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INTRACRANIAL HISTOPLASMOSIS – A REVIEW OF LITERATURE

Neurology

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ABSTRACT

CNS infection occurs in 5 to 10% of patients with disseminated histoplasmosis. The recognition, diagnosis, and treatment of CNS histoplasmosis is not well-characterized. Over one third of cases reported, have occurred in immunocompetent individuals. Morbidity, and mortality appear to be high in patients with CNS histoplasmosis with high rates of relapse. Despite prolonged courses of treatment, the case fatality was 39% with half of the survivors relapsing in a prior study. Clinicians should have a low threshold for considering histoplasmosis as a cause for meningitis, brain lesions, vascular events, or hydrocephalus in immunocompromised, and non-immunocompromised patients who reside in endemic areas, and for whom an alternative diagnosis has not been established.

KEYWORDS

Histoplasmosis, Meningitis, H. capsulatum, Immunocompromised

INTRODUCTION –

Mycotic infections of the central nervous system are life threatening and have occurred with greater frequency since the 1970s with the increased use of corticosteroids, cytotoxic drugs, and antibiotics as well as the AIDS epidemic [1]. CNS fungal infections can take the form of meningitis, mass lesions or abscesses. Aspergillus species are the most common fungal pathogens causing intracerebral granulomas or abscesses, while Cryptococcus neoformans is the most common pathogen causing fungal meningoencephalitis [1]. CNS infection occurs in 5 to 10% of patients with disseminated histoplasmosis. The recognition, diagnosis, and treatment of CNS histoplasmosis is not well-characterized. Over one third of cases reported, have occurred in immunocompetent individuals [2]. Morbidity, and mortality appear to be high in patients with CNS histoplasmosis with high rates of relapse. Despite prolonged courses of treatment, the case fatality was 39% with half of the survivors relapsing in a prior study [2].

In a recent American study, it was found that, among AIDS patients with CNS histoplasmosis, 3 of 5 patients died, and 1 relapsed despite treatment with deoxycholate amphotericin B (AMB-D) followed by fluconazole, or itraconazole. Although adherence appears to have been suboptimal in that study, this experience shows that the outcome may be poor in some patients [3]. Clinical syndromes include subacute or chronic meningitis, focal brain or spinal cord lesions, stroke syndromes, and encephalitis. CNS involvement may be a manifestation of widely disseminated disease or an isolated illness, occurring as the initial manifestation of PDH or relapse at a "privileged" body site poorly penetrated by antifungal therapy. Often, the diagnosis is not suspected, leading to chronic, untreated infection and, in some cases, to placement of ventricular shunt for normal-pressure hydrocephalus.

Histoplasma:

Histoplasma capsulatum, a dimorphic fungus, causes histoplasmosis, a disease that is endemic in certain regions of North America and Latin America, including the Ohio and Mississippi River valleys of the United States. H. capsulatum var. duboisii causes disease in Africa. The precise reasons for the geographical distribution of histoplasmosis remain incompletely defined, but climate, moisture, and particular soil characteristics are probably important. Bird and bat droppings enhance the growth of the mycelial phase of H. capsulatum, and soil in close proximity to chicken coops and starling roosts and within caves inhabited by bats may contain high numbers of infectious microconidia [4]. Humans are infected via inhalation of airborne microconidia, which the wind can carry for miles. Activities that disturb contaminated soil, such as construction, spelunking, and dismantling of old chicken coops, increase the risk of exposure. Once in the lung, the microconidia are converted to pathogenic yeast forms that disseminate hematogenously to multiple organs, including the brain, spinal cord, and meninges [4].

Epidemiology:

Histoplasmosis is widely distributed on the South America. In Brazil, prior to the onset of acquired human immunodeficiency syndrome, histoplasmosis was rarely diagnosed and was a curiosity observed only in patients with lymphoma or other neoplasms. In the years 1980 to 1990, with the advent of HIV infection, hundreds of cases of histoplasmosis were observed among patients with the AIDS [5].

Pathogenesis:

The man acquires the infection through inhalation of the conidia present in nature. Most infections are mild or subclinical. Most inhaled conidia remain intact in the pulmonary alveoli. These antigens stimulate an inflammatory response of the host, composed of mononuclear cells [6]. H. capsulatum multiplies within the cells of the monocytic-macrophagic system. From the lungs, they gain the para-hilar and mediastinal lymph nodes. Then they reach the systemic circulation, producing inflammatory foci in other organs such as spleen and bone marrow. After the second week of the onset of infection, a lymphocyte T helper 1 cellular response is developed. This cell will produce interferon-gamma and other cytokines, which activate macrophages. These cells acquire the ability to lyse the intracellular yeasts of H. capsulatum [7]. This response promotes the formation of epithelioid granulomas, with giant cells and caseous necrosis. These factors later give way to fibrosis and calcifications. Specific antibodies are also produced in the patient's serum. However, the antibodies have no protective effect on histoplasmosis. Immunodepression seems to be another important factor in triggering the reactivation of a previous infection [6].

Disseminated Histoplasmosis:

The development of disease associated with the initial dissemination of H. capsulatum is dependent on the host. Patients who are immunosuppressed and are unable to develop effective cell-mediated immunity against the organism are likely to manifest symptomatic disease during the period of acute dissemination (Table 1) [8]. This includes patients with AIDS, transplant recipients, those with hematologic malignancies, and those on corticosteroids [9]. Infants, presumably because of the immaturity of their cell-mediated immune system, are a special group that develops severe life-threatening infection when exposed to H. capsulatum [10]. A person who develops immunosuppressive status, years after leaving the area of endemicity may reactivate a focus of infection and, through that mechanism, develop severe disseminated histoplasmosis [8].

Table1- Risk factors for disseminated histoplasmosis [8].

Risk factors for disseminated histoplasmosis
• Age (infants)
• AIDS
• Hematologic malignancies
• Solid organ transplant
• Hematopoietic stem cell transplant
• Immunosuppressive agents
• Corticosteroids
• Tumor necrosis factor antagonists
• Congenital T-cell deficiencies
• Gamma interferon receptor deficiency
• Hyperimmunoglobulin M syndrome
• Others

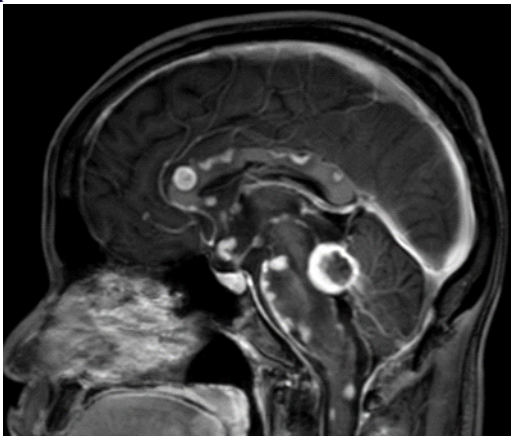
Clinical features:

Patients can have involvement of the central nervous system (CNS) either as one manifestation of a disseminated infection or as an isolated focal infection. CNS involvement occurs as a result of hematogenous dissemination to the meninges or brain. Chronic meningitis is the most common manifestation and is characterized by basilar meningeal involvement that can lead to communicating hydrocephalus. Symptoms of meningitis include headache, mental status changes, and cranial nerve palsies. Behavioral changes and ataxia also can occur [8].

Approach to Diagnosis:

With the increased use of magnetic resonance imaging (MRI) scans, it has become clear that small ring-enhancing lesions can frequently be found throughout the brain and spinal cord. We had a patient who had such ring enhancing intracranial histoplasmosis (proven on biopsy) lesions (Figure -1). These occur with meningitis or exist as isolated lesions without meningeal involvement. Larger, more typical brain abscesses can also be found [8]. The cerebrospinal fluid changes with meningitis are similar to those noted for other fungal meningitides and tuberculous meningitis. Protein is elevated, the glucose is modestly low, and white blood cells usually number between 50 and 500 cells/µl, and they are predominantly mononuclear.

Table 2- Ring enhancing histoplasma lesions in brain and spinal cord



For diagnosis of Histoplasmosis, no single test exhibits high sensitivity, which supports the use of multiple tests. Also important is the possibility of false-positive results from non–culture-based tests, including the *Histoplasma* antigen assay. Although diagnosis may be simple for patients with widely disseminated PDH—since organisms may be identified in multiple organs—difficulty occurs for those with isolated CNS involvement [11]. For such patients, positive results may only be found with testing of the CSF, meninges, or brain tissue. Several cases have been reported in which a single positive culture result was obtained from more than 10 specimens that were submitted, and the positive result was from culture of 15–43 mL of CSF. Thus, at least 10 mL of CSF should be cultured, to increase the sensitivity for isolating small numbers of yeast organisms (Table 2) [12]. Although PCR is suited for detection of low concentrations of yeast, its use in diagnosis of histoplasmosis remains uncertain, and there are no reports of using PCR for diagnosis of *Histoplasma* meningitis. Without validation of PCR by comparison with the standard methods, the accuracy of PCR findings remains unknown, and their significance for patient management remains uncertain; a positive result should not be assumed to support the diagnosis, or a negative result to exclude it [12].

Table 3- Recommendations for evaluation of suspected Histoplasma [12].

Specimen type, class of case, recommended test or procedure
CSF; all cases, repeat at least once, and preferably twice, if there is no diagnosis
Culture of a large-volume sample (110 mL)
Histoplasma antigen testing
Anti-Histoplasma antibody testing by complement fixation, beginning with undiluted CSF
Blood; all cases
Fungal culture, 3 sets
Histoplasma antigen testing, to assist in determination if CSF antigen positivity may have been caused by contamination of the CSF with blood
Anti-Histoplasma antibody testing
Urine; all cases
Histoplasma antigen testing
Biopsy of non-CNS site, if there is a clinical or laboratory finding indicating involvement at the site
Histopathologic examination for fungi
Fungal culture
Cisternal or ventricular fluid, if the diagnosis is uncertain after the performance of the evaluations above
Histopathologic examination for fungi
Fungal culture
Histoplasma antigen
Anti-Histoplasma antibody
Brain or meninges, if the diagnosis is uncertain after the performance of the evaluations above
Histopathologic examination for fungi
Fungal culture

Treatment of Histoplasma:

The response to therapy of focal brain or spinal cord lesions, so-called histoplasmomas, is variable. Such lesions may be isolated findings of disseminated histoplasmosis, may be associated with meningitis, or may complicate disseminated disease [11]. Although most cases have been treated with amphotericin B, success has been reported with itraconazole [13] or fluconazole alone, as has been failure [14]. In patients who are not severely ill, who do not have meningitis or widespread dissemination, and who have no underlying immunosuppression, a brief course of amphotericin B followed by 1 year of a triazole may suffice. After 2–4 weeks of amphotericin B treatment, MRI of the brain should be repeated. If the patient's condition responded clinically and the lesions improved, as seen on MRI, then treatment with amphotericin B could be replaced with itraconazole, 200 mg 2 or 3 times daily, or fluconazole, 600–800 mg daily. Lesions may appear to worsen during the first month of eventually successful therapy, and this does not mandate a change in the regimen [11].

One study showed caspofungin (dose was 5–10mg/kg/d) to be an effective treatment for histoplasmosis (H capsulatum in mold phase) [15]. Another study demonstrated that caspofungin at 5 to 10mg/kg twice daily did not reduce the burden of H capsulatum in yeast phase [16]. Thereby, the phase of H capsulatum might explain the differences observed between the 2 studies.

CONCLUSION –

- Clinicians should have a low threshold for considering histoplasmosis as a cause for meningitis, brain lesions, vascular events, or hydrocephalus in immunocompromised, and non-immunocompromised patients who reside in endemic areas, and for whom an alternative diagnosis has not been established.
- A diagnosis of CNS histoplasmosis can be established in a timely manner by detection of antigen, or anti- Histoplasma antibodies in the CSF. The current IDSA guidelines [17] that recommend treatment with AMB-L administered for 4 to 6 weeks followed by itraconazole for at least 1 year are supported with this study.
- Although not specifically addressed in this study, it is well known that itraconazole levels should be carefully monitored, and maintained above 1mg/ml when treating systemic fungal infections [17].

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