal pathogen count, and the routine CSF cultures produce poorer results. In patients with chronic *Candida* meningitis, large-volume (10 to 20 mL) spinal taps are frequently necessary to collect enough CSF for culture. The microbiology laboratory should be asked to culture the entire sample or to filter the sample through a Millipore filter and culture the filter on appropriate media.

The cell wall of several fungi, notably *Candida* species, contains 1,3-beta-D-glucan (Fig. 12.1). Several commercial assays are available that detect serum beta-D-glucan. Positivity of the assays indicates toward an invasive fungal infection including invasive candidiasis. Importantly, this test can be positive in the setting of many different fungal infections, and cutoffs to define positivity in CSF are not defined. Test results must therefore be interpreted with caution.

12.4.2 Neuroimaging

In central nervous system candidiasis, neuroradiological abnormalities are frequently nonspecific and are frequently mistaken for meningitis due to Mycobacterial tuberculosis, or are misinterpreted as CNS tumors, or pyogenic abscesses (Jain et al.

Table 12.3 Laboratory techniques to diagnose neuro-candidiasis

Laboratory techniques	Comments
API20C and API32C biochemical assays	–
BactiCard Candida test	–
Cerebrospinal fluid (CSF) biochemistry	• Glucose—May be slightly decreased • Leukocytes—100 s per microliter (mononuclear cell predominance) • Opening pressure—May be increased (>150 mmH_2O) • Protein—Increased (>1000 mg per dL)
CHROMagar	–
Cultures	• CSF culture • Blood culture
Direct microscopy/histopathology	• Potassium hydroxide mount • Periodic acid–Schiff • Grocott methenamine silver stain • Calcofluor staining • Hematoxylin and eosin stain of fixed tissue
Germ tube formation	–
Gram stain, lactophenol cotton blue (LPCB) wet mount, etc.	–
In situ hybridization	• *C. albicans* peptide nucleic acid fluorescence in situ hybridization test
Matrix-associated laser desorption/ionization time-of-flight mass spectrometry	–
Molecular methods	• Polymerase chain reaction • DNA probe-based assays
Murex *C. albicans* test	–
Neuroimaging	–
Sabouraud's dextrose agar, cornmeal agar, etc.	–
Serology	Antibody detection • Agglutination and complement fixation tests • Enzyme-linked immunosorbent assay • Fluorescent antibody tests • Radioimmunoassay Antigen detection • Cytoplasmic antigens • Enolase assay • Glycoproteins • Candida mannan assay • Proteinase • Candida heat labile antigen assay • D-arabinitol assay • (1, 3) β-D-glucan assay
T2 Candida panel	Direct blood test to identify *C. albicans/krusei/glabrata/parapsilosis/tropicalis*

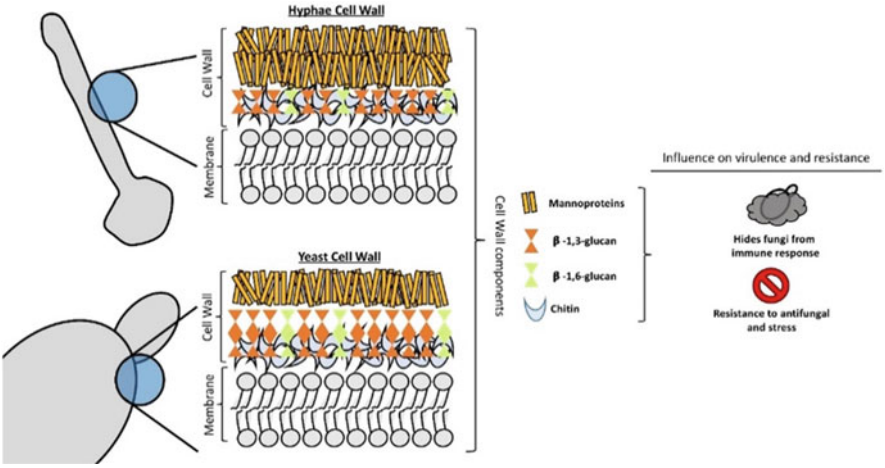

Fig. 12.1 Basic structure of Candida cell wall. (*Image source: Frontiers in Microbiology: Volume 10* (Garcia-Rubio et al. 2020)—*Copyright restrictions: none; this image is from an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY) and thus free of any copyright restriction)*

2007). Microabscesses found at the grey–white junction, cerebellum, and basal ganglia are the most frequent pathologic finding, followed by meningitis and macro-abscesses (Pendlebury et al. 1989; Sánchez et al. 2000). Computed tomography (CT) can detect hydrocephalus, which is particularly common in patients with infected CNS shunts (Chiou et al. 1994; Sánchez-Portocarrero et al. 1994). However, the CT scan is often normal and may not detect microabscesses (Pendlebury et al. 1989; Sánchez et al. 2000). In comparison, magnetic resonance imaging (MRI) can detect microabscesses, which appear as multiple, small, enhanced ring lesions, sometimes with a hemorrhagic component (Lai et al. 1997). MRI scans may be utilized to monitor the effectiveness of antifungal medications whenever these types of lesions are present.

12.5 Treatment

The most thoroughly researched medication for the medical management of neurological candidiasis is amphotericin B deoxycholate; however, optimal treatment evaluation through a randomized controlled trial is still lacking (Geers and Gordon 1999; Nguyen and Yu 1995; Pappas et al. 2016; Sánchez et al. 2000; Voice et al. 1994). In comparison to amphotericin B lipid complex, 5 mg/kg intravenously, daily, liposomal amphotericin B may produce higher CNS concentrations (Groll et al. 2000). After a positive response to lipid amphotericin B is achieved, either with or without flucytosine (5-FC), fluconazole is advised to serve as a step-down regimen. 5-FC is administered 4 times a day to individuals having normalized

kidney functions, at an oral dosage of 25 mg/kg. Treatment ought to be maintained for several weeks to months till resolution of CNS manifestations, CSF anomalies, and radiological clearing has taken place. The specialists advise that contaminated ventricular devices be removed (Alothman et al. 2014).

In neonates, amphotericin B deoxycholate (1.0 mg/kg IV once daily) is the formulation used. Neonates tolerate the deoxycholate formulation better than adults, and there is little experience using the lipid formulations in this group (Fernandez et al. 2000; van den Anker et al. 1995). Flucytosine is not recommended because adverse effects are frequent in neonates (Benjamin et al. 2006).

12.5.1 Duration

Antifungal treatment ought to be continued till any abscess(es), if present at presentation, have cleared on MRI, the patient's clinical symptoms/signs have disappeared, and CSF cell counts (pleocytosis), glucose levels, protein concentration, and CSF culture have normalized. The aforementioned steps could take weeks or months to complete, particularly in those suffering from chronic *Candida* meningitis.

There are no data available concerning the frequency of testing, but the following approach seems reasonable:

- Repeat MRI scans for patients with brain abscesses are advised to be done after 2 weeks (or sooner if their condition is deteriorating) and then every month till the abscess clears up.
- In order to confirm that all CSF alterations are reverting to normal as well as that CSF cultures will remain negative, lumbar punctures should be performed weekly during the initial few weeks, in acute meningitis cases.
- For patients with chronic meningitis, lumbar puncture should be repeated as for acute meningitis. The best parameters to follow are the CSF white cell count and protein and glucose concentrations. A negative CSF culture is insufficient to assess treatment response since the microorganism exists in low quantities and routine CSF cultures of CSF provide poor yields (Voice et al. 1994).

Patients who have cerebral abscesses, are markedly immunocompromised, or have chronic *Candida* meningitis need longer courses of therapy, and patients who have infected ventricular shunts or implantable CNS devices must have the device removed to achieve cure for the infection (Chiou et al. 1994; Nguyen and Yu 1995; Pappas et al. 2016; Sánchez-Portocarrero et al. 1994).

If at all possible, infected CNS devices such as chemotherapy delivery biopolymer wafers, prosthetic reconstructive devices, shunts, stimulators, and ventriculostomy drains should be removed. In those with a ventricular device that is impractical to remove, amphotericin B deoxycholate may be injected directly into the ventricle via the device (Pappas et al. 2016).

Adjuvant immune therapies, particularly for CARD9-deficient individuals reported by some authors, are abnormalities in GM-CSF seen in myeloid cells

with the p.Y91H CARD9 mutation, corrected by recombinant GM-CSF, and the use of GM-CSF therapy to rectify cytokine (IL-17) production errors in p.Q295X-mutant CARD9-deficient patients (Celmeli et al. 2016; Gavino et al. 2014, 2016).

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