Disseminated histoplasmosis and aids: relapse and late mortality in endemic area in north-eastern Brazil

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Summary

The State of Ceará in north-eastern Brazil has one of the highest rates in the world of relapse and death due to disseminated histoplasmosis (DH) in acquired immunodeficiency syndrome (AIDS) patients. The objective of this study is to characterise the relapse and mortality of DH in AIDS cases residents in Ceará. We performed a retrospective analysis of the medical records of AIDS patients who had a first episode of DH from 2002 to 2008. We analysed the outcomes until December 31, 2010. A total of 145 patients participated in the study. The mean clinical follow-up duration was 3.38 years (SD = 2.2; 95% CI = 3.01–3.75). The majority of the subjects were male with a mean age of 35 years (SD = 2.2; 95% CI = 3.01–3.75) and were born in the capital of Ceará. DH was the first manifestation of AIDS in 59% of the patients. The relapse rate was 23.3%, with a disseminated presentation in 90% of these patients. The overall mortality during the study period was 30.2%. The majority of patients who relapsed or died had irregular treatment with antifungals or highly active antiretroviral therapy and did not have active clinical follow-up. High rates of recurrence and mortality were found in AIDS-associated DH in this area of the country.

Key words: disseminated histoplasmosis, AIDS, mortality, mycoses.

Introduction

Disseminated histoplasmosis (DH) is considered to be present when Histoplasma capsulatum is found in extrapulmonary and/or extranodal organs.1 Before the acquired immunodeficiency syndrome (AIDS) pandemic, cases of DH were rarely observed and were limited to patients with malignant haematological diseases, immunosuppression due to drug use, primary cellular immunodeficiencies,2–4 advanced age, chronic alcoholism, diabetes mellitus or in children less than 2 years of age.5,6

Currently, AIDS is the most important risk factor for DH,7 affecting predominantly male young adults due to primary acquisition or reactivation of a latent infection.7–10 The estimated incidence of histoplasmosis varies from 5% to 25% in HIV residents of endemic areas.11,12 The Ceará State in the north-east region of Brazil reports one of the largest numbers of cases of DH in the world.11

Relapses for histoplasmosis in immunodeficiency virus (HIV) patients in endemic areas of the US and Panamá occur in less than 6%,14,15 However, a preliminary study conducted in Ceará from 1999 to 2005 in patients with this co-infection indicated a relapse...
index greater than 20% during a 2-year follow-up period.16 There is no consensus regarding the suspension of secondary prophylaxis; however, clinical follow-up data have demonstrated that interruption is possible once immune recovery is achieved after highly active antiretroviral therapy (HAART).11,17–21

Mortality due to DH and AIDS is variable throughout the world and is ~10% in developed countries and ~30% in areas with limited financial resources.16,17 In the early 2000s, the mortality of the first DH episode in AIDS patients in the state of Ceará was 32.8%, with a higher figure of 47.8% if the deaths occurred in the 2-year period of follow-up.16 The purpose of this study was to better characterise the relapse and late mortality (death after the hospital discharge) of AIDS patients after the first DH episode that were followed up in the reference units of an endemic area from 2002 to 2008.

**Methods**

The medical records of AIDS patients with a first episode of DH diagnosed during hospitalisation in reference units from 2002 to 2008 were reviewed. Three public reference health units for HIV patients participated in the study: Hospital São José of Infectious Diseases (HSJ), Hospital Universitário Walter Cantidio (HUWC) and the outpatient clinic Centro de Especialidades Médicas José de Alencar, located in Fortaleza, the capital of Ceará State in north-eastern Brazil, with 2.5 million inhabitants. The HSJ is responsible for attending to 85% of the HIV patients in Ceará.

The patients were identified through a review of the laboratory records of HSJ and the Specialized Medical Mycology Center, which provides mycology laboratory support to HUWC. The study included AIDS patients who were diagnosed according to the Brazilian Ministry of Health criteria,22 males and females who were over 18 years of age and who had confirmed DH by *H. capsulatum* identification for microscopy (histology or stained smears) and/or culture.11,23 That is a common practice in AIDS patients cared for in the studied hospitals. Active clinical follow-up was considered to be at least three outpatient visits per year. The Ministry of Health of Brazil recommends clinic visits at 3–4-month intervals.

Epi-Info, version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA), was used for data entry. Parametric and non-parametric tests were performed using the software program STATA 9.0 (StataCorp LP, College Station, Texas, USA). We performed a descriptive analysis of the variables studied. The study protocol was reviewed and approved by the ethical boards of HSJ (protocol no. 029/2008) and HUWC (protocol no. 115.09.09).

**Results**

We identified 264 patients with DH and AIDS from 2002 to 2008. As 79 (30%) patients died during the first DH episode, 185 were included in the study. Of
these, 40 patients were excluded due to being cared for at another institution or because of missing records; consequently, 145 patients participated in the analysis.

Figure 1 shows the annual distribution of the patients who were followed in this study, with a mean of 38 cases per year (SD = 10). The epidemiological, laboratory, treatment and outcome characteristics are presented in Table 1. The subjects had a mean age of 35 years (SD = 8.67; 95% CI = 33.2–36.0) and the majority were males who were born in Fortaleza (the state capital) and did not have a known risk activity for histoplasmosis. DH was the first AIDS manifestation in 59% of the patients, and the mean CD4+ count at that time was 71 cells mm−3 (SD = 112.8; 95% CI = 46–94).

Amphotericin B deoxicholate was used in 97% of the patients during the first DH event. The mean cumulative dose of ABdes was 798 mg (SD = 373; 95% CI = 733–862). The mean total induction time (ABdes plus 400 mg itraconazole) was 67 days (SD = 46.8; 95% CI = 46.7–87.2). Determining the total induction time of the antifungal treatment was possible in only 23 medical records due to the lack of information concerning the itraconazole induction dose. The maintenance dose of itraconazole was better recorded, and it was initiated in 92% of the patients, only 51% of whom used it regularly.

The clinical mean follow-up time was 3.38 years (SD = 2.2; 95% CI = 3.01–3.75). Active clinical follow-up was observed in 79 (54.5%) patients. At the end of the study, 86 (59%) patients had information concerning the use of the antifungal maintenance dose. Discontinuation of the antifungal on medical advice was observed in 27 of 86 patients; the mean CD4+ count at the time of the suspension was 378 cells mm−3 (SD = 147.65; 95% CI = 317–438), and all of the patients had undetectable viral loads. The mean follow-up period after discontinuation was 2.85 years (SD = 1.47; 95% CI = 2.24–3.46) and one patient relapsed with the pulmonary form of histoplasmosis by the end of the study; this patient had a history of being lost to clinical follow-up 1 year before the diagnosis of recurrence. The remaining 59 patients continued in antifungal prophylaxis.

Of the 145 patients, 19 were lost to follow-up, with more than 12 consecutive months without a medical assessment.

**Table 1** Characteristics and outcomes of patients with disseminated histoplasmosis and AIDS, Fortaleza, Ceará, Brazil, 2002–2008.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
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<tbody>
<tr>
<td><strong>Epidemiological</strong></td>
<td></td>
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<tr>
<td>Mean age in years (SD; 95% CI)</td>
<td>35 (8.67; 33–36)</td>
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<tr>
<td>Males (%)</td>
<td>121/145 (83)</td>
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<tr>
<td>Origin – Fortaleza (%)</td>
<td>97/136* (71)</td>
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<tr>
<td>Risk activity for histoplasmosis* (%)</td>
<td>23/115* (20)</td>
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<tr>
<td>DH as the first manifestation of AIDS (%)</td>
<td>85/145 (59)</td>
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<tr>
<td><strong>Laboratory</strong></td>
<td></td>
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<tr>
<td>Mean CD4+ count in the diagnosis of DH (SD; 95% CI)</td>
<td>71 (112.85; 48–94)</td>
</tr>
<tr>
<td>Recovery CD4+ count &gt;150 cells mm−3 (%)</td>
<td>42/66* (64)</td>
</tr>
<tr>
<td>Mean CD4+ count at time of relapse (SD; 95% CI)</td>
<td>44 (50.2; 15.5–73.5)</td>
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<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Mean cumulative dose of ABdes (mg – SD; 95% CI)</td>
<td>798 (373; 733–862)</td>
</tr>
<tr>
<td>Mean time of antifungal use (induction dose) – days (SD)</td>
<td>67 (47–82)</td>
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<tr>
<td>Mean time of antifungal use (maintenance dose) – months (SD)</td>
<td>19 (10–29)</td>
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<tr>
<td>Itraconazole used in maintenance dose (%)</td>
<td>111/120* (92)</td>
</tr>
<tr>
<td>Mean time to initiation of HAART due to a DH episode (SD; 95% CI)</td>
<td>33 (40.4; 24.2–42.8)</td>
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<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td>Additional hospitalisation (%)</td>
<td>80/145 (55.2)</td>
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<tr>
<td>Relapse (%)</td>
<td>30/126* (23.3)</td>
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<tr>
<td>Relapse disseminated form (%)</td>
<td>27/30 (90.0)</td>
</tr>
<tr>
<td>Mean time of relapse – days (SD; 95% CI)</td>
<td>499 (395; 351–646)</td>
</tr>
<tr>
<td>Overall mortality (%)</td>
<td>38/126* (30.2)</td>
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<tr>
<td>Mortality due histoplasmosis (%)</td>
<td>10/126* (8.0)</td>
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*Risk activity for histoplasmosis: the patient had an occupation that was related to soil tillage (excavation, construction, demolition, or agriculture), working directly with chickens or visiting caves.

A total of nine patients has not registered about origin; b30 patients has not registered about risk activity for histoplasmosis; cOnly 66 patients has registered about recovery CD4+ count; d25 patients has not registered about antifungal use in maintenance dose; e19 patients were lost to follow-up before the end of the study.

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Figure 1 Annual distribution of disseminated histoplasmosis and AIDS, Fortaleza, Ceará, Brazil, 2002–2008.
visit until the end of the study and thus 126 patients were submitted to an analysis of the outcomes. Relapse was detected in 23.3% (30/126) of the patients, and the shortest time to relapse was 71 days. The mean time to relapse was 499 days (SD = 395.75; 95% CI = 351–646). Eighty per cent (24) of the patients had one relapse, and 20% (6) had more than one relapse. The disseminated form was observed in 27 patients (90%), and the localised form presented in three patients (two patients with involvement in the lungs and one patient with involvement in the lymph nodes). Of the patients who relapsed, 78% used antifungals irregularly, 73% had no active medical supervision and 6% were taking HAART regularly; 55% of the patients who relapsed used efavirenz (EFZ) in the HAART regimen, and, of those who had not relapsed, 53% were also taking EFZ as a part of their drug regimen. In 14 patients, the mean of the CD4+ counts at the time of relapse was 44 cell mm−3 (SD = 50.2; 95% CI = 15.5–73.5). All patients diagnosed with HIV and AIDS (59%) due to a DH episode had HAART initiated in a mean time of 33 days (SD = 40.4; 95% CI = 24.2–42.8) after the identification of the fungus. For those cases with a previous AIDS diagnosis (41%), the majority of the subjects (92%) were already using HAART, with a mean time of 1.4 years of therapy (SD = 2.5; 95% CI = 0.29–2.3). The antiretroviral regimens used by the majority of the participants were two nucleoside analogue reverse transcriptase inhibitor (NRTI) combined with EFZ (53%) or lopinavir plus ritonavir (27%). More than 60% of the patients recovered to a CD4+ count >150 cells mm−3 during the clinical follow-up period.

After discharge from the hospital following the first DH episode, 55.2% (80/145) of the patients were readmitted. Of these, 38 (47.5%) patients had one readmission after a mean time of 405 days (SD = 498.9; 95% CI = 291–519), whereas 42 (52.5%) patients required readmission more than once. The most frequent diagnoses in the first additional hospitalisation period were DH (19%), neurotoxoplasmosis (17%), presumed DH (15%), pulmonary tuberculosis (11%) and other opportunistic diseases (38%).

The 126 patients followed until the end of the study had an overall mortality of 30.2%. The mean time until death was 1.5 years (SD = 1.83; 95% CI = 0.85–2.17). The primary causes of death were confirmed histoplasmosis (10/38 – 26%), presumed DH (6/38 – 16%) and another opportunistic diseases (13/38 – 34%). In nine (24%) patients, the primary cause of death was not identified. Of the patients who died, 72% did not use antifungal medication regularly, 68% had not had active clinical follow-up and 92% did not take HAART regularly; 20% (6/30) of the patients who relapsed died during their first relapse episode and the mortality by confirmed histoplasmosis was 8% (10/126).

Discussion

This study found that concurrent DH and AIDS illness is a common presentation in this region of Brazil, with high rates of recurrence and overall mortality. A high number of cases of this co-infection (38 cases per year) was detected in this study when compared with a previous series (19 cases per year) from the same area and with other endemic areas of Panama (28 cases per year) and Guyana (9 cases per year). This larger number of DH cases appears to be consistent with the increased number of AIDS cases detected in the same study period in Ceará. According to data from the Ministry of Health of Brazil from 2002 to 2008, 5899 new cases of AIDS were detected in Ceará, with 48% of these detected in the last 3 years. It is likely that our results represent the involvement of more than one centre and a greater sensitivity of physicians to the diagnosis of new cases rather than to an actual increase in disease occurrence. Further studies based on the population at risk for DH are needed to better understand the occurrence of this disease in the area.

The epidemiological characteristics of the patients in this study were similar to those that have been observed in other studies. The mean age of 35 years was in accordance with studies conducted in the US and French Guiana in the same population and with the most frequent age group of people with HIV/AIDS in Ceará (20–39 years of age). No risk activity was associated with DH in this study. Unis et al. (2004) evaluated 70 patients with DH and AIDS and found microfoci that were contaminated with H. capsulatum in 5.7% of the cases. Chang et al. (2007) found an association between histoplasmosis and risk factors in a small proportion of patients (26.7%).

The number of patients who had DH as the first manifestation of AIDS varied from 34% to 100% in the literature. In this series, the proportion was ~60%. It is estimated that a late diagnosis of HIV infection occurs in 20–60% of patients throughout the world. In Brazil, patients first detected with a CD4+ count below 200 cells mm−3 or AIDS clinical symptoms ranged from 33% to 43.6%.
et al. (2011) analysed the survival of adult patients with AIDS in the southern and south-eastern regions of Brazil in a cohort from 1998 to 1999 and observed that a late diagnosis of AIDS was a significant predictor of mortality. Other studies conducted in Brazilian children showed similar results. Fagundes et al. (2010) analysed 175 patients in Brazil who had opportunistic infections in the pre- and post-HAART era and found that 42.3% of the patients had an opportunistic disease, including oral thrush, diarrhoea and pneumocystosis, in the post-HAART era. The same observation was found in a study from French Guiana conducted by Nacher et al. (2011) that observed a high incidence of histoplasmosis in the post-HAART era.

Regarding treatment, ABdes was used in the majority (97%) of cases as the initial induction therapy and the mean cumulative dose in excess of 700 mg was compatible with the current recommendations published in 2009. In the Infectious Diseases Society of America (IDSA) guideline of 2007, the induction time was modified for 12 months instead of 12 weeks as was previously recommended in 2000. The current study found a mean induction time that was below the recommendation (12 weeks) for that period (because the study was done primarily before the 2007 guideline update). The duration of antifungal use (induction and maintenance) could have been underestimated due to the lack of information in many of the outpatient medical records concerning the itraconazole 400 mg dose.

The relapse rate of 23.3% was similar to the rate that was observed in a study by Pontes et al. (2010) in the same area. This rate is considered very high compared with other endemic regions, such as Panama and the US, where rates of recurrence range from 0% to 6%. Based on these data, Ceará became one of the regions with the highest rates of relapse due to histoplasmosis in the world. This rate may be even higher because several patients had presumed DH (22 patients) and their symptoms subsided after specific treatment. The sensitivities of smear staining and culture are ~50% and 77% respectively; therefore, several of the presumed DH cases could have been unable to be confirmed.

The Brazilian distribution programme of antiretrovirals had a remarkable effect on morbidity and mortality of AIDS in Brazil. However, opportunistic infections remain the major cause of morbidity and mortality of AIDS patients, predominantly in north-eastern Brazil. In this study, very few patients who relapsed were taking HAART regularly, and, in more than 50% of the studied cases, the patients were readmitted during follow-up, with the majority of the readmissions due to opportunistic diseases. Consequently, new strategies to care for the AIDS population in this part of Brazil are urgently needed.

Histoplasma antigen detection has become an important tool in the US for the rapid diagnosis of histoplasmosis. This antigen test can be performed in blood or urine and has a high sensitivity and specificity. These tests are used for the diagnosis of DH in AIDS patients and to predict relapse. Patients with signs or symptoms of histoplasmosis and positive antigen tests (a value greater than 4.1 UI) or asymptomatic patients with an increased value in test levels and a drop in the basal CD4+ count are considered to be in relapse. Unfortunately, these diagnostic tests are not available in Brazil or in most countries that are endemic for histoplasmosis.

There is no consensus in the literature regarding the discontinuation of antifungal maintenance doses for histoplasmosis. A study of 32 patients in the US and a study of 20 patients in Argentina demonstrated that discontinuation of secondary prophylaxis is possible when patients use itraconazole prophylaxis for more than 12 months and there is immunity reconstitution due to HAART. These studies did not find an episode of recurrence after a follow-up that was longer than 24 months. The 27 patients who had medical advice for prophylaxis discontinuation in this series exhibited immune recovery (CD4+ count >150 cells mm⁻³) with HAART; one patient relapsed by the end of the study, but this patient had abandoned clinical follow-up 1 year before the recurrence.

The overall mortality (30.2%) in our study was considered high when compared with the study by Gutierrez et al. (2005), in which mortality rate was 12.5% after following 104 patients in Panama. Baddley et al. (2008) detected a mortality of 39.0% during a short period of observation (3 months) after a diagnosis of histoplasmosis in patients in Alabama, US. Pontes et al. (2010) found an overall mortality of 47.8% in Ceará after studying 134 patients with DH and AIDS at HSJ during 2 years of follow-up; however, the authors included the obituaries that occurred during the first event in the analysis, which accounted for the majority of the deaths (69%).

Less than 10% of the patients who relapsed or died were in regular compliance with HAART and approximately 30% had regular treatment with antifungal medicine and active clinical follow-up. These factors may be associated with the high number of relapses and deaths, as well as the fact that the EFZ with NRTI
were preferred drugs used in the HAART by the study participants (taken by more than 50% of the patients). It is known that the use of EFZ or lopinavir plus ritonavir (used by 27% of the patients) interacts with itraconazole, decreasing or increasing serum levels of this antifungal respectively.\textsuperscript{46–49} This could have influenced the higher number of relapses and death noticed here, as well as increased risk drug toxicity. In the hospitals studied, the serum level of itraconazole was not monitored, so data concerning drugs interactions were not obtained and consequently limited the evaluation of this issue; no modification in the HAART or antifungal dosage to optimising treatment was mentioned in the records as this is not a common procedure in hospitals from Ceará. An important fact revealed in this study was that of those who had not relapsed, 53% were also taking EFZ as a part of their drug regimen. Another study determining the factors related to these outcomes is in course and the results will be submitted for publication soon. It is necessary to monitor patients effectively regarding treatment and clinical follow-up, as well as to provide greater training to physicians regarding the treatment of this co-infection.

Some limitations should be considered in this study. The retrospective design did not allow a standardised collection of data, and the deficit of registers concerning the time of antifungal treatment (induction and maintenance) caused some difficulty with the actual evaluation of this variable. The missing records were another important aspect that prevented a more complete analysis of the outcomes variables. However, this study was of primary relevance because it more effectively characterised the relapse and the late mortality rates in patients with DH and AIDS in the post-HAART era and corroborated previous findings of the possibility of a suspension of prophylactic antifungal medication after immune recovery with the use of HAART.

In summary, this study has demonstrated that DH is a common opportunistic disease in people living with HIV/AIDS in Ceará, with high rates of relapse and late mortality during the follow-up period.

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Conflicts of interest

We declare that there are no conflicts of interest.

References


