



Magnetic resonance imaging findings in AIDS patients with central nervous system cryptococcosis

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Summary Cryptococcosis is an opportunistic fungal infection caused by *Cryptococcus neoformans*. Generally, the disease affects the central nervous system, especially in patients with human immunodeficiency virus infection. Central nervous system involvement can be either meningeal or parenchymal. As the infection spreads along the Virchow-Robin spaces these structures may dilate with the mucoid and gelatinous material produced by the organism's capsule. The lesions associated with the dilatation of Virchow-Robin spaces are referred to as gelatinous pseudocysts. Bigger lesions are known as cryptococcomas. In this article we describe five patients with neurocryptococcosis associated with AIDS and parenchymal lesions compatible with gelatinous pseudocysts and cryptococcomas.

Key words *Cryptococcus neoformans*, Neuroimages, Cryptococcomas, Gelatinous pseudocysts, AIDS, Virchow-Robin spaces

Hallazgos en las imágenes por resonancia magnética en pacientes con sida y neurocriptococosis

Resumen La criptococosis es una micosis oportunista causada por *Cryptococcus neoformans*. Por lo general compromete el sistema nervioso central de individuos inmunodeprimidos, en especial aquellos con infección por el virus de la inmunodeficiencia humana. A nivel del sistema nervioso central puede comprometer las meninges o el parénquima encefálico. Como la infección se disemina a través de los espacios de Virchow-Robin, éstos pueden dilatarse por efecto del material gelatinoso que produce la cápsula del microorganismo. Estas lesiones se denominan "seudoquistes gelatinosos" y aquellas de mayor tamaño reciben el nombre de "criptococomas". En este trabajo, se presentan cinco pacientes con diagnóstico de neurocriptococosis asociada a sida, y presencia de lesiones cerebrales parenquimatosas compatibles con seudoquistes gelatinosos o criptococomas.

Palabras clave *Cryptococcus neoformans*, Neuroimágenes, Criptococomas, Pseudoquistes gelatinosos, Sida, Espacios de Virchow-Robin

Cryptococcus neoformans is the most frequent opportunistic fungal infection that involves the central nervous system (CNS) in patients with advanced HIV/AIDS disease and in other immunocompromised patients

(corticosteroid therapy, lymphomas, solid organ transplant recipients, chemotherapy). The most common clinical form of neurocryptococcosis is the diffuse meningoencephalitis that presents with fever and headache in the majority of AIDS patients. Less frequently, patients may also present meningeal signs, confusion, seizures, vision loss due to papilledema and, rarely, focal neurological deficit [6,12].

The meningeal infection typically affects the basal brain and may also involve the adjacent parenchyma or may extend along the Virchow-Robin spaces [1]. In some patients with cryptococcal meningitis, the neuroimaging studies show the presence of cryptococcomas and "gelatinous pseudocysts" [14].

We report five patients with advanced HIV/AIDS disease and cryptococcosis of the CNS, with unusual imaging findings, rarely described in the past for this kind of patients.

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Patients and Methods

We analyzed retrospectively the epidemiological, clinical, microbiological, immunological and the neuroimaging findings in five patients with AIDS associated CNS cryptococcosis. The diagnosis of meningeal cryptococcosis was made based on findings in the cerebrospinal fluid (CSF) after lumbar puncture, India ink test and cultures. The polysaccharide cryptococcal capsular antigen in the CSF was detected by latex agglutination. The fungi were visualized with the India ink test and the organism was isolated in cultures. Blood cultures by lysis centrifugation and CD4 T-cell counts were obtained in all cases. Magnetic resonance imaging (MRI) was performed in all cases.

Results

All patients were men; the mean of age was 34.6 years (range 30-42 years). The risk factor for HIV infection was intravenous drug use (IVDU) in 2 patients and unprotected sexual contact in the other 3. Headache and fever were the most common symptoms and were present in all the patients. Lumbar puncture showed increased CSF pressure in all the cases. Mild to moderate pleocytosis and elevated protein levels were detected in 4 patients. India ink test and CSF cultures were positive in all cases. The levels of polysaccharide capsular antigen titers in CSF correlated with the severity of the disease. *C. neoformans* was detected in blood from three of the five patients (60%). The mean CD4 T cell count at the time of diagnosis of neurocryptococcosis was 84 cells/ μ l (range 22 to 139 cells/ μ l).

MRI showed multiple and bilateral hypointense T1 and hyperintense T2 lesions located relatively symmetrically in the basal ganglia and the periventricular white matter with mild perilesional edema and without mass effect in all the patients. In addition, in two patients, MRI revealed the presence of large lesions compatible with cryptococcomas. MRI spectroscopy performed with the voxel in the lesion demonstrated decrease in N-acetyl-aspartate (NAA), slight increase of the choline (Cho) peak

and presence of lipids and, in some cases, presence of lactic acid. The epidemiological, clinical, mycological, immunological and the neuroimaging findings are summarized in table 1.

Discussion

Cryptococcosis is a disease caused by *C. neoformans*, an encapsulated yeast that in most cases affects AIDS patients. Less frequently, it has been found in other immunocompromised patients and also eventually in HIV-negative patients [4]. *C. neoformans* is the third most common intracranial pathogen in AIDS patients, only surpassed by HIV itself and *Toxoplasma gondii*. In AIDS patients, cryptococcal infection generally manifests as meningoencephalitis or disseminated disease. In a Brazilian series of 96 patients with cryptococcosis confirmed by clinical and laboratorial diagnosis, cryptococcal meningoencephalitis was detected in 56.3% of cases [3].

CNS involvement is secondary to haematogenous spread, and usually results from a reactivation of a prior pulmonary infection [13]. The basal meninges of the brain are particularly affected; in the meninges, the organism appears to be suspended in a mucoid material derived from the capsule of *C. neoformans*. Meningeal infection may involve the brain parenchyma or may extend along the Virchow-Robin spaces [1,14]. Virchow-Robin are perivascular spaces at the level of the thalamus, basal ganglia, periventricular white matter and the cerebellum [3,8]. As *C. neoformans* spreads along these spaces, the perivascular spaces may dilate with the mucoid gelatinous material produced by the capsule of the fungus [5,11,14,16] (Figure 1). In these cases, neuroimaging studies show multiple and small, round or oval lesions in the basal ganglia, thalami nucleus and periventricular white matter, hypointense in T1 and hyperintense in T2-weighted [14] (Figure 2). On diffusion-weighted images, there may be restricted diffusion in some of the lesions due to the high viscosity of their contents. These cysts are also named as "gelatinous pseudocysts" or "soap bubble lesions", and they do not enhance with the gadolinium [10,12]. MRI spectroscopy performed with a single voxel in the lesion demonstrated

Table 1. Epidemiological, clinical, mycological, immunological and neuroimaging findings in five patients with cryptococcosis

	Age	Risk factor	CD4	Blood		CSF			MRI	
				BC	Ag	Protein and cells	India Ink	Culture		Capsular antigen
1	36	Unprotected sexual contact	139	+	1/1000	Elevated protein level and mononuclear pleocytosis	+	+	1/1000	Bilateral and perivascular lesions, hypointense on T1 and hyperintense on T2
2	42	Unprotected sexual contact	22	-	1/1000	Elevated protein level and mononuclear pleocytosis	+	+	1/5000	"Gelatinous pseudocysts" and dilatation of perivascular spaces of periventricular white matter
3	30	IVDU	116	+	NA	Normal	+	+	1/1000	Cryptococcoma and bilaterally periventricular lesions, hypointense on T1 and hyperintense on T2 and FLAIR
4	35	IVDU	33	+	1/10000	Elevated protein level and mononuclear pleocytosis	+	+	1/1000	Cryptococcoma and bilaterally basal ganglia lesions
5	30	Unprotected sexual contact	110	NA	+	Mononuclear pleocytosis	+	+	1/10	Bilateral basal ganglia and periventricular lesions

IVDU: Intravenous Drug Use, BC: blood culture, Ag: blood antigen, NA: not applicable

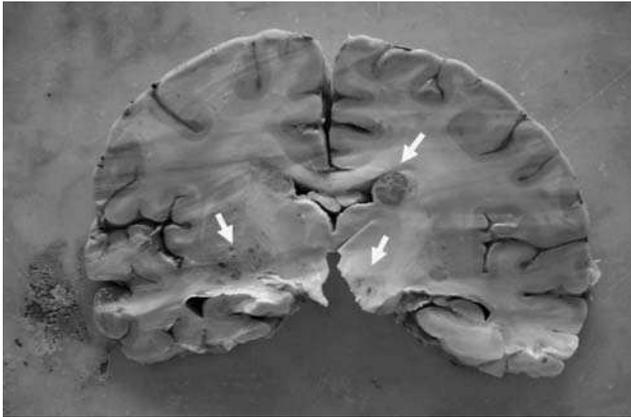


Figure 1. Cerebral cortex showing a cryptococcoma and gelatinous pseudocysts due to the dilatation of Virchow-Robin spaces by the mucoid material produced by the capsule of the fungus (arrows).

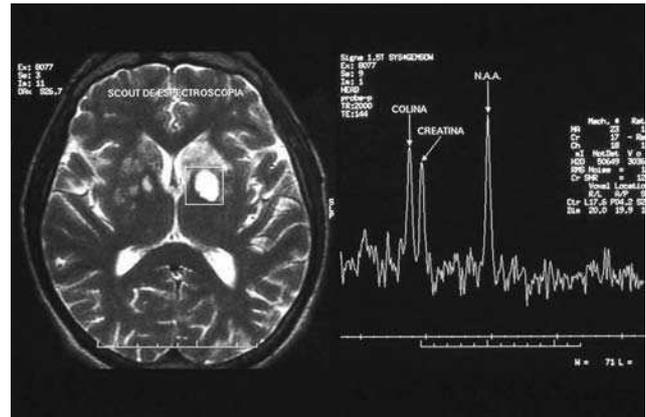


Figure 3. MRI spectroscopy with the voxel in the lesion evidence a focal inflammatory process with deficit of N-acetyl-aspartate (NAA), a small increased in the peak of choline (Cho).

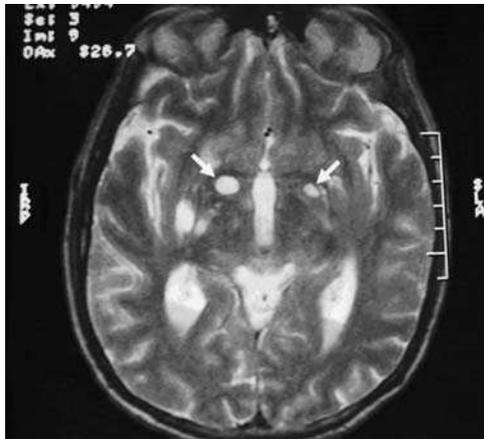


Figure 2. MRI-T2-weighted showing multiple and small hyperintense lesions in the basal ganglia, thalami nucleus and periventricular white matter (arrows).

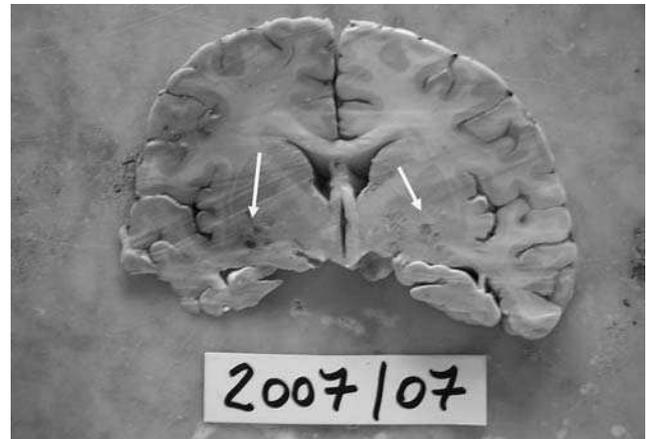


Figure 4. Cerebral cortex: dilatation of Virchow-Robin spaces filled with fungi in the basal ganglia in correlation with MRI findings (arrows).

biochemical changes compatible with a focal inflammatory process (figure 3). In some cases, MRI showed a mixed pattern including dilated of Virchow-Robin spaces filled with mucoid material, gelatinous pseudocysts in the basal ganglia and disseminated parenchymal and leptomeningeal nodules [2,9]. In a previous study by Tien et al (4) autopsies of three patients revealed dilated Virchow-Robin spaces filled with fungi in the basal ganglia that correlated with the described MRI findings. Those findings are in accordance with our findings in one of our patients (figure 4).

In conclusion, cystic lesions in the basal ganglia consistent with cryptococcal invasion of the Virchow-Robin spaces may help the diagnosis of cryptococcal meningoencephalitis. These lesions reflect the pathological mechanism of invasion by the fungus and, in our point of view, may be specific, to some extent, for the diagnosis of neurocryptococcosis [7,15]. Therefore, cryptococcosis should be considered in the differential diagnosis in any immunocompromised patient with dilated Virchow-Robin spaces [8].

References

1. Cornell SH, Jacoby CG. The varied computed tomographic appearance of intracranial cryptococcosis. *Radiology* 1982; 143: 703-707.
2. Corti ME, Villafañe MF, Palmieri OJ. Fungal opportunistic infections. In: Corti ME, Villafañe MF, Palmieri OJ, eds. *Atlas of neuroimages and neuropathology of the HIV/AIDS disease*. 1ª ed. Buenos Aires, 2007. p 29-35.
3. de Aquino Moreira T, Simao Ferreira M, Marques Ribas R, Borges AS. Cryptococose: estudo clinico-epidemiológico, laboratorial e das variedades do fungo em 96 pacientes. *Rev Soc Bras Med Trop* 2006; 39: 255-258.
4. Diamond RD, Bennett JE. Prognostic factors in cryptococcal meningitis: a study in 111 cases. *Ann Intern Med* 1974; 80: 176-181.
5. Everett BA, Kusske JA, Rush JL, Pribram HW. Cryptococcal infection of the central nervous system. *Surg Neurol* 1978; 9: 157-163.
6. Harris DE, Enterline DS. Fungal infections of the central nervous system. *Neuroimaging Clin N Am* 1997; 7: 297-320.
7. Kumazawa K, Yamada T, Nakamori T, Hoshino A, Terao S, Mitsuma T. Serial MRI findings in patients with CNS cryptococcosis. *Rinsho Shinkeigaku* 1998; 38: 831-837.
8. Kwee RM, Kwee TC. Virchow-Robin spaces at MR imaging. *Radiographics* 2007; 27: 1071-1086.
9. Mathews VP, Alo PI, Glass JD, Kumar AJ, Mc Arthur JC. AIDS-related CNS cryptococcosis: radiologic-pathologic correlation. *Am J Neuroradiol* 1992; 13: 1477-1486.
10. Offiah CE, Turnbull IW. The imaging appearances of intracranial CNS infections in adult HIV and AIDS patients. *Clin Radiol* 2006; 61: 393-401.
11. Ruiz A, Post MJ, Bundschu CC. Dentate nuclei involvement in AIDS patients with CNS cryptococcosis: imaging findings with pathologic correlation. *J Comput Assist Tomogr* 1997; 21: 175-182.
12. Saigal G, Donovan Post J, Lolayekar S, Murtaza A. Unusual presentation of central nervous system cryptococcal infection in an immunocompetent patient. *Am J Neuroradiol* 2005; 26: 2522-2526.
13. Subramanian S, Mathai D. Clinical manifestations and management of cryptococcal infection. *J Postgrad Med* 2005; 51: S21-S26.
14. Tien RD, Chu PK, Hessellink JR, Duberg A, Wiley C. Intracranial cryptococcosis in immunocompromised patients: CT and MR findings in 29 cases. *Am J Neuroradiol* 1991; 12: 283-289.
15. Ueda H, Toribe Y, Kuwae Y, Takeuchi M, Nakayama M, Ida S. An autopsy case of cryptococcal meningoencephalitis: correlation of MRI and pathologic findings. *No To Hattasu* 2003; 35: 499-504.
16. When SM, Heinz ER, Burger PC, Boyko OB. Dilated Virchow-Robin spaces in cryptococcal meningitis associated with AIDS: CT and MR findings. *J Comput Assist Tomogr* 1989; 13: 756-762.