Cryptococcus neoformans (CrN) infection is the most common infection of the central nervous system (CNS) in immunocompromised patients. This group comprises many patients with HIV/AIDS and some with chronic diseases on long-term corticosteroid therapy. In the first group, the infection has an incidence of 5-8% when the account of CD4 T lymphocytes is less than 500 cel/µL (1). It also represents the third cause of infection following HIV encephalitis and toxoplasmosis. The fungus is acquired by inhalation. The homogeneous dissemination of lung lesions or reactivation compromises the CNS. Clinically, the infection reveals itself as meningitis or meningoencephalitis (2).

The objective of this paper is to review the different ways in which CNS cryptococcosis is present in images in immunocompromised patients and to review the bibliography about this subject.

The fungus: Cryptococcus neoformans

Cryptococcus is composed of two pathogenic strains, neoformans and gattii. The former is a fungus of universal geographic distribution with an ample habitat. It is found in fecal matter and nests of doves or other type of birds. There are two varieties of this fungus, grubii and neoformans, corresponding to serotypes A and D. Serotype A is responsible for most cases of disseminated cryptococcosis associated with HIV/AIDS in South America. The gattii species is predominant in tropical and subtropical areas corres-
ponding to serotypes B and C. There is also a hybrid AD (3, 4, 5, 6).

All the varieties mentioned have a capsule of polysaccharides. Thanks to this particular characteristic, they were given the name of sugar-coated killer yeast (7). The capsule inhibits phagocytosis and the formation of antibodies conditioning the inflammatory effects in infections of the CNS, which will depend also upon the immune state of the host (8). (Figure 1)

Symptoms can be grouped according to the semiology of:

- Meningitis: the patient has fever, headaches and lack of energy. A third of the patients suffer from stiff neck and dazzled vision.

- Encephalitis: characterized by lethargy, alteration of conscience, personality disorders and loss of memory.

Approximately 50% of patients with disseminated infection suffer from pulmonary pathologies with coughing, dyspnea and skin lesions (2). In the lumbar puncture, the cerebrospinal fluid (CSF) has an increased level of proteins, a normal or low level of glucose, a minimum quantity of lymphocytes and multiple micro-organisms. Pressure of lumbar puncture is elevated (>20cm/H2O) in 75% of cases. Definite diagnosis is established through the observation of encapsulated yeast in the direct microscopic study or through a direct contrast of CSF with diluted Chinese Ink. It throws a positive result in 80% of cases. It can also be established through agglutination of latex particles or ELISA (9, 10, 11). CNS infections caused by cryptococcus neoformans have a high morbidity including neurologic sequela with hydrocephalus, convulsions, insanity, motor or sensitive deficiency. The morbidity varies from 30 to 65% in countries like Brazil and Argentina (12).

Findings and Patterns in Neuroimages

The study of this group of patients with contrast CT can be disappointing. Findings, when evidenced, have low sensitivity and specificity. The use of MRI with Gadolinium injection is recommended, especially in those patients with HIV/AIDS with a recount of CD4 T lymphocytes is less than 200 cel/µL (13). CT and MRI signs can be grouped into the following patterns:

a) Communicating hydrocephalus. It is one of the most frequent findings, but the least specific. (Figure 2)

b) Parenchymatous cryptococcus or miliary nodules. They correspond to small nodules caused by a granulomatous reaction in the brain parenchyma. Generally, they are located in the perivascular Virchow–Robin Spaces (VRS) at the basal ganglia, thalamus, and subcortical region level. They are hyper-intense in T2 and can be surrounded by vasogenic edema, with little contrast enhancement of a punctiform or lineal aspect. (Figure 3)

c) Gelatin pseudo-cysts in basal ganglia. It corresponds to the dilation of VRS due to the accumulation of gelatin produced by the encapsulated yeast. They contribute to giving an aspect of soap bubbles. This pattern is characteristic although it is not frequent. In MRI, they are seen hypo-intense in T1 and hyperintense in T2, without restriction in diffusion sequences or contrast enhancement. (Figure 3)

d) Intraventricular. It is an exceptional pattern and it simulates a racemose neurocysticercosis. Multiple in-
traventricular gelatin cysts, without contrast enhancement, and obstructive hydrocephalus can be seen. (Figure 5)
e) Meningoencephalitis. Infrequent form that can appear as hyperintense areas in T2 related to local edema and leptomeningeal enhancement in post-contrast phase (2). This pattern, published in the bibliography, was not identified in this study.

Fig. 2: 40-year-old male patient with HIV/AIDS and cryptococcal meningitis.
CT images of the skull with ev contrast. Note the hydrocephalus and the absence of meningeal enhancement.

Fig. 3: 36-year-old male patient with HIV/AIDS and cryptococcomas.
MRI images: A) FLAIR axial view, B) and C) T1 axial views with Gadolinium. Note multiple hyperintense focal lesions in FLAIR, with punctiform and lineal enhancement of cryptococcomas located in the VRS of the basal and subcortical region of the brain (white arrows).

Fig. 4: 35-year-old male patient with HIV/AIDS and gelatin pseudo-cysts due to cryptococcus neoformans.
A and B) T2 axial views, C) T2 coronal view, D) FLAIR axial view, E) diffusion and F) T1 axial view with Gadolinium. Note the gelatin pseudo-cysts in dented nuclei, mesencephalon and thalamus (white arrows) and in the basal ganglia (pointed white arrows). Also, note the absence of expression in diffusion sequences and in enhancement through contrast agents.
The international bibliography about CNS Cryptococcosis in immunologically compromised patients show normal results in various percentages, although they are always elevated. In our practice, suspected cases of CNS Cryptococcus neoformans infections are studied first of all with CT when there are neurological symptoms. The objective of this clinical practice algorithm is to detect signs of intracranial hypertension, before lumbar puncture. It makes it possible to make a quick diagnosis and treatment. The use of MRI is restricted to detect concomitant lesions or in some particular situations like bad clinical evolution or due to academic reasons.

In this experience, out of 22 patients who suffered from HIV/AIDS with CNS cryptococcosis, 70% of the CT exams with contrast were normal. In some series, normal exams go from 46 to 50%, and other authors express that there are brain lesions only in 5% of cases (8, 14, 15). The administration of a double contrast doses in CT does not improve the results mentioned above (16).

CT and MRI effectiveness in a series of 13 HIV/AIDS patients with CNS Cryptococcosis with a histopathology correlation showed the underestimation of findings in images. None of them showed imaging signs of meningitis (enhancement of the meningeal membranes). In addition, it helped to prove that there is a greater sensitivity of MRI over CT for the identification of cryptococcomas and gelatin pseudo-cysts (14, 15, 17).

Gelatin granulomas and cysts caused by cryptococcus neoformans can persist in CT and MRI images, with or without calcification, 5 years after the patient's recovery and after the appropriate response to antifungal treatment (18).

Immunocompetent patients show an enhancement of meningeal and parenchymatous lesions mentioned in CT and MRI studies. The literature also describes the following patterns in images:

- Pseudo cysts in basal and periventricular ganglia with diffusion restriction due to high cellularity and dense pus, annular enhancement and serious surrounding vasogenic edema, similar to brain abscess (19).
- Intra-axial brain mass with heterogeneous enhancement and surrounding vasogenic edema, with or without central calcification. In Hydrogen Proton Spectroscopy, they have a peak of Choline, a decreased N-Acetylaspartate curve and an increase of Lipids/Lactic Acid concentration. They seem tumors of a glial origin (20, 21).
- Intraventricular mass due to choroid plexitis enhanced with contrast creating a mold of part of the ventricular system, with obstructive hydrocephalus and periventricular edema (22, 23).
- Calcifications and huge gelatin pseudo-cyst surrounding the brain stem (24).
- Intraventricular cysts simulating a racemose neurocysticercosis (25).

So, taking into account the immunological state of the patient, the conclusion is that in the HIV/AIDS population, the recount of CD4 T lymphocytes has a direct relationship with enhancement of CNS lesions. A slight inflammatory reaction was identified in the histopathological study of autopsy in 45 patients with HIV/AIDS and CNS cryptococcosis (26). The fewer the quantity of these
lymphocytes the less inflammatory reaction there will be and less uptake of the contrast agent in CT and MRI.

**Differential Diagnosis**

The dilation of VRS originated by the presence of gelatin pseudo-cysts must be differentiated from other entities. These include: a) anatomic variations, b) mucopolysaccharidoses and c) vesicular state of neurocysticercosis. Cryptococcomas must be differentiated from other infectious granulomas, like those caused by tuberculosis and lesions in basal ganglia toxoplasmosis, pyogenic abscess and lymphoma (2, 27).

**Treatment**

The treatment for cryptococcal meningitis consists in the intravenous administration of liposomal amphotericin B or lipid complex amphotericin B and oral administration of flucytosine. The selective lumbar-peritoneal derivations or transitory lumbar drainage can be effective to control a persistent increase of CSF pressure (more than 25 cm/H2O). Surgical treatment is indicated in the resection of cryptococcomas measuring more than 3 cm with mass effect and ventricular derivations in symptomatic hydrocephalus (28, 29, 30).

**Conclusion**

A low percentage of patients have characteristic imaging patterns of Cryptococcus Neoformans meningitis in immunocompromised patients. MRI studies facilitate their identification. Although the CT has low sensitivity, it is the initial study when there is clinical suspicion prior to the performance of a diagnostic lumbar puncture.

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