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Central Nervous System Involvement in Patients with AIDS-Associated Histoplasmosis

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ABSTRACT

Central Nervous System (CNS) histoplasmosis is a rare manifestation of the *Histoplasma capsulatum* infections, often misdiagnosed due to the wide spectrum of neurological presentation. CNS histoplasmosis occurred most often in immunocompromised individuals, but some patients were previously, healthy. The diagnosis can be established by culture and antigen and antibody testing of the cerebrospinal fluid. Treatment with liposomal Amphotericin B (AMB-L) followed by itraconazole, is recommended for the majority of patients.

Here we describe the epidemiology, clinical presentation, diagnosis and follow up of a short series of 4 patients with AIDS who developed disseminated histoplasmosis with CNS involvement.

INTRODUCTION

Central Nervous System (CNS) histoplasmosis is a severe complication of acute or subacute disseminated or chronic progressive disease in patients with deterioration of the cellular immune response [1-3]. Involvement of the CNS by *Histoplasma capsulatum* in AIDS account only 5% to 10% of these patients and it is not easy to recognize and diagnose because its clinical presentation is unspecific and may mimic other more common etiologies [4,5].

Involvement of CNS in AIDS-associated histoplasmosis is uncommon [6]; the objective of this manuscript is to present 4 cases of CNS histoplasmosis in HIV-infected patients.

MATERIAL AND METHODS

The epidemiological, clinical, and microbiological characteristics of 4 AIDS patients with Central Nervous System (CNS) involvement caused by *Histoplasma capsulatum* were retrospectively analyzed. We performed this retrospective and descriptive study in a single center specialized in infectious diseases in Buenos Aires, Argentina. CNS histoplasmosis cases were identified retrospectively by reviewing clinical, microbiology and reference laboratory records from January 2005 to July 2019. Clinical and neurological examinations were performed in every patient included in this study. All of them displayed neurological symptoms or signs during the physical examination and showed no contraindications for undergoing a lumbar puncture. All the samples of Cerebrospinal Fluid (CSF) were evaluated for white blood cell counts, protein level and glucose level and were analyzed searching for bacteria, mycobacteria, fungi, parasites, neuroherpes virus and JC virus. Anti *Histoplasma*

capsulatum antibodies were looked for in CSF and serum samples by the immunodiffusion and contra-immunoelectrophoresis techniques in all patients. India ink wet mount observation and culture in Sabouraud and Brain Heart Infusion Agar at 28 and 37° were included in the mycological exam of the CFS samples. Blood cultures were performed by the Lysis-Centrifugation (LC) technique. CD4 + T cell counts and plasma viral load for HIV were made for all the patients. Computed Tomography (CT) scan of the brain was available from the four patients.

Additionally a research for cases published in the literature was performed.

RESULTS

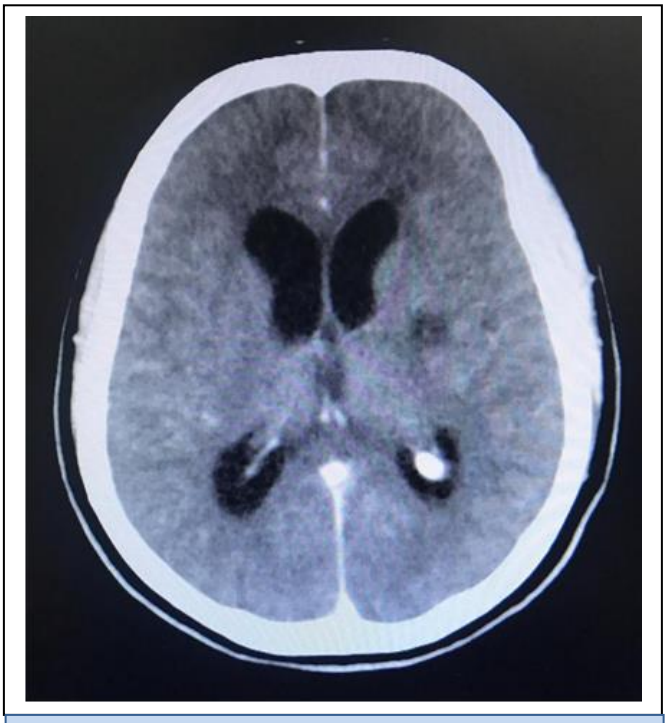

Figure 1: CT scan of the brain showing a hypodense mass lesion on the left hemisphere and ventricular enlargement.

During the time of the clinical study 435 cases of Disseminated Histoplasmosis (DH) in patients with AIDS were identified. Only 4 of them had proven CNS histoplasmosis, with an incidence of 1%. The mean age was 39 years and 3 were female. One of them was from Paraguay; 2 of them had HIV diagnosis less than a year before. Seventy per cent were on Highly Active Antiretroviral Therapy (HAART) and 2 of them had HIV undetectable plasma viral load. All patients had CD4-T-cell counts less than 150 cells/µL. Fever, headache, sensory engagement and stick neck were the most frequent clinical findings. No patient had oral mucosa or cutaneous lesions. Two patients had previous history of disseminated histoplasmosis and were under antifungal maintenance therapy with itraconazole and HAART. Laboratory abnormalities included anemia, thrombocytopenia and accelerated erythrocyte sedimentation rate. Computed Tomography (CT) scan of the brain revealed mass lesions and ventricular enlargement in 2 cases (Figure 1) and diffuse edema in the other 2 patients.

Table 1: Clinical, immunological characteristics and cerebrospinal fluid findings in a series of 4 patients with CNS involvement due to *Histoplasma capsulatum*.

	Patient 1	Patient 2	Patient 3	Patient 4
LT-CD4+ (cells/µL)	20	112	109	116
HIV viral load	Not available	Not available	Undetectable	Undetectable
HAART	Yes	No	Yes	Yes
CSF (protein mg/dL/glucose g/L/cells µL)	0,7/23/80	1,2/30/45	3,7/11/10	2,94/19/200
Brain CT	Diffuse edema	Diffuse edema	Ventricular enlargement and mass lesion	Ventricular enlargement and mass lesion
Chest-X-Ray	Miliary pattern	Normal	Normal	Normal
Direct examination of CSF	Negative	Negative	Negative	Negative
CSF culture	Positive	Positive	Positive	Positive
Blood culture	Positive	Negative	Negative	Negative
Serum antibodies	Negative	Negative	Positive	Positive
CSF antibodies	Negative	Negative	Negative	Positive
Outcome	Death	Survival	Death	Death

Everyone had abnormal CSF parameters, including hyperproteinorrachia, hypoglycorrhachia and lymphocytic pleocytosis. Chest X ray was found normal in 3 patients; one of them presented miliary pattern on radiography. Those who were undetectable have no evidence of non-CNS organ involvement. Direct examination of CSF was negative in all cases. Diagnosis was confirmed by positive culture of CSF in 100% of patients. Blood culture by LC was positive in only one

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case. Histoplasmosis serum serology was positive in 2 patients (50%, one of them had undetectable HIV plasma viral load and his CD4-T-cell count was 109 cells/μL). CSF antibodies detection was positive in only one patient (25%). Initially these four patients were treated with antituberculous drugs with initial diagnosis of tuberculosis meningoencephalitis. Later, all patients were treated with amphotericin B plus fluconazole. Three patients died during the first month of therapy. Only one survived in a good clinical condition. Clinical, immunological status and CSF findings are summarized in table 1.

DISCUSSION

Fungal organisms can cause infections of the CNS; the most commonly of these include *Cryptococcus neoformans* and less frequent *Aspergillus* species. In AIDS patients, *Cryptococcus neoformans* is the most frequent cause of diffuse meningoencephalitis [7]. CSF involvement in patients with disseminated histoplasmosis may be seen in only 5 to 10% of cases, with the most common manifestation being meningitis. In our series, only 4 AIDS patients with CNS involvement caused by *Histoplasma capsulatum* from January 2005 to July 2019 (1%) reflects an incidence below that described in the literature. This lower incidence could be explained for the fact that the majority of patients do not usually present signs or symptoms that make suspected CNS involvement. Also, Nyalakonda H et al [6] identified only 5 cases from 2004 to 2014 of CNS histoplasmosis in a single institution. Other manifestations of CNS infection include encephalitis, myelopathy, and solitary mass-like lesion or abscess resembling neoplasms. Patients may also present as infarcts or small microabscesses secondary to septic emboli from endocarditis [7-9]. There are few reports of Histoplasmosis associated brain abscesses; all cases were caused by *Histoplasma capsulatum* var. *capsulatum*. Recently, Konan L et al [10] report the unique case of brain abscess caused by *H. capsulatum* var. *duboisii* in an AIDS patient.

Immunosuppression is the major risk factor for the development of CNS disease including immunocompromised patients in the setting of advanced HIV/AIDS disease, solid organ transplant, stem cell transplant and the use of immunosuppressive agents, especially high doses of corticosteroids [9].

CNS histoplasmosis include 4 clinical forms: 1) isolated subacute or chronic meningitis without other manifestation of the disease; 2) sub acute or chronic meningitis with other locations of histoplasmosis; 3) focal brain lesions, named as histoplasmomas of the CNS; 4) acute encephalitis during the course of the acute disseminated forms of histoplasmosis, associated with multi-organ failure and high mortality, in patients with severe immunocompromised [11,12]. Other clinical forms include the acute or subacute myelitis and the neuroradiculits [13,14].

More than 50% of cases are chronic or subacute meningitis with a clear cerebrospinal fluid with hyperproteinorrachy, hypoglucorrachy and a pleocytosis with a lymphomononuclear predominance in more than 80% of patients [3,13]. Clinically is a typical basal meningitis with frequent involvement of oculomotor cranial nerves (II, IV and VI). Fever, chronic headache and cranial nerve palsy are the most frequent clinical manifestations. Meningeal syndrome is present in only 10% of patients [15,16].

In every case, it is important to detect other locations of histoplasmosis. In 60% of cases, the chest X-ray can show focal or disseminated infiltrates. However, in our series, only one patient showed a lung compromise with a miliary pattern in the chest X-ray. This finding could be explained for the fact of being reactivations of previous infections in patients with advanced HIV/AIDS disease. Abdominal ultrasonography or computed tomography scan can reveal hepatosplenomegaly, adrenal involvement and lymphadenopathy conglomerates [3,17].

CSF studies include the direct examination and cultures. Direct examination is generally negative and the gold standard for confirming a diagnosis of CNS histoplasmosis is CSF culture [18,19]. CSF culture has a low sensitivity for detecting *Histoplasma* and culture growth may take several weeks, potentially delaying diagnosis and treatment selection. A recent multicenter retrospective study showed that the sensitivity for CNS culture was 19%, the specificity was 100%, and the positive predictive value was 100% [18]. However, in our series, all patients had positive CSF cultures for Histoplasma, much higher than the usual low sensitivity of this assay. The quantity and volume of CSF smears, increases the positive culture results [18-20]. In the chronic disseminated forms the antibody detection is a very important test. But in the sub acute disseminated clinical forms of the disease that we generally see in HIV/AIDS patients, this is just positive in less

than 30% of cases, probably due to the severe immunodeficiency of these patients. Histoplasmosis serum serology was positive in 2 patients of our series (50%). CSF methods to detect antibodies against *H. capsulatum* are positive in more than 70% of cases. CSF antibodies detection was positive in only one patient of our series (25%). Antigen detection in CSF is positive in more than 90% of patients with CNS histoplasmosis [21,22]. It would be very useful to have some technique to detect histoplasma antigen in CSF, but now it is validated only in urine samples.

Stereotactic brain biopsy it's just useful in cases of focal brain lesions (histoplasmomas of the CNS) [10,14,17,23].

Current and recommended antifungal treatment strategy included the use of Amphotericin B (AMB) and itraconazole. Treatment with liposomal amphotericin B (AMB-L) for at least 1 month; followed by itraconazole for a year is associated with a good clinical response and survival [5,7]. Survival is best among patients treated initially with amphotericin B, and was highest with AMB-L or deoxycholate, compared with amphotericin B lipid complex [5]. The best triazolic antifungal drug for continued treatment is uncertain. Experimental studies demonstrated that fluconazole, which achieves excellent concentration in the CSF, was inferior to itraconazole, despite his inadequate CSF penetration. It is interesting to highlight that 2 of the patients included in our series were receiving itraconazole when developing the clinical manifestations of CNS involvement. Patients should be followed for relapse for at least 1 year, after stopping therapy [5]. Wheat et al [5] showed a relapse rate of 6% of surviving patients followed for at least one year. Mortality is higher in immunocompromised patients, as we can see in our series. Early started on HAART can modify the poor prognosis of this kind of patients.

CONCLUSION

In conclusion, although CNS histoplasmosis is an uncommon but severe complication of disseminated histoplasmosis, we suggest to include cerebral histoplasmosis in the differential diagnosis of CNS involvement in AIDS patients, particularly after negative microbiological studies for the more common pathogens [5-7]. We suggest to use a long induction treatment based on AMB, followed by high doses of fluconazole or voriconazole instead itraconazole for the treatment of CNS histoplasmosis due to his better concentration in CSF and the brain [24].

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