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Childhood histoplasmosis in Colombia: Clinical and laboratory observations of 45 patients

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Abstract

Histoplasmosis is an important mycosis in the Americas; and in children with no immune system abnormalities, histoplasmosis is typically a self-limited process. In contrast, in children with immune problems, disease manifestations are frequently more severe and include dissemination. From 1984 to 2010, a retrospective study of paediatric patients who had been diagnosed with histoplasmosis was performed. A total of 45 pediatric cases of histoplasmosis were identified. The most important risk factor was malnutrition (37%), followed by environmental exposure (33%). The patients exhibited pulmonary infiltrates (83%), fever (76%), cough, constitutional symptoms (38%), headache (35%), and lymph node hypertrophy (33%). Concerning the clinical forms, 64% of the patients presented with the progressive disseminated form that frequently affected the central nervous system (48%). Diagnostic laboratory tests indicated that the cultures were positive for 80% of the patients, the agar gel immunodiffusion was reactive in 95%, the M band of the precipitate was more commonly observed (81%), and the complement fixation tests were reactive in 88% of the patients. The timely diagnosis of histoplasmosis is important, and for this reason, it is hoped that the results of this study will lead pediatricians toward a better understanding of this mycosis in children.

Key words: Histoplasmosis, Children, Diagnosis.

Introduction

Histoplasmosis is a disease caused by the fungus *Histoplasma capsulatum*, which was once thought to be a single species but has since been found to consist of eight different clades based on molecular studies.[1] This mycosis is most prevalent in the American continents but can also be found in other geographic regions.[2,3] Histoplasmosis is an opportunistic infection in individuals with innate or acquired

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cellular immune dysfunction that can be caused by acquired or iatrogenic factors.[2,4,5]

In pediatric patients, the clinical forms of histoplasmosis vary according to age group. In infants, the acute progressive disseminated form predominates (80%). In preschoolers, the most common clinical form is acute pulmonary illness, and in schoolchildren and older children, the most frequently observed clinical presentation is the subacute form.[6,7] In immunocompetent children, histoplasmosis is usually a self-limited illness, whereas in immunocompromised infants, the manifestations are frequently more severe and include progressive dissemination.[4]

In Colombia, histoplasmosis is not only the most frequently reported endemic systemic mycosis, but it is also characterized by a wider distribution.[8,9] Nonetheless, because the reporting of histoplasmosis is not compulsory, subregistration is to be expected. Case reports and series of pediatric cases have been published in some Latin American countries, including Panama, Venezuela, Brazil, Ecuador and Costa Rica.[4,6,10,11,12]

The present report is the first such Colombian study and describes 45 cases of histoplasmosis in children and characterizes the clinical and laboratory findings to orient pediatricians toward proper diagnoses of this mycosis.

Materials and methods

A retrospective study was performed during the period of 1984–2010 based on data derived from the Histoplasmosis Colombian National Survey organized by the Corporación para Investigaciones Biológicas (CIB) and the Colombian Instituto Nacional de Salud (INS) in addition to patients seen prospectively at the CIB and a group of childhood patients reported in a thesis.[13,14] This study analysed 45 Colombian patients below the age of 17 years with microbiological and/or serological diagnoses of histoplasmosis. Patients were assigned to the following four groups according to the recommended paediatric guides: 1) infants, that is, children younger than 2 years old; 2) preschoolers, that is, children between 2 and 6 years old; 3) schoolchildren, that is, children between 6 and 10 years; and 4) older children (adolescents), that is, 10–17 years old.[15]

A database was constructed that included demographic information, risk factors, and the pulmonary radiographic and clinical abnormalities. The latter were grouped into five categories according to the organs involved as follows: 1) bone marrow involvement (anemia, neutropenia, and thrombocytopenia); 2) systemic manifestations (hepatic, splenic, and lymphatic abnormalities); 3) respiratory symptoms (cough, dyspnoea, and expectoration); 4) constitutional symptoms (fever, anorexia, adynamia, asthenia, and weight loss); and 5) gastrointestinal disturbances (diarrhoea, vomiting). The type of antifungal treatment prescribed was also recorded and included fluconazole (FCZ), itraconazole (ITZ), ketoconazole (KTZ), and amphotericin B (Ampho B).

To establish the diagnosis of histoplasmosis, several laboratory tests, such as the isolation of *H. capsulatum* in cultures from different tissue samples, and various indirect specific antibody tests, such as complement fixation (CF) and agar gel immunodiffusion (AGID); the former tests is reported as the antibody titre and the latter as the presence of precipitin lines M, H, or both as indicated.

The inclusion criteria were those provided by the EORTC/MSG Consensus Group.[16] A proven diagnosis was defined by the isolation of the fungus by culture. A probable diagnosis was determined according to the following criteria:

1. Immunocompetent patients: a) reactivity to histoplasmin with serum titers $\geq$ 1:32 in the CF assay, b) presence in serum of precipitin bands in the AGID, c) patient with environmental exposure or those affected by a histoplasmosis outbreak with reactive serological tests and improved symptoms following antifungal therapy.[16]
2. Patients with immune abnormalities (i.e., human immunodeficiency virus [HIV] infection/AIDS immature immune responses, malnutrition, and hematologic malignancy): a) the presence of precipitin bands in the AGID test or any antibody titre against histoplasmin in the CF test or reactive serology from the cerebrospinal fluid independently of the patient's immune status; b) patients with clinical diagnoses of histoplasmosis without laboratory evidence who exhibited clinical responses to specific antifungal treatment.[16]

Meningeal histoplasmosis was defined on any of the following criteria:

- Isolation in culture of *H. capsulatum* from cerebrospinal fluid (CSF)
- Presence in CSF of precipitin bands in the AGID test; and any titer anti-*H. capsulatum* antibodies in the complement fixation test.
- Presence of signs and symptoms of meningeal irritation.

Statistical analyses

The data were collected into a database using Microsoft Excel. The statistical analyses were performed with EPIDAT 3.1, STATA 8.0 and the statistics software R-Project version 3.2.3. A descriptive analysis of the different variables was performed using the means of the frequencies and the central tendency measurements. A between-groups bivariate analysis was subsequently performed with the aim of estimating the prevalence ratio (PR) to a confidence level

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of 95% and to identify the factors associated with the diagnosis according to the demographic group using 2 × 2 tables. A multivariate descriptive analysis was performed with multiple correspondence analysis (MCA) to observe the possible relationships among the selected variables and to obtain dimensions that best represent all variables, considering the level of significance (weight) of each, to explain total sample variability (inertia) and with a Joint-Plot (Rows/Columns) to observe the associations of the groups. In the plot, the representations of the variables are points including 95% confidence ellipsoids in two colours represented the grouped ages and symptoms. The correlations resulting from these methods correspond to the non-parametric Kendall tau (τ), which represents the degree of association between two variables independent of their behaviors; this is accomplished via a nonlinear transformation of the original values of the variables to a scale based on ranks. In 1994, Hatcher recommended that the number of subjects should be greater than five times the number of variables.[17] To achieve a correct interpretation, it is important to know that grey dashed thin points and ellipsoids indicate the variables under consideration. The coverage and closeness between the ellipsoids thus indicate the strength of their association as follows. Considering variables A and B independent of each other, nearby points between A and B indicate that existing relationship between A and B. Far points indicate some interdependence between A and B; on the other hand, if the 95% confidence ellipsoids touch each other, this suggest some influence between the variables.[18]

Results

In this study, 27 of the 45 patients (60%) were males, 18 (40%) were females, and the mean age was 7 years with a range of 7 months to 17 years (SD ± 4.9 years). The age distribution was as follows: 11 (24%) infants, nine (20%) preschoolers, 13 (29%) schoolchildren, and 12 (27%) older children.

According to the EORTC criteria, there were 20 proven and 25 probable diagnoses (24 with reactive serologies and one based on clinical, epidemiological and treatment criteria). In 33 patients it was possible to establish the clinical form of histoplasmosis, 4 patients presented acute epidemic histoplasmosis, and 29 the progressive disseminated form.

In 27 patients (60%), a risk factor for developing histoplamosis was identified; these risk factors were malnourishment in 10 (37%) cases, environmental exposure in an endemic area (e.g., soil removal and exposure to bird excreta or bat guano) in nine (33%) cases, and in lesser proportions, other factors such as AIDS in four (15%) and the presence of tumours in four (15%). In one patient, two simultaneous factors, that are, malnutrition and environmental exposure were present. In 18 patients (40%), no risk factors were detected.

Analyses of the 26 (58%) available lung X-rays revealed abnormalities in 18 (69%) patients, whereas the remaining eight (31%) were normal. The most frequent abnormalities were the presence of infiltrates (15 of 18 patients, 83%), infiltrates as the sole finding (8, 53%) cases, and infiltrates co-existing with calcifications (4, 27%) and with cavitations (3, 20%). In lesser proportions, the following findings were observed: nodules in one patient (6%), calcified nodules in one patient (6%), and calcifications in one patient (6%).

The most common clinical manifestation at the moment of diagnosis among the 45 patients was fever, which was present in 34 (76%) patients, followed by cough and constitutional symptoms (i.e., anorexia, adynamia, and asthenia), which were observed in 17 (38%) patients. The other manifestations were as follows: headache in 16 (35%), lymph node hypertrophy in 15 (33%), vomiting in 14 (31%), hepato-splenomegaly in 11 (24%), seizures in eight (18%), and other signs (e.g., meningeal irritation, anemia, and weight loss) in 12 patients (26%). Patients who presented gastrointestinal symptoms had no underlying disease reported, so the presence of these symptoms could be attributed as such to histoplasmosis.

An analysis of the age groupings and the signs/symptoms, which were grouped into six categories according to syndromes in this case, correspondence between the ages grouped and symptoms, are represented the points including 95% confidence ellipsoids, in addition the percentage of variability of the phenomenon in two dimensions is 97.5%. Gastrointestinal and constitutional symptoms share partnership with the older and preschool children; on the other hand, a strong association between school-aged children and neurologic abnormalities was established. It is remarkable the influence of systemic manifestations and bone marrow involvement with infants. Finally, respiratory symptoms are presented in older, school-aged and preschool groups (Figure 1). The PR values and their respective 95% confidence intervals (95% CI), and *P* values are summarized in Figure 2. Notably, bone marrow involvement was more commonly associated with the infants than the preschoolers, schoolchildren and older children (PR: 4.63, 15.45, and 3.70, respectively). Systemic manifestations were more frequent in the infants than in the noninfants and constitutional symptoms predominated in the infants and preschoolers compared with the remaining two groups. Finally, meningeal involvement was most frequent in the schoolchildren (Figures 1 and 2).

Twenty-nine of the 45 children (64%) presented with progressive disseminated histoplasmosis with involvement of extra-pulmonary organs, including 14 (48%) patients with infections that affected the central nervous system.

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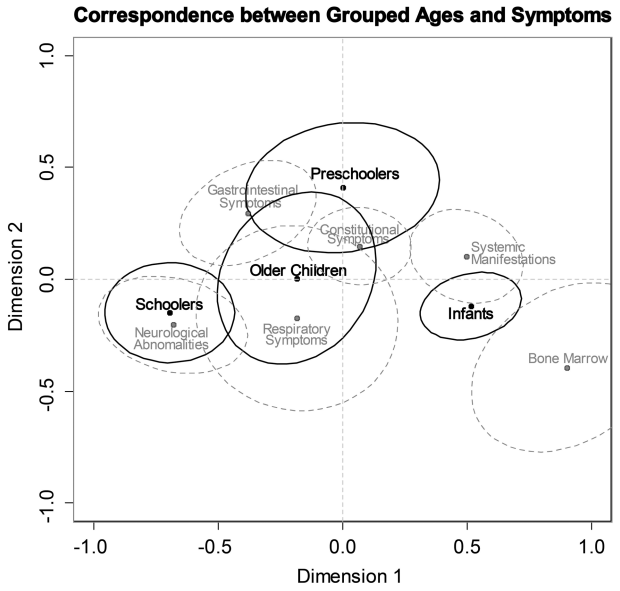

Figure 1. Histoplasmosis in Children: Correlations among syndromes and age associations. Gastrointestinal and constitutional symptoms share partnership with the older and pre-school children. A strong association between school-aged children and neurologic abnormalities was evidenced. Systemic manifestations and bone marrow involvement were associated with infants while, respiratory symptoms were present in older, school-aged, and pre-school children.

Among these latter patients, nine were male, and eight were school students. Lung X-rays were taken in nine of these 14 patients and revealed four patients with abnormalities, the most frequent of which was the presence of infiltrates with or without calcifications.

Meningeal involvement is manifested as signs of meningeal irritation and headache[2], and both of these manifestations were present in 11 of 14 (79%) children, followed by fever and vomiting in 10 (71%) and seizures in six (43%). Specific diagnoses were accomplished based only on cerebrospinal fluid serologies in six (43%) patients, based on *H. capsulatum* isolation from culture in one patient (7%), and with the combination of both methods (serologies and isolation from culture) in the remaining seven (50%) cases.

The results of the various laboratory tests utilized for the diagnosis of histoplasmosis in this study are presented in Table 1. The AGIDs performed in 39 cases revealed reactivity in 37 (95%) cases, with M band present in 81% of the cases. The CF test revealed antibodies against the histoplasmin antigen with titers $\geq$ 1:32 in 25 of the 36 (69%) tests performed. In contrast, the cultures performed in 25 of the 45 patients were positive in 20 (80%).

The records indicated that 35 of 45 patients (78%) received antifungal treatment. Among these patients 14 (40%) were treated with ITZ, nine (26%) were treated with Ampho B, and seven patients (20%) received sequential Ampho B plus ITZ. Fewer patients received other antifungal medications such as KTZ or FCZ.

Discussion

The present study of childhood histoplasmosis in Colombia is the report with the greatest number of cases to date in the literature. In this study, the epidemiological, clinical and laboratory data of 45 Colombian patients were analyzed with the goal of achieving more precise diagnoses of this disorder in children, who do not always present with the expected signs and symptoms due to variations in the manifestations of mycosis between patients.

No differences according to gender or age were observed. The predominance of males (60%) has been observed in earlier studies. Similarly, the mean age of 7 years coincides with other reports, which have indicated a range from 6 to 9 years.[4,6,11,12,19]

A review of the risk factors related to the acquisition of histoplasmosis in children revealed that malnutrition is the most frequent contributing factor and is present in 37% of all patients. This finding agrees with that of a previous report by Ávila et al. (2007).[10] Other studies have reported smaller proportions of approximately 27%.[6,19] Malnutrition is one of the leading causes of childhood mortality in developing countries, particularly in children under 5 years of age.[20,21] This condition increases the risks of both infection and death due in part to influences on nutritional status and the immune system that are mediated by epigenetic mechanisms.[22] Additionally, protein-caloric malnutrition is considered to be the leading cause of secondary immunodeficiency in the world because it diminishes the host´s immune responses including cell-mediated immunity.[21]

Other important risk factors are those related to fungal exposure (33%) and concomitant AIDS (15%), which occupy the second and third places, respectively. The latter figure differs in the adult population in which AIDS accounts for 70% of the risk factors for the development of histoplasmosis.[3] The presence of environmental exposure in the working-age population has been reported to range from 25% to 100%.[3,4,12]

The regular presence of pulmonary infiltrates in the X-ray studies (83%) observed here has been described by certain authors, and others have reported lower frequencies (54 to 66%).[23–26] The type of involvement is similar to one that has been reported for pulmonary tuberculosis.[4,27] Cavities were observed in 20% of the childhood cases in our series, which revealed that disease caused by *H. capsulatum* in children infrequently elicits this symptom. This finding contrasts the reported presence of cavities in adult patients with chronic pulmonary histoplasmosis and chronic obstructive pulmonary disease

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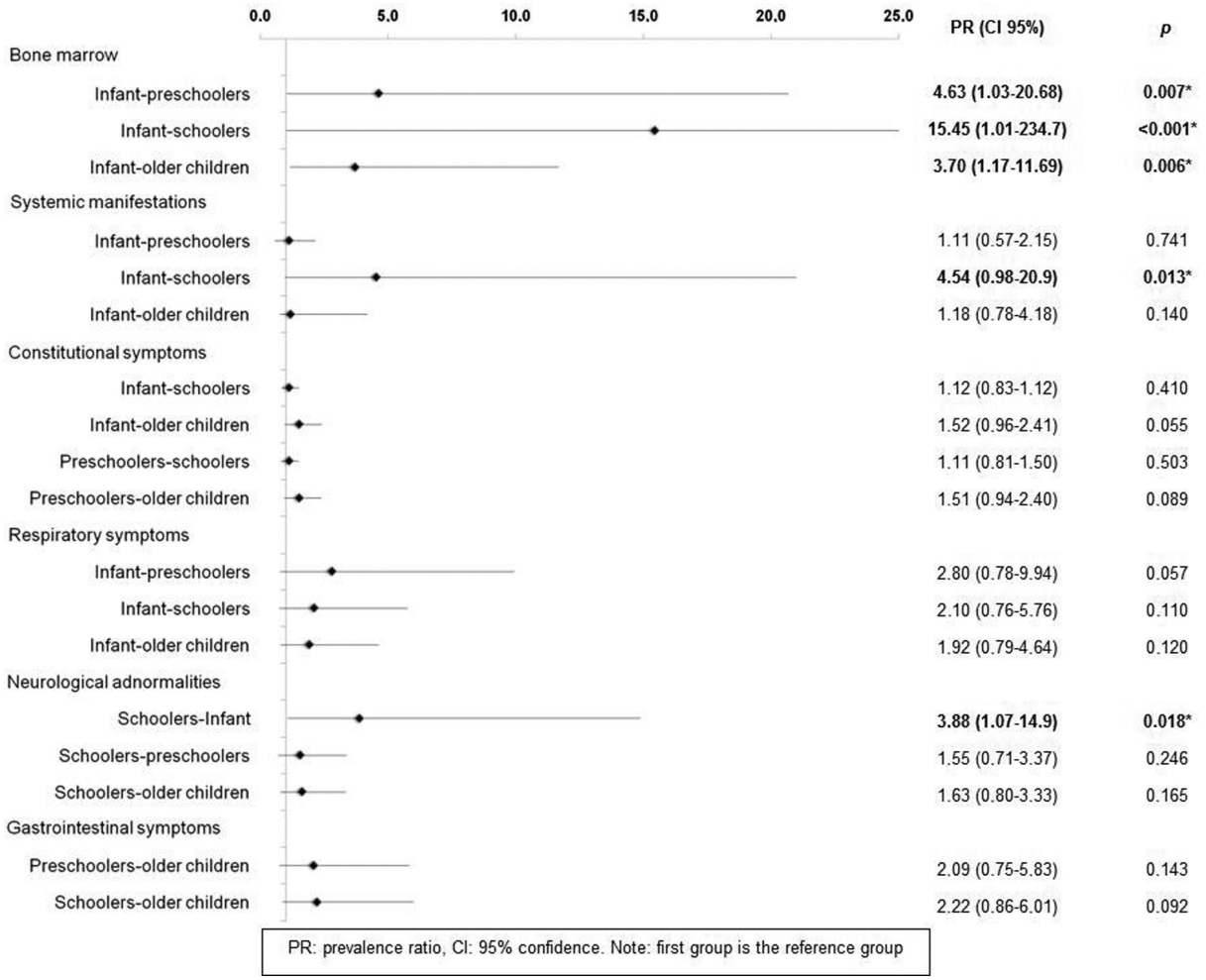

Figure 2. Clinical findings for the four groups of children with histoplasmosis, i.e., infants, preschoolers, schoolchildren and older children.

Table 1. Results of the laboratory tests employed for the diagnosis of histoplasmosis.

Diagnostic tests	Positive/total performed	% Reactivity
Agar gel Immunodiffusion (AGID)^	37/39	95
Only band H	2/37	5
Only band M	30/37	81
Both bands: H and M	5/37	14
Complement fixation (CF) titres+	36/41	88
Mycelium ≥ 1:32	25/36	69
Mycelium ≤1:16	11/36	31
H. capsulatum isolated in culture*	20/25	80

Note: the denominator is the number of patients in whom the tests were performed.
(^) 13 tests were performed in cerebrospinal fluid and 26 in sera.
(+) 14 tests were done in cerebrospinal fluid and 27 in sera.
(*) Samples used for the diagnosis of histoplasmosis by culture were: cerebrospinal fluid (8), LBA (4), lymph node (4), bone marrow (2), blood culture (2), liver (1), bone (1) and spleen (1). Some patients were diagnosed by means of one or more samples.

(COPD) in which bullous emphysema is more common.[28] Relatedly, the correlational analyses between the infiltrates and cavitations in the infants (data not shown) revealed a positive correlation, but it was not possible to confirm that the cavitations were indeed caused by histoplasmosis and not by other infectious processes, such as tuberculosis, because the analyzed database did not contain appropriate information.

Bone marrow involvement is frequent in infants, which is likely due to the immaturity of the cell-mediated immune responses. Progressive disseminated infection is characterized by pancytopenia and disseminated intravascular Coagulopathy.[29,30] Ávila et al. reported that 60% of the studied population consisted of infants who presented with bone marrow alterations in 60% to 85% cases in addition to dissemination.[10] Odio et al. and Tobón et al. reported that 100% of the studied patients had disseminated disease with observable bone marrow abnormalities.[12,19]

The frequencies of fever (76%) and cough (38%) in our patients coincided with the observations of other studies

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dealing with histoplasmosis in children indicating that fever was present in 74% and cough in 57% of the patients.[25] In other reports, fever has been observed in 76% and cough in 38% of patients. Variations in these frequencies have previously been observed.[11,12]

In the children in this study, the most common clinical form of histoplasmosis was the progressive disseminated disease (64%). This observation is in accordances with those of other studies in infants below the age of two years.[6,10–12] This form involved the central nervous system in as many as 48% of our patients, whereas other studies have reported lower frequencies (12–22%).[6,19] In this meningeal form, the neurological manifestations are nonspecific (e.g., meningeal irritation and headache).

As shown in this series of children with histoplasmosis, central nervous system involvement is frequent (48%) and should be taken into consideration despite its low detection rate in daily clinical practice. Due to its importance, it is recommended that in patients with signs of meningeal irritation or central system involvement, CSF fungal studies should be done regularly whether by culture, indirect serologic tests (ID or CF), or molecular DNA amplification systems such as the polymerase chain reaction (PCR), as well as by detection of urinary antigen.[30–34]

As shown here, most patients with neurological symptoms were diagnosed as tuberculosis because of the similarity of the spinal fluids biochemical studies,[14] an observation that indicates the difficulties in distinguishing these two disorders with the possibility of establishing an erroneous anti-tuberculosis treatment providing no beneficial results and, consequently, increasing mortality or development of neurological sequela attributable to improper diagnosis and inappropriate treatment. In Mata-Essayag et al. study in Venezuela, 15% of patients with meningitis due to *H. capsulatum* died undiagnosed and up to 99% of nonbacterial meningitis was misdiagnosed as tuberculosis. *H. capsulatum* is capable of mimicking the activities of the tuberculosis bacilli presenting the clinical manifestations of fungal meningitis as they are similar to those associated with tuberculosis, including abnormalities of the spinal fluid such as mononuclear pleocytosis with predominance of lymphocytes and increased protein contents once the illness nears its regular fatal outcome.[35]

The above findings should alert the medical community, especially pediatricians, on this particular fungal process, one that should be differentiated from other meningeal entities, especially tuberculosis, in order to avoid treatment failures. At present, the regular medical practice fails to promptly arrive to a diagnosis of fungal meningitis and does so only when the patient fails to respond to the anti-TB therapy, thus allowing the causative fungus to induce increased damage.

Our objective is to alert on the increased frequency of histoplasmosis of the central nervous system being reported in children and on the importance of establishing the correct diagnosis leading to specific therapy in order to reduce the sequelae and morbidity that characterize this fungal disease.

In this study, the rate of cerebrospinal fluid culture positivity was high (80%), and this rate compares favourably with the information in the literature regarding patients with the disseminated form and those with certain degrees of immune dysfunction.[36] Unfortunately, this method is not always available in all clinical laboratories.[37]

This study was a retrospective analysis; thus, it was not possible to obtain data concerning mortality, follow-ups, or outcomes for the overall group of patients studied in this cohort. Additionally, molecular and antigen tests were not used in the present report because the period of patient observation preceded the standardization of such tests.

In conclusion, the timely diagnosis of histoplasmosis is of vital importance. One can rely on clinical, epidemiological, and laboratory procedures to achieve this goal. In this group of children with histoplasmosis, the most common clinical findings were fever, anorexia, asthenia, and adynamia. The most relevant risk factor was malnutrition. In the infants, bone marrow involvement was frequent and was often accompanied by pancytopenia. The most frequent clinical presentations were the disseminated form, and in the school-aged children, central nervous system abnormalities were most frequent. The most common radiographic abnormality was pulmonary infiltrates similar to those observed in tuberculosis. All laboratory tests done in this study (AGID, the CF, and the fungal culture) were also useful for the diagnosis of histoplasmosis in children. At present, the most promising procedures are those related to antigen testing and molecular procedures because these tests provide specific, reliable, and timely diagnosis.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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