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Review Article

Histoplasmosis of the Central Nervous System

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Abstract Histoplasmosis of the central nervous system (CNS) is not an uncommon complication of *Histoplasma capsulatum* infection since it occurs in ∼2% to 20% of disseminated cases. CNS histoplasmosis carries a mortality rate that ranges from 11.1% to 100%, and the risk factors for dissemination to the brain have yet to be determined. Diagnosis is often difficult and time consuming, which can result in delayed initiation of treatment. The recommended treatment for CNS histoplasmosis involves a high dose liposomal amphotericin B followed by maintenance azole therapy, usually for at least a year; however no comparative trials have been performed to prove efficacy of one regimen over another. Further, prospective and in vivo studies are necessary to more effectively combat this disease.

Keywords *histoplasma*; meningitis; central nervous system infection

1 Introduction: mycotic infections of the central nervous system (CNS)

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 [7]. 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 [7]. In fact, *C. neoformans* is associated with CNS infections in ∼1 million individuals annually with a ∼60% mortality rate, especially impacting patients with HIV [33]. However, the frequency of infectious organisms causing CNS disease varies according to individual studies and in different regions of the globe. For instance, in a retrospective investigation of CNS fungal infections occurring in India from 1988 to 2004 there were 130 identifiable cases, with the three most common infections being aspergillosis ($n = 73$), zygomycosis ($n = 40$), and candidiasis ($n = 5$) [45]. A study in a Brazilian neurology ward between 1999 and 2007 documented 374 neurological infections, of which 25 (9.6%) were caused by fungal pathogens and documented as meningoencephalitis. The leading fungal pathogens causing disease were *C. neoformans* ($n = 8$) and *Histoplasma capsulatum* ($n = 6$).

2 *H. capsulatum* infections of the CNS

2.1 *H. capsulatum*, general information

H. capsulatum is a dimorphic fungus endemic to the Ohio Mississippi River valley in the United Sates and parts of Latin America, Asia, and Africa. It grows as a mycelium in soils enriched by organic nitrogen sources such as bird and bat droppings. As such, high numbers of microconidia capable of causing infection can be found near chicken coops and within caves. *H. capsulatum* causes disease in humans upon inhalation of aerosolized mycelia after disturbances of contaminated soil or droppings [16]. Within human lungs the pathogen converts to its infectious single, budding yeast form and is phagocytosed. These intracellular yeasts can subsequently be transported to any tissue in the body, including the CNS [29].

An estimated 40 million people in the United States are infected with *H. capsulatum* and patients can present with an extensive range of clinical manifestations based upon the degree of exposure and inoculum inhaled, immunological status of the host, and virulence of the infecting strain [22]. In immune-competent patients, the pathogen most commonly causes an asymptomatic infection or a self-limited lower respiratory illness. An asymptomatic course occurs anywhere from 50% to 90% of infections, while 80% of symptomatic infections are self-limiting and require no therapy [57]. According to other sources, 95–99% of primary infections are not recognized in immune-competent patients [14,21,39]. The size of the inoculum impacts disease outcome, as high inoculum exposures pose a greater risk for symptomatic or even life

threatening infections. Histoplasmosis is much less benign in immune-suppressed patients who are more likely to suffer from disseminated disease. Among HIV positive patients diagnosed with histoplasmosis, 90% or more may present with disseminated disease, the mortality rate of which can approach 80% [10,17,55].

In 2002, there were 3,370 patient discharges documented for histoplasmosis in the United States, with a mortality rate of 8% despite application of first line therapeutics [8]. In this study, 14% of infected patients were immune-compromised. A higher rate of immune-suppression was found in Venezuela where 33.5% of 158 reported cases of histoplasmosis were associated with HIV infection [26]. There was an 8.3% mortality rate among the 48 adults in this study with documented treatment with amphotericin B, amphotericin B and itraconazole, or itraconazole alone.

2.2 CNS histoplasmosis epidemiology, clinical manifestations, risk factors and selected case reports

Histoplasmosis of the central nervous system is not an uncommon presentation of *H. capsulatum*, occurring in 10% to 20% of disseminated histoplasmosis cases and in increasing frequency as a focal disease. The most common manifestation of CNS histoplasmosis is either acute or chronic meningitis [54]. Other presentations include cerebral vascular accidents as a result of septic emboli from infectious endocarditis, encephalitis, myelopathy, and solitary cerebral or spinal cord mass lesions that can resemble neoplasms [5,6,23,27,54]. Multiple pathologies, such as meningitis with miliary brain lesions [4], or chronic meningitis and meningovascular histoplasmosis resulting in stroke, acute myelopathy and chronic recurrent hydrocephalus [6], can and often do occur simultaneously.

As CNS histoplasmosis has multiple possible manifestations, there is no typical clinical picture. Instead, patient symptomatology generally reflects the underlying pathological process. For instance, mass lesions will usually result in headaches, focal deficits, seizures, and altered mental status, while meningitis presents with typical signs such as neck stiffness [38]. CNS histoplasmosis patients have been reported to present with fever, confusion, headaches, lethargy, weakness, hydrocephalus, and focal neurological deficits reminiscent of a cerebral vascular [11,58]. Clinical manifestation of CNS disease associated with disseminated histoplasmosis may differ from focal CNS involvement [41]. In Schestatsky's review of 11 immune-competent patients with isolated CNS histoplasmosis the most common symptoms included headache (81.8%), nuchal rigidity and mental status changes (45.4%), ataxia (36.4%), fever (27.3%), and cranial nerve palsies (27.3%) [41]. Headache, meningeal irritation, ataxia, and focal signs were less common in a larger study consisting of a high proportion of immune-suppressed patients [54]. In this investigation, fever was present in 80% of the patient population perhaps indicative of widespread disseminated disease.

Specific risk factors for CNS histoplasmosis remain to be determined. No studies have elucidated what factors may aid the fungus in penetrating the blood brain barrier, or what factors may place some patients at increased risk for a CNS infection. Thus, at this point in time the risk for developing CNS sequelae is related to primary infection with *H. capsulatum*. As mentioned earlier, these risk factors include immune system dysfunction, degree of exposure, and virulence of the infecting strain. As virulence factors have not yet been elucidated, immune dysfunction, particularly cellular immunity impairment, and large inoculum exposure are most significant and often go hand-in-hand. Direct iatrogenic inoculation may also play a minor role, as a CNS histoplasmosis infection after rhinoplasty has also been documented [13].

Among various epidemiologic investigations of CNS histoplasmosis, immune-suppressed patients have represented 16.7% [25], 35.3% [41], and 60% [38] of patient populations. Aside from AIDS patients, immune-suppressed patients with reported CNS manifestation of histoplasmosis include recipients of solid-organ and stem cell transplants, and patients requiring immune modulating drugs including corticosteroids and tumor necrosis factor-α antagonists [24, 37,54].

Fifty percent of all CNS infections manifest as a result of disseminated disease, the latter of which is usually a result of immune system compromise [38,51]. For example, 41% of disseminated histoplasmosis infections were associated with HIV infection in a recent Australian report [28] and 95% of tested infants with disseminated histoplasmosis were found to have low T and B cell counts [30]. As mentioned earlier, among cases of disseminated histoplasmosis, 10% to 20% result in CNS manifestations [54]. This data is supported by a 2008 Venezuelan epidemiologic study that found CNS involvement in 10 of 79 (12.7%) patients with disseminated disease [26]. Higher and lower rates of CNS involvement in disseminated disease have been described by other authors. For example, among 27 cases of disseminated histoplasmosis none involved the CNS [28], while among 40 infants with disseminated disease, 25 (62.5%) involved the CNS. Disseminated disease can also occur in the absence of immune-suppression as evidenced by a 2008 study that included 10 CNS infections in the setting of disseminated histoplasmosis in immune-competent patients [26]. The patient population within this study included 53 (33.5%) patients who suffered from AIDS, none of whom developed CNS manifestations.

The rate of CNS penetration by the fungus in disseminated disease may be higher than is seen clinically. In autopsy studies, CNS involvement was discovered in up to a quarter of patients who suffered from disseminated

disease; meaning not all patients with CNS involvement are symptomatic [54]. In earlier autopsy studies, a higher rate of CNS involvement, 6 of 11, was discovered [42].

Focal CNS involvement without evidence of disseminated disease may be the initial or secondary presentation of a previously undocumented infection in up to 50% of CNS histoplasmosis cases [2,37,58]. While focal disease may occur in immune-competent or suppressed patients, cases involving the former have garnered increased attention in the literature for their indolent course and diagnostic difficulty [41,48]. As *H. capsulatum* is generally regarded as a pathogen of the immune-suppressed, low clinical suspicion along with the relatively low sensitivity of diagnostic tests (discussed below) often leads to missed diagnoses resulting in chronic, untreated infections with high morbidity and mortality. As a result, the literature has recommended that *H. capsulatum* be considered in patients with unexplained neurological symptoms, chronic meningitis, or parenchymal lesions with unknown etiology, particularly if other infectious causes (e.g., tuberculosis and crytpococcosis) have been eliminated. A detailed history is paramount to proper diagnosis and histoplasmosis should be suspected if the patient has ever visited or lived in endemic areas as the pathogen has been shown to remain quiescent in lungs, adrenal glands and other "privileged" body sites for years before causing neurological disease [47].

H. capsulatum mass lesions most commonly take the form of miliary granulomas, occasionally with larger sized histoplasmomas [7,50]. The term histoplasmoma was defined by Shapiro et al. in 1955 as a lesion that "might attain sufficient size to suggest the presence of an intracranial neoplasm by virtue of its location, or by the production of increased intracranial pressure" [42]. On histology, a histoplasmoma may show caseating or, more commonly, non-caseating granulomas [23]. These lesions can take the form of ring-enhancing lesions on MRI [2,31], as can abscesses, although the former is a less frequent manifestation of *H. capsulatum* [32]. Focal histoplasmosis is nevertheless uncommon relative to other causes of focal neurological disease, even in the setting of HIV infection. In a review encompassing 11 studies and 629 AIDS patients with focal neurological diseases diagnosed by a stereotactic brain biopsy, only 1 patient was identified with *H. capsulatum* although 7 were identified as "mycotic" infection without specification [43]. A 2007 review of the literature identified only 27 cases of isolated histoplasmomas that presented with focal neurological signs [2]. The mortality rate identified among these 27 cases was 29.6% ($n = 8$).

CNS histoplasmosis is associated with high mortality rates even in the setting of aggressive treatment. A 1990 review indicated that CNS histoplasmosis carries a 25% mortality rate [54]. Among various case investigations the mortality rates reported ranged significantly, including reports of 11.1% ($n = 1/9$) [26], 20% ($n = 2/10$) [38], 27.3% ($n = 3/11$) [41], 100% ($n = 8/8$) [25], and 100% ($n = 4/4$) [1]. Of the two studies that included CNS histoplasmosis in immune-competent patients only, the mortality rate was still significant at 20% ($n = 4/20$) [26,41].

There are a number of case reports illustrating the difficulty of diagnosing CNS histoplasmosis in immune-competent patients whose only risk factor for disease was prior exposure [6,18,23,31,44,48,49]. We will highlight three published cases that illustrate the difficulty in diagnosis, diversity of physical manifestations, and the fact that prior exposure is the only common factor shared by these patients.

A 72-year-old male diagnosed with fibrosing alveolitis and cryptogenic cirrhosis was begun on steroids [47]. Ten months after initiating steroid therapy, the patient developed weakness and numbness bilaterally in his lower extremities with urinary incontinence, flaccid paraparesis, and areflexia. His neurological deterioration continued over several weeks and the patient expired after developing a nosocomial pneumonia. *H. capsulatum* was identified on sections of the patient's brain and adrenal glands. It was hypothesized that an indolent infection had remained quiescent in his adrenals for 38 years since his move to England from India and that the initiation of immunosuppressive therapy permitted disease reactivation leading to CNS infection. Asymptomatic adrenal involvement by *H. capsulatum* is apparent in half of autopsy cases and suggests that the adrenals may serve as a long term safe haven for the pathogen [47].

A 46-year-old female who lived in Uganda as a child presented with headaches, vomiting, meningismus, and confusion in the setting of a normal chest X-ray, brain MRI, and negative CSF cultures [46]. Based upon cerebrospinal fluid examination, the patient was presumed to have tuberculous meningitis and was treated on two different occasions with steroids and anti-tuberculosis therapy. The patient remained symptomatic and a laryngeal biopsy showed non-caseating granulomas on two separate occasions, believed to be related to sarcoidosis and treated with high dose steroids. Six years after her initial presentation, a CSF culture grew *H. capsulatum* and a re-examination of the tissue biopsy showed yeast consistent with this pathogen. Interestingly, *H. capsulatum* antibody tests were previously negative.

A 20-year-old female from Indiana presented with headache and diplopia believed to be caused by a neoplastic process due to the presence of a 0.5 cm, lesion at the thalamomesencephalic region [23,40]. The patient further developed signs of meningitis and additional neurological deficits. A diagnosis of histoplasmosis was obtained 5 months later based upon *Histoplasma* complement-fixation antibodies to cells isolated from ventricular CSF. The original surgical specimen obtained at 1 month had

shown multiple non-caseating granulomas indicative of an infectious process, but with negative fungal staining. Her only risk factor was living in an endemic area and there had been recent excavation around her home.

As briefly illustrated in the above cases, one of the issues associated with CNS histoplasmosis without concomitant disseminated disease findings is that it is often mistaken for other pathologies. Before definitive diagnosis has been reached, CNS histoplasmosis has usually been misdiagnosed and the patient treated incorrectly. Other diagnoses have included CNS vasculitis [44], neoplasm [31], tuberculosis [46], sarcoidosis [46], and normal pressure hydrocephalus. Hydrocephalus, in particular, poses a problem for CNS histoplasmosis as it often occurs before the diagnosis of meningitis is made and results in the inappropriate and possibly dangerous placement of a ventricular shunt that can become infected and facilitate chronic infection or relapse of disease [18,23,26,46,58]. To illustrate how often shunts are placed in the setting of CNS histoplasmosis, one report found that 6 of 11 immune-competent patients with focal CNS manifestations had ventricular shunts placed for hydrocephalus of uncertain etiology before the correct diagnosis of histoplasmosis was reached [41].

2.3 Diagnostic tests

The diagnosis of CNS histoplasmosis has been previously reviewed [58] and, as illustrated in the select cases above, is often extremely challenging. The review by Wheat et al. recommends performing a workup for suspected *Histoplasmosis* meningitis that at the very least includes a CSF analysis comprised of a culture of at least > 10 mL CSF with a 35 day incubation, a blood analysis including 3 cultures, and *Histoplasma* antigen and antibody testing [58]. If the initial evaluation is unrevealing, it is appropriate to repeat it at least once and consider more invasive testing via biopsy of meninges or focal lesions for histopathologic examination and culture. Utilizing different modes of antigen and antibody testing may be helpful. Because of the difficulty in diagnosis, it is not uncommon for a 2 to 6 month delay in the diagnosis of chronic meningitis [41]. Delays of up to 4 [3], 8.5 [36] and 10 years [18] have also been reported.

Despite its low sensitivity, the overall gold standard for diagnosis is identification of *H. capsulatum* by culture or identification from CSF or brain tissue [38]. The sensitivity of CSF cultures range from 27% to 65% [58]. Typical CSF findings for *Histoplasma* meningitis include an increased white cell count, elevated protein, and low glucose levels [6, 54]. However, among 10 CSF samples in a study involving immune-competent patients, 8 had a lymphocytic predominance, 8 had an elevated protein concentration, but only 2 patients had an abnormally low glucose level [41]. Within this same study, only 3 of 11 CSF cultures were positive, and none of 11 attempts at direct visualization were positive. However, in another study, 8 of 10 patients with diagnosed CNS histoplasmosis had positive CSF Giemsa staining [26].

Non-culture based methods of diagnosis include antigen and serological testing. Although there is less experience with CSF antigen detection methods, individual case reports of Histoplasma meningitis have found higher antigen levels in the CNS versus serum or urine, providing supporting evidence of antigen production within the CNS versus diffusion across the blood brain barrier [58]. The sensitivity for CSF antigen ranges from 38% to 67% in meningitis cases while urine and serum antigen sensitivities are 71% and 38%, respectively. Detection of antibodies in the CSF to *Histoplasma* has a sensitivity of 80–89% for detecting *H. capsulatum* meningitis, and the sensitivity of serum antibodies is 92% [58]. Of note, non-culture-based methods have the possibility of false positives as a result of cross-reactivity, which can decrease their specificity. Antigen testing has also aided in the early detection of relapsing CNS histoplasmosis [23] while antibody studies are less likely to help diagnose a relapse.

Among 27 cases of isolated histoplasmomas reviewed by Azizirad et al., the majority of CSF analyses showed increased protein levels without pleocytosis and only 2 of 11 attempted CSF cultures were positive. However, 20 of 22 biopsy specimens were smear positive and 11 of 12 were culture positive. The authors argue that non-invasive testing may rule out most processes causing focal neurological deficits associated with a brain lesion, but may not necessarily diagnose *H. capsulatum*. Thus, in line with other studies that support the role of brain biopsy in evaluating CNS lesions with neurological deficits, particularly in AIDS patients, aggressive strategies including neuroendoscopic evaluation for rapid diagnosis may be appropriate if clinical suspicion is high [34,43].

2.4 CNS histoplasmosis treatment

Unfortunately and unlike other forms of histoplasmosis, the response of CNS infections to antifungals is relatively poor. Further, there are limited evidence based guidelines for the management of CNS histoplasmosis as there have been no prospective investigations studying treatment outcomes and minimal in vivo studies [58]. As such, the optimal regimen remains to be determined. Current practice favors early aggressive treatment to avoid the high rate of therapeutic failure previously reported as well as maintenance therapy to avoid relapse. According to studies from 20 years ago, the treatment of *H. capsulatum* meningitis with amphotericin B alone was associated with a 20–40% mortality rate, and half of the patients who responded to treatment eventually relapsed after discontinuation [54].

The three antifungals that have been used most in the treatment of CNS histoplasmosis are amphotericin B, fluconazole, and itraconazole. In general, amphotericin B has

poor penetration into the CSF; however liposomal amphotericin B achieves higher concentrations in brain tissue compared to other formulations and is less nephrotoxic allowing higher dosing [15]. Despite this, no amphotericin B formulation achieves a detectable concentration in the CSF and no formulation has ever been shown to be superior or more efficacious than another for CNS histoplasmosis [56]. Attempts at increasing the CSF concentration of amphotericin B, such as direct injections of amphotericin B into the ventricular system, were not efficacious or well tolerated [54].

Fluconazole can attain high levels within the CSF, in excess of 70% of serum levels, as it freely crosses the blood-brain barrier [9], and it has been used in the treatment of other fungal causes of meningitis. However, fluconazole has decreased activity against *H. capsulatum*, and the organism has been known to develop resistance to it [53]. Some studies have specifically stated that they do not recommend fluconazole because of its reduced activity against *H. capsulatum* [26]. Compared to fluconazole, itraconazole has increased activity against *H. capsulatum* [27,52] but only achieves a CSF concentration of 1% of serum levels [9].

In 2002, a murine model of CNS histoplasmosis was developed in which the efficacy of amphotericin B monotherapy, fluconazole monotherapy, itraconazole monotherapy, and combined therapy (amphotericin B paired with either fluconazole or itraconazole) was compared [19]. It was found that the fungal burden in the brains of mice treated with fluconazole was higher compared to amphotericin B, and that there was no significant difference in itraconazole treatment to either amphotericin B or fluconazole. Surprisingly, combination therapy of fluconazole and amphotericin B resulted in an antagonistic effect with increased fungal burden compared to amphotericin B alone. Combination therapy with itraconazole and amphotericin B had no difference compared to amphotericin B alone. One significant flaw of this investigation was the fact that liposomal amphotericin B (the recommended treatment as discussed below) was not used.

Based upon expert opinion and the limited available data, the treatment recommendations for CNS histoplasmosis, which includes both meningitis and focal lesions, by the Infectious Disease Society of America's 2007 Guidelines for Management of Histoplasmosis include 5.0 mg/kg of liposomal amphotericin B for a total of 175 mg/kg over 4–6 weeks followed by itraconazole (200 mg 2 or 3 times daily with blood levels drawn to ensure therapeutic dosing) for at least 1 year and until resolution of CSF abnormalities [56]. Liposomal amphotericin B was chosen by the committee as the formulation of choice because of the higher concentrations attained in brain tissue compared to other formulations as stated above [15]. Fluconazole was not included in the treatment recommendations because of its reduced activity against *H. capsulatum*, and because it resulted in a higher fungal burden compared to amphotericin B in the murine model mentioned above [19]. The IDSA guidelines state that itraconazole was more effective than fluconazole in the animal model, however, this statement is not completely accurate. Although there was a decrease in the fungal burden associated with itraconazole use compared to fluconazole, it was not statistically significant ($P = .825$) [19]. Overall, these recommendations received a B-III grade, meaning there is a moderate evidence for their use as based upon respected authorities, clinical experience, and expert committees.

To illustrate the fact that the best treatment strategy remains unknown, the recommendations to treat CNS histoplasmosis in a 2005 review were slightly different from the IDSA guidelines [58]. For meningitis, the authors recommended 3–5 mg/kg/day of liposomal amphotericin B for a total of 100–150 mg/kg over 6–12 weeks, followed by a year of maintenance therapy with either fluconazole (600–800 mg daily) or 200 mg itraconazole twice or three times daily. Life-long maintenance therapy was recommended for immune-suppressed patients who had no possibility of immune reconstitution. For the treatment of histoplasmomas, the authors recommended a shorter duration of amphotericin B, 2–4 weeks, followed by a 6–12 mo course of fluconazole or itraconazole. Both recommendations concur with the IDSA on the use of liposomal amphotericin, although the duration varies, and prolonged maintenance therapy with azoles, although the earlier study includes fluconazole as an option. It should be noted that both itraconazole and fluconazole have been effectively used as maintenance therapies, and overall the rate of relapse of CNS histoplasmosis infections may be decreasing because of azole maintenance [38,41].

It is important to note that other therapeutic regimens have been successful in treating CNS histoplasmosis. For example, four of five patients treated with lower doses of amphotericin B (40 mg/kg over 8 weeks) followed by a lower dose of maintenance fluconazole (200–400 mg) for a year made a full recovery [41]. Other studies have also reported success with shorter courses of amphotericin B prior to maintenance therapy [31,36,37]. Cure has also been attained at even lower doses (1 mg/kg) of amphotericin B for 2–4 weeks followed by itraconazole [26]. In this study 7 of 7 patients treated with this regimen were cured, however, none of these patients were immune-suppressed. The use of azoles as monotherapy without prior amphotericin B has also found success in the past as has been documented previously but is not currently recommended [56]. Furthermore, individual case reports have documented success at treating CNS histoplasmosis with newer azole compounds such as voriconazole [12,20] and posaconazole [35].

3 Conclusion

CNS histoplasmosis is a deadly disease that has become increasingly documented in the literature, particularly as an isolated process among immune-competent patients. As histoplasmosis is classically considered a disease of the immune-suppressed, this poses a diagnostic challenge that can be missed. As stressed in our work, *H. capsulatum* should be considered in any patient with unexplained neurological symptoms, chronic meningitis, or parenchymal lesions with unknown etiology, particularly after a negative work up for more common pathogens of CNS pathology. While the current treatment strategy of liposomal amphotericin B followed by azole maintenance may be improving the overall mortality of this disease, the strategy remains inadequate with an unacceptable failure rate. In particular, the paucity of in vivo studies comparing available therapeutic options is unfortunate. Further investigations and development of more efficacious antifungal compounds are necessary to help treat this disease.

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