Cryptococcosis in Colombian children and literature review

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Cryptococcosis is reported in adults and is often acquired immune deficiency syndrome (AIDS)-associated; however, its frequency in children is low. Based on the National Survey on Cryptococcosis conducted in Colombia, an epidemiological and clinical analysis was performed on cases of the disease observed in children less than 16 years old between 1993-2010. We found 41 affected children (2.6% prevalence) from the 1,578 surveys received. The country mean annual incidence rate was 0.017 cases/100,000 children under 16 years, while in Norte de Santander the incidence rate was 0.122 cases/100,000 ($p < 0.0001$). The average age of infected children was 8.4 and 58.5% were male. In 46.3% of cases, a risk factor was not identified, while 24.4% had AIDS. The most frequent clinical manifestations were headache (78.1%), fever (68.8%), nausea and vomiting (65.6%), confusion (50%) and meningeal signs (37.5%). Meningitis was the most frequent clinical presentation (87.8%). Amphotericin B was given to 93.5% of patients as an initial treatment. Positive microbiological identification was accomplished by India ink (94.7%), latex in cerebrospinal fluid (100%) and culture (89.5%). Out of 34 isolates studied, Cryptococcus neoformans *var.* grubii *(VNI 85.3%, VNII 8.8%) was isolated in 94.1% of cases and* Cryptococcus gattii *(VGII) was isolated in 5.9% of cases. These data are complemented by a literature review, which overall suggests that cryptococcosis in children is an unusual event worldwide.*

Key words: *Cryptococcus neoformans* - *Cryptococcus gattii* - cryptococcosis - cryptococcal meningitis - epidemiology - Colombia

Cryptococcosis is a systemic fungal infection that often affects adults, especially those who have an alteration in their cellular immunity. Within a year, approximately one million cases of meningeal cryptococcosis in people with acquired immune deficiency syndrome (AIDS) are diagnosed and of these people, almost two-thirds die (Park et al. 2009).

In contrast, worldwide literature has described less than one thousand cases of cryptococcosis in children (Meiring et al. 2012), including those occurring in immunosuppressed patients. The low frequency of cryptococcosis in children cannot be explained by lack of exposure; in fact, one study shows that the majority of children older than two years have serological evidence of infection by *Cryptococcus neoformans* (Goldman et al. 2001).

In Colombia, a National Survey on Cryptococcosis that has been conducted since 1993 has allowed us to estimate a more realistic picture of this mycosis (Lizarazo et al. 2007, Escandón et al. 2012). The mean annual incidence of cryptococcosis in the general population in Colombia was 2.4 cases per 10^6 people between 1995-2010; in the population with human immunodeficiency virus (HIV), the incidence ranged between 3-3.3 cases per 10^3 people (Lizarazo et al. 2007, Escandón et al. 2012). With the data obtained from the National Survey, we aimed to analyse the epidemiology and clinical manifestations of cryptococcosis in Colombian children.

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PATIENTS, MATERIALS AND METHODS

Study design - This is an observational descriptive study where epidemiological and clinical data from cases of cryptococcosis in children during the years of 1993-2010 were extracted from the National Survey mentioned above.

The National survey was designed in accordance with the guidelines given by the European Confederation of Medical Mycology, with the corresponding authorisation (Viviani 1997), and processed by clinicians and microbiologists of public, academic and private hospitals, as well as public health laboratories of Colombia.

The survey recorded patient data such as demographic data, sex, year of birth and department (Colombian political divisions), department of residence, risk factors (AIDS, corticosteroid therapy, autoimmune disease, transplantation, solid tumour, haematologic malignancy, diabetes mellitus, kidney failure and cirrhosis), date of clinical diagnosis, signs and symptoms (fever, headache, nausea or vomiting, confusion, mental changes, cough, abnormal vision or loss of vision, focal neurological signs, meningeal signs, hydrocephalus, intracranial hypertension without hydrocephalus, seizures), chest radiographic findings, computerised tomography (CT) and magnetic resonance imaging (MRI). The laboratory results of the tests included the origin of the positive sample for the fungus, results of the direct examination, culture and antigenaemia. Additionally, information was requested for the initial treatment given for cryptococcosis.

The surveys and isolates of the fungus were sent to the two focal points of the study: the National Institutes of Health (INS), in Bogotá, and the Corporation for Biological Research (CIB) of Medellin. With these data, we created a database using the program Epi Info 6.0 that was used for analysis (Dean et al. 1994). Children were considered as individual minors of 16 years.

Ethical considerations - This study was approved by the Ethical Committee of the CIB. Additionally, this study was endorsed by the technical and ethical committees of the INS.

Case definition - A case of cryptococcosis was defined in subjects who presented clinical findings compatible with cryptococcosis in addition to the presence of one or more of the following laboratory results: visualisation of the fungus under direct examination with India ink of cerebrospinal fluid (CSF) from a skin lesion or from a histopathological examination, isolation of *C. neoformans* or *Cryptococcus gattii* from a normally sterile site, bronchoalveolar lavage or skin lesion and a titre ≥ 8 capsular antigen in serum or any titre in the CSF.

An AIDS case was considered in those where HIV infection was reported in the survey and AIDS was not considered in those who were negative for HIV infection or in those for whom this information had not been registered.

Epidemiological analysis - Prevalence - The proportion of the number of cases in children was established from the total number of surveys received. This was established at both the national and regional levels.

Incidence - The average annual incidence was determined by using as a denominator the average of the population of both Colombia and the departments from 1993-2010, as determined by the National Administrative Department of Statistics (DANE 2013). However, an important consideration is that this is a passive and voluntary survey.

Statistical analysis - The national incidence rate was determined for each department as well as nationally. Subsequently, these rates were compared using a ratio with the respective confidence interval of 95% using the Poisson distribution and the *p* value was calculated according to a value of 0.05 considered as statistically significant to determine differences in the incidence of disease.

Microbiology - The identification of disease was made using conventional methods and species determination was performed using culture in CGB medium (Kwon-Chung et al. 1982). In the first years, the serotype (B or C) was determined using specific antisera commercially available at that time (Crypto-Check, Iatron Laboratories, Japan).

Molecular type and mating type - The molecular type was determined in all isolates using polymerase chain reaction fingerprinting with the $(GTG)_5$ primer (Meyer et al. 2003). Mating type a or alpha was determined using specific primers described previously (Halliday & Carter 2003).

Review of the literature - A search was performed in the MEDLINE database from 1996 through 30 September 2013 using the following search terms in English: cryptococcosis, *C. neoformans* and *Cryptococcus gattii*, HIV, AIDS, children and epidemiology. In addition, we searched for articles in Spanish and Portuguese in the databases SciELO and LILACS. We took into account the articles that included epidemiological data. We removed the case reports or articles whose full text was not achieved. We added several references cited in articles obtained in the primary search.

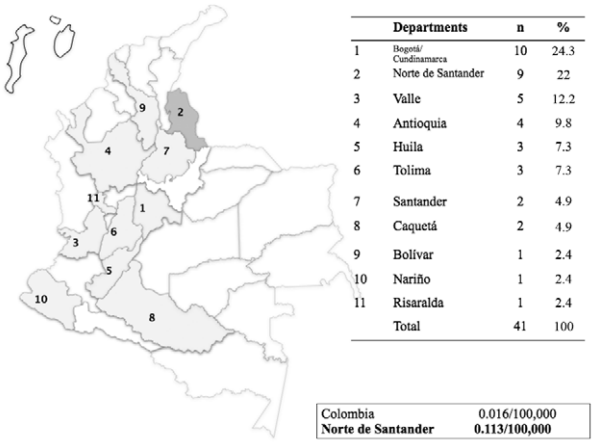
RESULTS

Prevalence, incidence of cases and origin - A total of 1,578 surveys were received from 76 centres and 25 departments and Bogotá DC over a period of 18 years (1993-2010). Forty-one surveys (2.6%) were from children under 16 years.

Children completing surveys were from the following departments: Cundinamarca/Bogotá DC [10 (24.3%)], Norte de Santander [9 (22%)], Valle [5 (12.2%)], Antioquia [4 (9.8%)], Huila [3 (7.3%)], Tolima [3 (7.3%)], Santander [2 (4.9%)], Caquetá [2 (4.9%)], Bolívar [1 (2.4%)], Nariño [1 (2.4%)] and Risaralda [1 (2.4%)] (Fig. 1).

The mean annual incidence of cryptococcosis in children in Colombia was 0.017 cases per 100,000 children under 16 years; however, in one of the northeastern departments, Norte de Santander, this incidence reached 0.122 cases per 100,000 ($p < 0.0001$).

Demographic information - The average age of the patients was 8.4 ± 4.7 years and 21 (58.5%) patients were male. The distribution according to age and sex is contained in Fig. 2.



	Departments	n	%
1	Bogotá/ Cundinamarca	10	24.3
2	Norte de Santander	9	22
3	Valle	5	12.2
4	Antioquia	4	9.8
5	Huila	3	7.3
6	Tolima	3	7.3
7	Santander	2	4.9
8	Caquetá	2	4.9
9	Bolívar	1	2.4
10	Nariño	1	2.4
11	Risaralda	1	2.4
	Total	41	100

Fig. 1: mean annual incidence of cryptococcosis in children < 16 years.

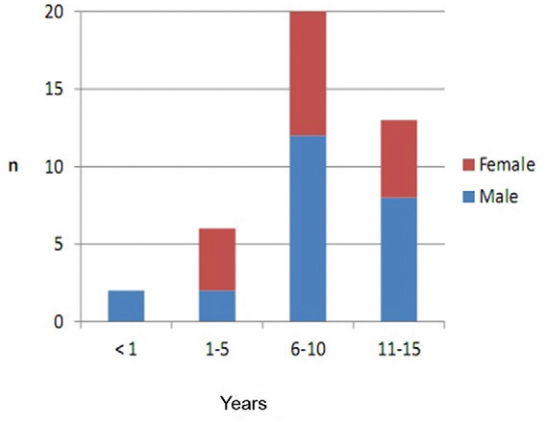


Fig. 2: cryptococcosis in Colombian children 1993-2010.

Risk factors - No risk factor was identified in 19 cases (46.3%). The risk factors were HIV infection in 10 patients (24.4%), autoimmune disease, corticosteroid use, haematologic malnutrition and malignancy in three cases each (7.3%) and renal disease, solid tumour and prematurity with one case each (2.3%).

Clinical findings - The most frequent clinical manifestations were headache (78.1%), fever (68.8%), nausea and vomiting (65.6%), confusion (50%) and meningeal signs (37.5%). The totals of the clinical manifestations informed are reflected in Table I.

The most common clinical form of presentation of the disease was neurocryptococcosis (87.8%) followed by the disseminated form (12.2%). Among the five patients with disseminated disease, two had skin involvement.

Diagnostic images - In five patients, one of them HIV+, results of a chest X-ray were reported and this diagnostic was abnormal in four of them. The abnormality described for each of these was the presence of pulmonary infiltrates. A skull tomography was performed in 14 patients, four of them HIV+, and abnormalities were reported in 10. The abnormalities described were brain hypodensities (3 cases), increase of the meningeal enhancement (3 cases), hydrocephalus (2 cases), calcifications (1 case), brain mass (1 case) and cerebral haemorrhage (1 case). Some patients had more than one abnormality.

Treatment - In total, 75.6% of the patients were treated with antifungal agents, two patients did not receive treatment and this information was not available for eight patients. The medication most often used was amphotericin B (AmB) (93.5%). The different therapeutic regimens are listed in Table II.

Laboratory diagnosis - Several diagnostic methods were performed: direct examination, determination of the capsular antigen in serum and CSF and CSF and respiratory samples culture. The results of these tests are described in Table III.

Serotypes and molecular types - From a total of 34 isolates studied, 94.1%, were serotype A (molecular pat-

TABLE I

Clinical manifestations of cryptococcosis in children

Clinical findings	n (%)
Headache	25 (78.1)
Fever	22 (68.8)
Nausea and vomiting	21 (65.6)
Confusion	16 (50)
Meningeal signs	12 (37.5)
Visual alterations	9 (28.1)
Seizures	9 (28.1)
Cough	6 (18.8)
Neurological signs	6 (18.8)
Hydrocephalus	6 (18.8)
Loss weight	2 (6.2)

n = 32.

TABLE II

Pharmacological treatment of cryptococcosis in Colombian children

Treatment	n/total (%)
Patients with treatment	31/41 (75.6)
Type of antifungal used	
AmB	29/31 (93.5)
5FC	4/31 (12.9)
FCZ	8/31 (25.8)
ITZ	1/31 (3.2)
Caspofungin	1/31 (3.2)
Therapeutic regimens used	
AmB only	19/31 (61.3)
AmB + FCZ	5/31 (16.1)
AmB + 5FC	2/31 (6.4)
AmB + 5FC + FCZ	1/31 (3.2)
AmB + ITZ	1/31 (3.2)
AmB+ caspofungin	1/31 (3.2)
5FC + FCZ	1/31 (3.2)
FCZ only	1/31 (3.2)
Patients without treatment	2/41 (4.9)
Patients without treatment information	8/41 (19.5)

AmB: amphotericin B; FCZ: fluconazole; ITZ: itraconazole; 5FC: 5-fluorocytosin.

TABLE III

Results of the laboratory examinations

Type of examination	n/total (%)
Positive direct examination	36/38 (94.7)
Capsular antigen detection	14/14 (100)
Serum reactive	4/4 (100)
CSF reactive	10/10 (100)
Positive culture	34/38 (89.5)
Serotype A	32/34 (94.1)
Serotype B	2/34 (5.9)
Molecular type	
VNI	29 (85.3)
VNII	3 (8.8)
VGII	2 (5.9)
Mating type	
a	1 (2.9)
alpha	33 (97.1)
Isolates recovered from	
CSF	27 (79.5)
CSF and blood	3 (8.9)
Blood	1 (2.9)
Skin	1 (2.9)
CSF, BAL and skin	1 (2.9)
Blood and BAL	1 (2.9)

BAL: bronchoalveolar lavage; CSF: cerebrospinal fluid.

TABLE IV

Age, sex, prevalence and incidence of cryptococcosis in children in diverse countries around the world

Region	Age (years)/ findings (%)	Reference
Colombia	8.4	This paper
Brazil	7.6 and 7.8 (most HIV-)	Severo et al. (2009)
	8.8 (all HIV-)	Corrêa et al. (2002)
Cuba	5.8 (85.7 immunocompetent)	Illnait et al. (2013)
China	7.25 (HIV-)	Yuanjie et al. (2012)
	10.9 (children up to 17 years)	Guo et al. (2012)
South Africa	7 (91 HIV +)	Meiring et al. (2012)
Taiwan	13.7 (all HIV- up to 17 years)	Huang et al. (2010)
Thailand	7 (all HIV+)	Likasitwattanakul et al. (2004)
United States of America	8 (all HIV+)	Abadi et al. (1999)
	9.8 (all HIV+)	Leggiadro et al. (1991)
	11.5 (all HIV+)	González et al. (1996)
	11.98 (79.4 immunocompromised, up to 18 years)	Joshi et al. (2010)

Region	Sex male (%)	Reference
Colombia	58.5	This paper
Brazil	52.8	Severo et al. (2009)
Northern Brazil	54.5	Corrêa et al. (1999)
Cuba	42.9	Illnait et al. (2013)
China	60.87	Guo et al. (2012)
South Africa	54.9	Miglia et al. (2011)
	57	Meiring et al. (2012)
Taiwan	22.2	Huang et al. (2010)
Thailand	57.9	Likasitwattanakul et al. (2004)
United State of America	60.3	Joshi et al. (2010)

Region	Prevalence (%)	Reference
Colombia	2.6	This paper
Norte de Santander	29.6	Lizarazo et al. (2012)
Northern/northeastern Brazil		
State of Bahia	32	Darzé et al. (2000)
State of Pará	24	Corrêa et al. (1999)
State of Piauí	9.5	Martins et al. (2011)
Africa		
Botswana	2.4	Mullan et al. (2011)
Ghana	6.9	Owusu et al. (2012)
South Africa	2	Miglia et al. (2011)

Region	Prevalence (%)	Reference
Thailand	3	Likasitwattanakul et al. (2004)
United States of America	0.85	González et al. (1996)
	1.4	Abadi et al. (1999)
	3.3	Harris et al. (2012)
French Guiana	4.6	Debourgogne et al. (2011)
Uruguay	1.3	Quian et al. (2012)
Venezuela	0.91	Pérez et al. (2009)

Region	Incidence (cases x 100,000)	Reference
Colombia	0.016	This paper
Norte de Santander	0.113	This paper
China	0.43	Guo et al. (2012)
South Africa	1	Meiring et al. (2012)
	47 (HIV+)	
Gauteng	38 (HIV+)	McCarthy et al. (2006)
United States of America	100 (HIV+)	González et al. (1996)

terns VNI (85.3%) and VNII (8.8%) and 5.9 % of the isolates belonged to serotype B, molecular type VGII (Table III). From the nine cases identified in Norte de Santander, six isolates were studied and all of them were serotype A, molecular type VNI.

Literature review - The results of the review are listed in Table IV.

DISCUSSION

As has been reported in the literature, cryptococcosis is a rare disease in children worldwide, including in Colombia (Abadi et al. 1999, McCarthy et al. 2006, Meiring et al. 2012).

Age - The average age of infected children (8.4 years) found in this study is similar to that found in other studies: seven years in South Africa (91% HIV+) (Meiring et al. 2012), seven years in Thailand (all HIV+) (Likasitwattanakul et al. 2004), 7.25 years in China (HIV-) (Yuanjie et al. 2012), 7.6, 7.8 and 8.8 years in Brazil (the majority HIV-) (Corrêa et al. 1999, 2002, Severo et al. 2009) and eight and 9.8 years in the United States of America (USA) (all HIV+) (Leggiadro et al. 1991, Abadi et al. 1999). The average age is greater in China, at 10.9 years (all HIV-) (Guo et al. 2012); in other studies from the USA, at 11.5 years (all HIV+) (González et al. 1996) and 11.98 years (79.4% immunocompromised) (Joshi et al. 2010) and in Taiwan 13.7% (all HIV-) (Huang et al. 2010). In an American study (Joshi et al. 2010), patients of up to 18 years old were included and in studies from China and Taiwan, patients up to 17 years old were included (Huang et al. 2010, Guo et al. 2012), a fact that could slant the result and increase the average value. In a small Cuban study, the average of age was younger, 5.8 years (85.7% immunocompetent) (Illnait et al. 2013). In our study, two children less than one year old appeared, a finding only frequent in South Africa, where cryptococcosis in children has a bimodal presentation with a peak at less than one year old and another that appears from five-10 years of age. The high incidence of cryptococcosis in children less than one year is explained in South Africa by the vertical transmission of HIV infection (Meiring et al. 2012).

Sex - In this study, there was a slight predominance of the male sex (58.5%) and similar results were observed in studies from Brazil, 52.6% (Corrêa et al. 1999) and 52.8% (Severo et al. 2009), South Africa, 54.9% (Miglia et al. 2011) and 57% (Meiring et al. 2012), Thailand, 57.9% (Likasitwattanakul et al. 2004), China, 60.87% (Guo et al. 2012) and the USA, 60.3% (Joshi et al. 2010). Some small studies have reported a predominance of the female sex in Taiwan, 77.8% (Huang et al. 2010), and Cuba, 57.1% (Illnait et al. 2013). The predominance of the male sex is more evident in adults, especially in the population infected by HIV (Dromer et al. 1996).

Risk factor - Almost half (46.3%) of the studied patients did not have a known risk factor, a quarter (24.4%) had HIV infection and the rest had other conditions that depressed cellular immunity. In the global literature, studies have been described where all or almost all of the patients had AIDS (Leggiadro et al. 1991, Abadi et al. 1999, Gumbo et al. 2002, Likasitwattanakul et al. 2004, Meiring et al. 2012). Additionally, studies exist describing patients without AIDS, but with a percentage of underlying disease, e.g., Guo et al. (2012) (26.1%) and Huang et al. (2010) (56%), as do studies of only immunocompetent patients (Yuanjie et al. 2012). Other studies exist that include patients with all these possibilities, such as ours and that of Joshi et al. (2010), with 20.6% immunocompetent patients, 22.2% displaying malignancy, 15.9% HIV+ and 41.3% displaying other co-morbidities and that of Severo et al. (2009), with 24.1% HIV, 25.9% immunocompetent (half of these infected with *C. gattii*) and 50% with another co-morbidity. It is important to highlight the high

percentage of immunocompetent patients in our series, which is similar to that described in China, Taiwan and Brazil (dos Santos et al. 2008, Huang et al. 2010, Martins et al. 2011, Freire et al. 2012, Guo et al. 2012).

Prevalence - In South Africa, it was estimated that between 0.9-2% of cryptococcosis occurs in children younger than 15 years (McCarthy et al. 2006, Meiring et al. 2012). Additionally, in this same country, 2% of clinical isolates of *Cryptococcus* sp. come from children and 96% of these are HIV+ (Miglia et al. 2011). In Ghana, cryptococcosis is responsible for 6.9% of meningitis cases, with positive cultures in children under 18 years (Owusu et al. 2012), and in Botswana, 2.36% of the meningeal cryptococcosis with positive cultures occur in children < 13 years (Mullan et al. 2011).

In the northern and northeastern regions of Brazil, a series of childhood cryptococcosis cases have been reported with a high prevalence rate: 32% in the state of Bahia (Darzé et al. 2000), 24% in the state of Pará (Corrêa et al. 1999) and 9.5% in the state of Piauí (Martins et al. 2011). In contrast, French Guiana reported a prevalence of 4.6% (Debourgogne et al. 2011). In the USA, the prevalence is lower (0.85-1.4%) in HIV-infected children (González et al. 1996, Abadi et al. 1999), as is the number of hospitalisations for cryptococcosis, which reached a rate of 6.2 million (Joshi et al. 2010). In Thailand, 2.97% of hospitalised HIV+ children under 16 years had cryptococcosis (Likasitwattanakul et al. 2004) and among those younger than 19 years of age hospitalised for pneumonia, 3.3% have positive serum antigen for *Cryptococcus*, all of them HIV+ (Harris et al. 2012). In Latin America, Uruguay registers a prevalence of 1.3% of cryptococcosis in HIV+ children (Quian et al. 2012) and Venezuela reported a prevalence of 0.91% in the general population (Pérez et al. 2009). The prevalence of 2.6% in Colombian children is equally low; however, in a study of meningeal cryptococcosis in HIV- patients in Norte de Santander, 29.6% were children under the age of 16 years (Lizarazo et al. 2012), a fact similar to the one reported in northern Brazil (Corrêa et al. 1999, Darzé et al. 2000). Significantly, northern Brazil and Norte de Santander are characterised by a high prevalence of *C. gattii* infection in immunocompetent patients (Corrêa et al. 1999, Lizarazo et al. 2012).

Incidence - Additionally, there are few data on the incidence of cryptococcosis in children. In South Africa, it was calculated that for the year 2007, there was an incidence of one case per 100,000 children in the general population and 47 cases per 100,000 HIV+ children (Meiring et al. 2012).

In that same country, in the Gauteng province, which has a high rate of prevalence of HIV infection, the incidence of disease is estimated at 38 cases per 100,000 HIV+ children (McCarthy et al. 2006). In an USA study from the end of the last century, an annual incidence of 0.1% among the paediatric population of HIV+ individuals was reported (González et al. 1996). Recently, China reported an incidence of 0.43 cases per 100,000 children less than 18 years (Guo et al. 2012). The incidence of 0.016 cases per 100,000 children under the age of 16 years reported for Colombia in this study is very low compared with what has been reported in other countries; however, in Norte de Santander, the mean annual incidence is seven times higher (0.122 per 100,000), a significant difference from the rest of the country ($p < 0.0001$).

The reason for the low presentation of cryptococcosis in children has not been established. It is thought that it is not because of a lack of exposure because a study revealed the presence of IgG and IgM antibodies against the capsule glucuronoxylomannan of *Cryptococcus* sp., both in HIV+ and HIV- children, a fact that supports the idea of an exposure to the fungus or the presence of a subclinical infection early in childhood (Abadi & Pirofski 1999). Another study carried out in the Bronx, New York, showed that the vast majority of children had antibodies against *Cryptococcus* sp. at the age of two years and that this response persisted throughout childhood (Goldman et al. 2001).

The clinical presentation of disease was mainly neurocryptococcosis (87.8%), a fact also recognised by the majority of the case series (Leggiadro et al. 1991, Abadi et al. 1999, Corrêa et al. 1999, Gumbo et al. 2002, Likasitwattanakul et al. 2004, Severo et al. 2009, Huang et al. 2010, Guo et al. 2012, Meiring et al. 2012, Yuanjie et al. 2012), with the exception of the study of Joshi et al. (2010) where the extraneural cryptococcosis was more frequently observed than meningeal cryptococcosis (62% vs. 38%). The most frequent clinical manifestations of headache, fever, nausea and vomiting, mental confusion and meningeal signs are common in most of the published cases. It should be noted that, as in adults, the meningeal signs have a low positivity (37.5%) (Lizarazo et al. 2007, Escandón et al. 2012). Unfortunately, the value of the opening pressure of the CSF is not specified and, therefore, we could not establish the percentage of children with intracranial hypertension without hydrocephalus, which in adults exceeds 50% (Lizarazo et al. 2012). In only two paediatric series, the value of the CSF pressure was determined and, in both, the percentage of patients with intracranial hypertension was very high: 73.9% in Guo et al. (2012) and 83% in Likasitwattanakul et al. (2004). Almost a fifth of the patients had hydrocephalus, a serious complication of meningeal cryptococcosis. Respiratory compromises were rare and only observed in two patients (4.9%) where the fungus was able to be recovered from bronchoalveolar lavage; likewise, in very few patients (12.2%) were the results of the chest X-ray reported. However, the majority of these patients displayed abnormalities. In only a third of patients, the results of a skull CT were reported, which were abnormal in two-thirds; the abnormalities were multiple, but non-specific. Corrêa et al. (2002) reported a series of immunocompetent children with meningitis caused by *C. gattii* with the presence of hypodense nodules in all of them. To a lesser degree, diffuse cerebral atrophy and hydrocephalus was observed; these last two abnormalities coexisted in some cases. In this series, we do not report results of MRI studies.

Treatment was mostly with AmB, alone or in multiple combinations. The treatment of choice for the meningeal cryptococcosis, which was the prevailing form of presentation in our series, is the association of AmB + 5-fluorocytosin. Although there are no controlled stud-

ies in children, the results of studies in adults have been extrapolated to children and their use has been recommended by international guidelines for management of this disease (Perfect et al. 2010).

The mycological diagnosis was made in the vast majority of the cases in the CSF through direct visualisation of the encapsulated yeast cells in the CSF (sensitivity of 94.7%) and for CSF, blood, bronchoalveolar lavage or skin cultures (sensitivity 85.4%). On a smaller scale, the detection of the *Cryptococcus* capsular antigen in CSF and serum was used. These findings are similar to those reported by other investigators (Abadi et al. 1999, Corrêa et al. 1999, Likasitwattanakul et al. 2004, Severo et al. 2009, Huang et al. 2010, Guo et al. 2012, Meiring et al. 2012) and highlight the utility of direct studies and of culture in the diagnosis of cryptococcosis.

A few of the published reports determined the type of species responsible for cryptococcosis (Severo et al. 2009, Meiring et al. 2012). *C. neoformans* var. *grubii* is responsible for the majority of cryptococcosis in the world and, to a greater extent, in patients who are HIV+ (Antinori 2013). The percentage of 5.9% *C. gattii* in Colombian children is high if compared with the findings of cryptococcosis in the general population of Colombia (3.4-3.8%) (Lizarazo et al. 2007, Escandón et al. 2012). In South Africa, 7% of paediatric infections are caused by *C. gattii* (Meiring et al. 2012) while in Brazil the percentage is much higher, 29.6% (Severo et al. 2009).

In recent years, interest in cryptococcosis in children has been on the rise. The National Survey on Cryptococcosis that is being conducted passively in our country has allowed us to estimate the prevalence of cryptococcosis in children in Colombia. However, epidemiological data are still scarce, the factors that determine its relative rarity in the childhood population are still poorly understood and there are no own management guides. Undoubtedly, new studies are needed to improve the handling of children affected by this fungal infection.

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