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Review

Infections of the central nervous system by *Candida*

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At present, the species of *Candida* are the increasing causes of infections in neutropenic and non neutropenic patients, and they enable the production of important morbimortality. Invasive candidiasis is the most frequent opportunistic mycosis and when there is central nervous system (CNS) involvement, mortality associated to mycosis increase. Unfortunately, studies based in autopsies prove that the prevalence of CNS disease by fungi is undervalued in clinical practice. The clinical presentation includes meningitis, microabscesses, macroabscesses, vascular and medullar injury. The initial symptoms of acute meningitis by *Candida* are indistinguishable from those produced by bacterial infection and its diagnosis requires a high level of suspicion in the cases of isolation of *Candida* in cerebrospinal fluid (CSF), in any sterile liquid in patients with pleocytosis in the CSF or in blood cultures and when there is no improvement of clinical condition in spite of proper treatment. Clinical evidence, although limited, suggests that the combination of antifungals produces faster CSF sterilization when compared to mono-therapy. Regrettably, in spite of appropriate treatment, the mortality associated with this entity is of 10 to 30% and the percentage of neurological sequels goes from 18 to 29% which highlights the importance of timely recognition and management of *Candida* related CNS infections.

Key words: *Candida*, central nervous system infections.

INTRODUCTION

At present, the species of *Candida* are the increasing causes of infections in neutropenic and non neutropenic patients, and they enable the production of important morbimortality (Richardson et al., 2008; Cannon et al., 2009; Denning et al., 2010; Zarrin et al., 2010). Every time, invasive candidiasis is more common, with a yearly incidence from 72 to 228 cases per million, being opportunistic with the mycosis that is more frequent (Bodey et al., 1992; Berger et al., 2002) with a tendency to increase diseases caused by non-albicans species that are probably associated with routine use of fluconazole. Consequently, it changes the resistance profile acquired by them (Montagna et al., 2009). When there is central nervous system (CNS) involvement, mortality associated with mycosis increases (Venditti, 2009; Edwards, 1995); unfortunately, studies based in autopsies prove that the prevalence of CNS disease by fungi is underestimated in clinical practice (Ostrosky Zeichner, 2007).

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EPIDEMIOLOGY

The first case of meningitis by *Candida* was described in 1933 (Espinel-Ingroff, 1996). Most of CNS infectious caused by species of Candida involve meninges (Oyesiku et al., 1999); however, intraparenchymatous abscesses can occur, which tend to be small and multiple as part of an invasive disease in an immunocompromised host, associated or not with meningitis. In few cases they are solitary or epidural (Edwards, 1995; Pappas et al., 2009). Although less frequent, it is possible to show vascular effects (Burgert et al., 1995) and medullar compromise (Bonomo et al., 1996; Eileen et al., 2008).

Meningitis by *Candida* can be seen in three scenarios:

1. Manifestation of disseminated candidiasis (premature infants).

2. Ventricular drainage devices infections.
3. Chronic isolated meningitis.

These kinds of presentation are directly related to microorganism access into the CNS, through the bloodstream (Zarrin et al., 2009) or associated to craniotomy procedures and devices implantation (Richardson et al., 2008; Chakrabarti, 2007; Pfaller et al., 2006).

Most of these infections have been associated with *Candida albicans* (Zarrin et al., 2010; Hooper, 1988; Nguyen et al., 1996), but actually *Candida parapsilosis* and *Candida tropicalis* are also isolated. Unusual cases are owed to *Candida glabrata* (Shankar et al., 2007). These infections caused by non albicans species, are frequently related to resistance to antifungals and higher mortality (Pfaller et al., 1998; Parker et al., 1981).

As happens with systemic infections by *Candida* species, CNS involvement occurs mainly in predisposed individuals, and in critically ill patients, or patients with congenital or acquired defects in the immune system, who have required the recent use of broad spectrum antibiotics, intravenous drug abusers, premature infants and patients that had neurosurgery (Richardson et al., 2008; Montagna et al., 2009; Edwards, 1995; Harou et al., 2010; Chimelli et al., 1997). However in 10% of the cases, a correlated risk factor is not possibly identified; it is believed that in these patients, meningitis by *Candida* is the first manifestation of a latent chronic granulomatous disease (Edwards, 1995).

Approximately half the patients with candidemia have CNS involvement (Zarrin et al., 2010); fungus ranks fourth among microorganisms responsible for septic settings (Edwards, 1995; Wisplinghoff et al., 2004; Richet et al., 2002; Marchetti et al., 2004) and second in brain abscesses on bone marrow transplant patients (Harou et al., 2010).

PATHOPHYSIOLOGY

Little is known about the histopathology lesions caused by *Candida* in CNS; autopsy studies prove that supratentorial region is the most affected area, with largest compromise of grey matter and cortex deepest layers, where arterioles are more curved and tortuous (Harou et al., 2010).

When systemic candidiasis becomes evident with diffuse encephalopathy and consciousness impairment, the predominant lesions are intraparenchymatous microabscesses (Edwards, 1995); these usually are located at grey and white matter joint, in disseminated manner, basal ganglia and cerebellum being the most frequently affected sites. Injuries are characterized by a necrotic background surrounded by polymorphonuclears making up a non-caseating granuloma containing yeasts and hyphae. In some cases, immunosuppression may not be present. The severity of disease and its chronicity depends upon the amount of inoculum (Edwards, 1995).

Macroabscesses, vascular lesions and leptomeningeal invasion, are sometimes found (Edwards, 1995). There is a variable latency time between an invasion of the CNS by species of *Candida* and the appearance of symptomatic disease.

CLINICAL MANIFESTATION

The initial symptoms of acute meningitis by *Candida* are indistinguishable from those produced by bacterial infection (Vazquez et al., 2003), most frequent report are (Richardson et al., 2008):

1. Fever
2. Headache
3. Neck stiffness
4. Mental status impairment

A first manifestation of this entity can be decrease in consciousness, which can be masked in a critically sick patient's context, by the use of sedative medications (Edwards, 1995).

However, meningitis by *Candida* generally has a sub-acute onset (Edwards, 1995) and presents itself in a similar manner to *Cryptococcus* or the tuberculous bacillus CNS infections. Its main symptoms are headache, neck stiffness and fever, but also they manifest vomiting, visual alterations, paralysis of cranial nerves and confusion (Voice et al., 1994). In patients infected by the human immunodeficiency virus (HIV), headache and fever can be the unique symptoms; in general they have CD4 counts of 135 /mm^3 or less (Sanchez Portocarrero et al., 2000) and their clinical course often does not relate to oropharyngeal affection (Casado et al., 1997). The meningeal involvement can also be isolated, like chronic meningitis affecting the base of the skull or associated to microabscesses (Edwards, 1995).

At times, fever can be the only clinical sign but in others the multi-organic involvement predominates; patients with microabscesses can be present with encephalopathy at onset and those with hematogenous dissemination can have ocular, heart, cutaneous and renal compromise.

Microabscesses by *Candida* are often small (<3 mm), multiple and clinically, patients present a fluctuating unfocalized encephalopathy (Edwards, 1995); in initial studies, its diagnosis was made only post-mortem because in these cases, computerized tomography (CT) and lumbar puncture are usually normal (Moyer et al., 1993). This suffers important changes with use of new images techniques such as nuclear magnetic resonance imaging (MRI).

The presence of macroabscesses by *Candida* is unusual and they have been described both in patients

without immune system impairment and in those with severe immunosuppression; most of these lesions have been seen in parietal-occipital regions and they are exceptionally found in the cerebellum (Edwards, 1995). Clinically, they behave as space occupying lesions generating convulsions and neurological focal signs.

Pachymeningitis with progressive involvement of cranial pairs can also occur (Edwards, 1995; Burgert et al., 1995).

The CNS infections by *Candida* associated with devices, usually happen months after the surgical procedure, probably due to secondary colonization; frequently cause dysfunction of the system that generates hydrocephalus and alteration of consciousness without signs of meningeal compromise (Edwards, 1995); Usually these patients have a recent history of bacterial meningitis, antibiotic therapy and a lot of surgeries of CNS, they can happen even after surgical exploration of the mastoid region (Lipton et al., 1984) and abdominal complications, specifically perforation of the gastro intestinal tract (Nguyen et al., 1995; Sanchez Portocarrero et al., 1994).

Vascular manifestations related to neuroinfection by *Candida* appear in 25% of the patients (Edwards, 1995; Burgert et al., 1995). Ischemic lesions mainly occur in basal ganglia, which cause neurological transient or permanent deficit; although in cases of endocarditis by *Candida*, cerebral mycotic aneurysms have been reported (Edwards, 1995). The described vascular lesions can be the initial step for the formation of an abscess.

Two studies based on postmortem examination of patients with neuroinfection by *Candida* describe myocardial and valvular cardiac involvement in 80% of the cases (Moyer et al., 1993; Sanchez Portocarrero et al., 1993).

Occasionally, there are subdural granulomas by Candida, myelitis and exceptionally syringomyelia secondary to chronic arachnoiditis at the level of the spinal cord (Burgert et al., 1995).

DIAGNOSIS

CNS infection by *Candida* should be suspected in every patient with neurological symptoms and signs presenting with one or more of the following:

1. Isolation of *Candida* in cerebrospinal fluid (CSF).
2. Isolation of *Candida* in any sterile liquid in patient with pleocytosis in the CSF.
3. Isolation of *Candida* in blood cultures. Although growth in blood is not demonstrated in all the patients with meningitis by this fungus, it had been estimated that only 25% of patients show candidemia simultaneously (Chadwick et al., 1980).
4. Lack of response in cases of bacterial or tuberculous meningitis in spite of being under suitable treatment.

The study of the CSF is mandatory in every patient with suspicion of CNS infection (Richardson et al., 2008). The cytochemical, the direct microscopy study, and the cultures themselves must be studied carefully (Sanchez Portocarrero et al., 2000). In typical cases, there was found pleocytosis, decrease of glucose and increase of proteins, but at times the white cell count can be normal; culture positivity had been estimated at 80%, and for that reason it must never be interpreted as simple contamination (Eileen et al., 2008). Exceptionally, the cytochemistry can be completely normal and the culture positive. Patients that went to neurosurgery present variable findings with neutrophilic or lymphocytic leukocytosis (Edwards, 1995). These infections are frequently poly-microbial (*Candida* associated with bacteria). Bear in mind that fungal infection booster up the levels of adenosine deaminase in CSF, similar to what happens in tuberculous meningitis (Bayer et al., 1976) and that the cerebral biopsies are only beneficial in the presence of macroabscesses.

In order to guarantee crop yield, adequate sampling technique and fast processing should be ensured, and the crops must never be refrigerated (Sanchez Portocarrero et al., 2000).

To date, the use of serological studies on this condition has not been standardized; antibody testing depends directly on the immunological condition of the patient, which is why at times direct detection of antigens and metabolites is preferred, which requires seldom available specialized techniques. The use of molecular techniques such as polymerase chain reaction (PCR) is promising, but now its use is limited by cost and lack of standardization (Eileen et al., 2008; Sanchez Portocarrero et al., 2000).

Data available on the usefulness of neuroimaging in meningitis by *Candida* are few. The cranial CT (computed tomography) evidences hydrocephalus in 20% of the cases, a frequent finding in patients with infected dysfunctional devices, but it is usually normal and it does not detect the presence of microabscesses, although it does detect macroabscesses and determines its extension. On the other hand, MRI helps to better identify the presence of microabscesses, which are little, multiple, ring enhanced and sometimes with hemorrhagic component. The enhancement of the meninges is in-frequent and occasionally vascular lesions are identified, so they are tools for response follow-up when they evidence injuries on initial evaluation (Edwards, 1995; Lai et al., 1997).

In the differential diagnosis, any CNS infection will have to be considered. The following are among the main entities to identify:

1. Encephalitis by Herpes simplex (HSV).
2. Tuberculous meningitis.

3. Chronic bacterial meningitis.
4. Infection by *Cryptococcus neoformans*
5. Aspergillosis.
6. Infection for *Coccidioides immitis*
7. Infection by *Histoplasma capsulatum.*
8. Sepsis of any origin.
9. Infectious endocarditis.
10. Syphilis.
11. Chronic subdural hematoma.
12. Carcinomatous meningitis.

TREATMENT

The standard treatment involves the combination of amphotericin B and flucytosine (Cannon et al., 2009; Pappas et al., 2009) given the fungicide qualities of amphotericin B, which covers against the different species of *Candida*, but since Amphotericin B has low CSF and cerebral tissue penetration ability, flucytosine is added on account of its very good availability in CNS and in antifungal activity (Pappas et al., 2009; Smego et al., 1984).

To date only *Candida krusei* presents some resistance to flucytosine, and *C. glabrata*, *C. lusitaniae* and *C. krusei* may prove to be more resistant to the action of the amphotericin B (Pappas et al., 2009).

Clinical evidence, although limited, suggests that compared to monotherapy, combining antifungal regimens results in faster CSF normalization (Ostrosky, 2008).

The use of liposomal amphotericin B in intravenous doses of 3 to 5 mg/kg is favored (Groll et al., 2000; Linden et al., 1999) for its better pharmacokinetic profile, *Candida* CNS eradication ability, and tolerance in adults, with minor potential of nephrotoxicity (Wingard et al., 2002; Bates et al., 2001), associated or not to flucytosine (100 mg/kg d divided in 4 doses in patients with normal renal function), taking special care in the serum levels of the later to avoid the medullar toxicity. Control lumbar puncture should be made 1 to 2 weeks after the beginning of therapy to demonstrate the reduction in the cell count and negative culture.

The intrathecal amphotericin B, in doses from 0.01 to 1 mg day, has also been used in this entity with contradictory results, specifically in patients with poor response or intolerance to intravenous therapy. Its administration is not exempt from risks and the main adverse effects are headache, fever, radicular pain, paralysis of cranial nerves, myelopathy, fallen foot, abdominal pain, alteration of sphincters and visual changes; its presence requires a reduced dose of medication. It has been said that concomitant administration of cortisone may reduce the risk of chemical meningitis and the correlated arachnoiditis (Gurses et al., 1996).

The use of a starting Fluconazole monotherapy has shown variable responses (Gurses et al., 1996) in spite of its good CNS penetration (Arndt et al., 1988); for that reason, it is recommended only after several weeks of standard intravenous treatment, in doses from 400 to 800 mg (6 to 12 mg/kg) oral, per day (Pappas et al., 2009) or as initial treatment if the use of the amphotericin B is contraindicated (Pappas et al., 2009). Successful treatments with a combination of fluconazole and flucytosine have been reported in a few patients (Marret al., 1994).

Voriconazole has also good availability in CSF and brain tissue (Lutsar et al., 2003) and it is active against most of the species of *Candida,* however, clinical experience is limited. It could be useful after initial treatment with amphotericin B, mainly in cases of unusual infections caused by *C. glabrata* or by *C krusei.* The use of Posaconazole is not indicated, granted that it does not penetrate the blood brain barrier (Torres et al., 2005) and therefore does not play any role on this type of infection (Pappas et al., 2009).

Caspofungin and other echinocandins do not attain suitable concentrations in the CSF to treat meningitis by *Candida* and they should not be used in CNS infections (Pappas et al., 2009; Prabhu et al., 2004). Some reports exist however where the use of these antimycotics proves to be effective from refractory neurocandidiasis (Liu et al., 2004).

The treatment should continue until resolution of abscesses show in MRI, normalization of the CSF becomes evident, and the patient has no symptoms (Pappas et al., 2009). MRI and control lumbar puncture frequency is not established, but it is considered prudent to accomplish the first controls two weeks after the start of the antifungal therapy or before if there is clinical deterioration; Periodicity must be individualized. The best follow-up parameters are given by the cytochemical of the CSF.

Patients with intracerebral abscesses and chronic meningitis require more extended courses of treatment; In case of associated devices, these should also be withdrawn supplementing the antifungal treatment, which can also be provided through the device before withdrawal (Pappas et al., 2009).

The suppressing therapy for long term is indicated in HIV patients.

Hypoglycorrhachia below 35 mg/dl, development of endocranial hypertension and neurological focal deficit are deemed criteria of poor prognosis (Porter et al., 1996).

Mortality associated to this entity has estimated to be between 30 and 53% in small series of cases (Denning et al., 2010; Nguyen et al., 1995; Sanchez Portocarrero et al., 1994; Gudlaugsson, 2003). Others report mortality between 80 and 97% in patients with candidemia with CNS involvement (Harou et al., 2010). After routine amphotericin B treatment, these percentages have decreased and mortality has been reported between 10 and

30% in patients receiving adequate treatment (Richardson et al., 2008; Edwards, 1995). Unfortunately, the percentage of neurological sequels is 18 to 29% (Amy et al., 2010).

CONCLUSION

At present, there is an increased incidence of invasive mycoses affecting the CNS, causing important morbimortality in neutropenic and non neutropenic patients; among them, neurocandidiasis is the most frequent opportunistic entity, with widely varying expressions, and its timely treatment, its outcome, and its long-term prognosis shall rest upon clinical suspicion.

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