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Cryptococcosis in children

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SUMMARY

Cryptococcosis is a systemic–opportunistic mycosis caused by two species of the encapsulated yeast-like organism, *Cryptococcus neoformans* and *C. gattii*, which cause infection in immunocompromised individuals and in immunologically normal hosts, respectively. Most susceptible to infection are patients with T-cell deficiencies. The spectrum of disease ranges from asymptomatic pulmonary lesions to disseminated infection with meningoencephalitis. After the emergence of AIDS, cryptococcal infections have become much more common. The mycosis occurs less frequently in children than in adults. The purpose of this article is to discuss the aetiology, clinical presentation, predisposing conditions and outcomes in cases of cryptococcosis in children. Emphasis is placed upon paediatric cases occuring in Brazil and in particular to highlight the difference between cases diagnosed in Porto Alegre (South - subtropical climate) and in Belem (North - equatorial climate).

Pulmonary cryptococcosis is caused by *Cryptococcus* and is an uncommonly recognised and often fatal disease in children.[1,2] The respiratory tract is the usual portal of entry of the organism, by inhalation from an environmental source. Following invasion of the lungs, the organism may become localised in non-immunocompromised hosts until an immune defect appears. The infection can then disseminate haematogenously to any part of the body, most notably the central nervous system (CNS).[3,4] Occasional sites of infection also include skin, bone, liver, spleen, adrenals, prostate, kidney, lymph nodes and elsewhere, especially in patients with profound cellular immune deficiency,[1,5,6] although an osteomyelitis case caused by *C. neoformans* had already been described in an immunocompetent child without another site of infection.[7]

Cryptococcosis usually occurs in individuals with human immunodeficiency virus (HIV) infection, followed by glucocorticosteroid therapy and solid organ transplantation.[3] When it is observed during childhood, the differential diagnosis includes pulmonary metastatic chest disease on chest radiographs.[8,9]

EPIDEMIOLOGY

Cryptococcosis has been considered a sporadic infection and varies widely with geographic location according to the aetiologic agent. The disease is endemic in Australia, Papua New Guinea, parts of Africa, the Mediterranean region, India, Southeast Asia, Mexico, Paraguay, southern California and northeastern and northern Brazilian regions.[10–13] *Cryptococcus neoformans* (serotypes A, D and AD based on capsular polysaccharide antigens) has a worldwide distribution and is associated with accumulations of avian guano, especially dried pigeon dung.[11] This species is predominantly opportunistic, involving immunosuppressed hosts.[14] In contrast, *C. gattii* (serotypes B and C), mainly distributed in trees of tropical and subtropical regions, emerged in 1999 in a distinct ecologic environment on Vancouver Island, Canada. It is usually pathogenic, causing respiratory and disseminated infections, predominantly in immunocompetent individuals.[11,14,15] Both species are aetiological agents of cryptococcosis in children in Brazil.[10,13,16]

CLINICAL FINDINGS

Human cryptococcosis can show a variety of clinical presentations, mainly related to the integrity of the immune system of the host. Due to the unspecificity of signs and symptoms, clinical diagnosis without laboratory tests is difficult. For instance, cryptococcosis ranges from the asymptomatic nodule in the lung to a widely disseminated disease.[3,17]

Cryptococcus is an important fungal pathogen that is recognised for its ability to cause subacute CNS disease.[18] However, infection is acquired as a result of inhalation of infectious particles from the environment. Lungs are the second most commonly involved site

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of disease, after the CNS. *Cryptococcus neoformans* is the commonest cause of fungal meningitis.[16] In contrast, in cryptococcosis due to *C. gattii*, large mass lesions in lung and/or brain (cryptococcomas) are characteristic and morbidity from this neurological disease is high.[16]

The most common symptoms seen in meningeal infection are headache, fever, nausea, vomiting, dizziness, irritability and somnolence.[19] However, meningitis may be virtually asymptomatic apart from a mild headache.[18] Disseminated cryptococcosis is a rare and often fatal disease in children.[1] The majority of cases usually occur in individuals with defective cell-mediated immunity, most commonly due to HIV infection.[20] In the lung, involvement of cryptococcosis may present as pneumonia, pulmonary nodules and masses or miliary lesions. The respiratory imaging abnormalities can be from asymptomatic individuals or those with chronic symptomatology.[21]

DIAGNOSTIC METHODS

The radiographic features of cryptococcosis are related to the underlying immune status of the patient. Isolated pulmonary or CNS nodules are often found in immunocompetent individuals and are easily mistaken for neoplasia. Thus, the differential diagnosis of these diseases must be considered in all cases.[8,9]

In order to confirm the diagnosis of cryptococcosis, microscopic observation, culture using a selective isolation medium and the detection of the capsular antigen are tests usually undertaken. In clinical specimens, yeast cells of *Cryptococcus* are mostly globose in shape surrounded by a polysaccharide capsule. *Cryptococcus* grows well on the majority of mycological media at 25 °C and 37 °C, presenting as white, shiny, moist and often mucoid colonies. Microscopically, the colonies are composed of spherical to oval, encapsulated yeast cells, budding by a narrow base and range from 2 to 20 μm in diameter but usually measure 4–10 μm in diameter. Cycloheximide should not be used because it inhibits the growth of the fungus. Its identification includes the production of a brown colony on niger seed (an aqueous extract of *Guizotia abyssinica* seeds that contains diphenolic compounds) agar. This pigment is a melanin-like compound produced by the fungus with phenoloxidase activity. For serologic diagnosis, latex agglutination for cryptococcal polysaccharide antigens in body fluids has been a specific and sensitive alternative and offers a significant improvement for rapid diagnosis. Lysis centrifugation (Isolator®) is the best technique for culture with highest sensitivity and shortest incubation period. An agar medium containing canavanine–glycine–bromthymol blue is a simple and efficient test for differentiating *C. neoformans* from *C. gattii*.[22]

On histopathologic analysis, it is evident that the host reaction to *Cryptococcus* is variable and this relates to the immunological status of the patient. Early lesions are characterised by their gelatinous texture, but older lesions become granulomatous. In cryptococcal granulomatous pneumonia, the yeast cells may be difficult to see with haematoxylin and eosin (Fig. 1). The more effective stain is the Gomori methenamine silver stain (commonly used in the histological study of mycotic diseases) (Fig. 2). However, the best and most specific stains are Mayer's mucicarmine (a distinctive diagnostic marker that stains the capsular material rose red) (Fig. 3) and Fontana-Masson (stains melanin in the cell wall) staining techniques (Fig. 4).[23]

MANAGEMENT

Treatment recommendations for cryptococcosis in children are based on the extrapolation of experience in adults, given the fact that paediatric cases are rare. Although spontaneous resolution of pulmonary cryptococcal infection is the usual course in immuno-

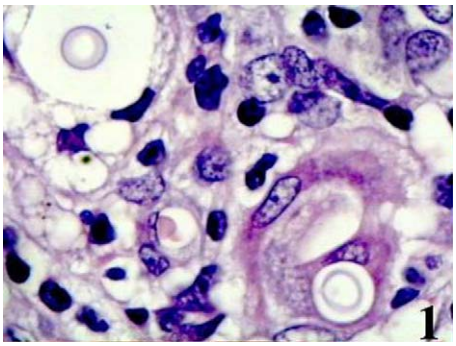

Figure 1. Pulmonary cryptococcosis. Strucutures are surrounded by optically clear spherical zones in the pulmonary interstitium, associated with minimal inflammation (Hematoxylin-Eosin, ×100).

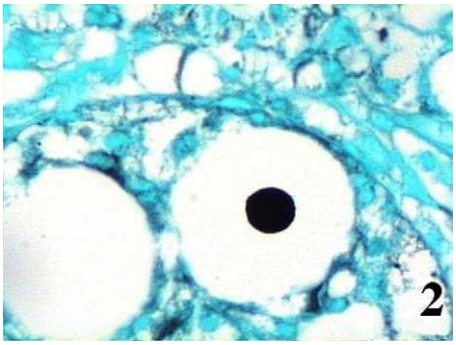

Figure 2. Cryptococci with clear zone around fungal cell represent the wide, unstained capsules (Gomori's methenamine silver, ×100).

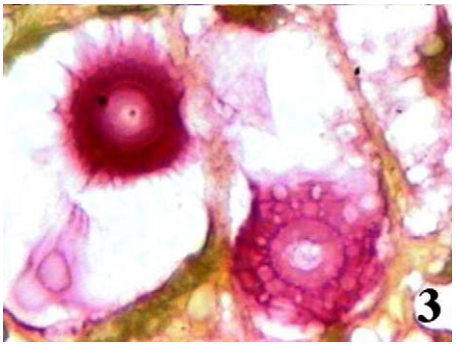

Figure 3. Single cryptococci distend the interstitium and are surrounded by brilliant, intensely carminophilic capsules that have a spinous or crenated appearance caused by uneven shrinkage during tissue processing (Mayer's mucicarmine, ×100).

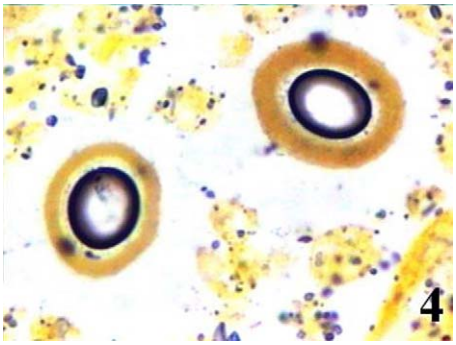

Figure 4. Cryptococcal cell wall contain silver-reducing substances, they react positively with a Fontana-Masson for melanin (×100).

Table 1
Brazilian children cryptococccosis cases reviewed from the literature

No.	Ref.	State	Sex/Age [years]	Clinical features	Underlying Illness	Treatment	Outcome
1	10	PA	M/1	Fever, cough, jaundice, irritability, blurred vision	Pneumonia	AmB	Cured
2	13	PA	F/8	Fever, headache, neck pain, vomit, cough, weight loss, hydrocephalus, irritability /2 months	CRF, sepse, pneumonia, arthralgia	AmB	Death
3	13	PA	M/12	Fever, headache, neck pain, vomit, blurred vision /21 days	Hypokatemia, anemia	AmB + 5Fc	Improved, 4 months
4	13	PA	F/6	Fever, headache, neck pain, vomit, hydrocephalus, confusion /2 months	Rheumatic fever	AmB + 5Fc	Improved, 2 months
5	13	PA	F/11	Fever, headache, neck pain, vomit, nausea, hydrocephalus, blurred vision/1 month	Arthralgia	Anfo B + 5Fc	Improved, 5 months
6	13	PA	M/8	Fever, headache, neck pain, vomit, malnutrition/5 months	Intestinal parasitosis, blindness	AmB + 5Fc + Flu	Improved, 5 months
7	13	PA	M/8	Fever, headache, neck pain, vomit/7 days	Ptiriasis versicolor	AmB + 5Fc	Improved, 6 months
8	13	PA	F/13	Fever, headache, neck pain, vomit, caquexia, weight loss, coma/1 months	Hydrocephalus, blindness, hypokatemia	AmB + Flu	Improved, 5 months
9	13	PA	M/12	Fever, headache, chest pain /1 month	Intestinal parasitosis, deafness, blindness, pnumonia	AmB + 5Fc + Flu	Improved, 4 months
10	13	PA	M/10	Fever, headache, neck pain, eye pain /20 days	Thyroid enlargment, hepatomegaly	AmB + 5Fc	Improved, 6 months
11	13	PA	M/11	Fever, headache, neck pain, vomit, nausea /20 days	Intestinal parasitosis, scabies	Anfo B + Flu	Improved, 6 months
12	13	PA	M/12	Fever, headache, vomit, hydrocephalus, nasal bleeding/20 days	Scabies, hypokatemia	AmB + 5Fc + Flu	Improved, 7 months
13	13	PA	F/8	Fever, headache, convulsions /2 months	Pneumonia, blindness, ventriculo peritoneal derivation	AmB + Flu	Improved, 7 months
14	13	PA	F/6	Fever, headache, vomit, convulsions/45 days	Pneumonia, malaria, malnutrition	AmB + Flu	Death, 2 months
15	13	PA	F/3	Fever, headache, vomit/1 month	Pneumonia, CRF, blindness	AmB + Flu	Death, 3 months
16	13	PA	M/5	Fever, headache, neck pain/3 days	Pneumonia, sepsis	AmB + Flu	Death, 1 months
17	13	PA	M/11	Fever, headache, neck pain, vomit/14 days	Pulmonar mass, encephalitis, sepsis, hypokatemia	AmB + 5Fc + Flu	Improved, 7 months
18	13	PA	M/11	Fever, headache, neck pain, vomit, lethargy, coma/4 days	Respiratory failure, sepsis	AmB	Death, 8 days
19	13	PA	F/8	Fever, headache, neck pain, vomit, sleepiness, lethargy, confusion, petechise/21 days	Pneumonia	AmB + 5Fc	Death, 30 days
20	13	PA	F/12	Fever, headache, neck pain, sleepiness/12 days	None	AmB + 5Fc	Improved, 3 months
21	17	RS	M/2	NA	None	AmB + 5Fc	Cured
22	27	RS	F/2	Fever, vomit, nuchal rigidity	Meningoencephalitis tubercular e bronchopneumonia	AmB	Cured
23	27	RS	F/3	Fever, productive cough, anorexia, sleepness, seizures, coma	Malnutrition, bronchopneumonia bacterial, stomatitis	AmB	Death, 5 days
24	27	RS	M/9	Headache, neck pain, fever, vomit/5 days	None	AmB + 5Fc	Death, 3 months
25	28	RJ	M/8	Headache, vomit, weight loss, fever	AIDS	AmB	Death, 1 month
26	28	RJ	F/5	Fever, headache, vomit/7 days	AIDS, sickle cell anemia	AmB	Death, 3 days
27	28	RJ	M/7	Generalized micropoliadenomegaly and hepatomegaly, weight loss, headaches, vomit	AIDS	AmB	Death, 3 months
28	28	RJ	F/7	Diarreia, weight loss, headache, vomit	AIDS	AmB	Cured
29	28	RJ	F/5	Fever, headache	AIDS	AmB + Flu	Cured
30	29	RJ	M/3	Fever, headache, vomit, inapetence, apathy, sleepiness, hydrocephalus	None	None	Death, 12 days
31	29	RJ	M/10	lesions in face and thorax, cough, diarreia, fever, headache, nausea, photophobia, hydrocephalus	AIDS, hemophilia	AmB + 5Fc	Death, 5 months
32	30	RS	F/7	NA	AIDS	NA	NA

PA: Pará; RS: Rio Grande do Sul; RJ: Rio de Janeiro; F: female; M: male; NA: data not avaiable; CRF: chronic renal failure; AIDS: acquired immunodeficiency syndrome; AmB: amphotericin B; Flu: fluconazole; 5-Fc: 5-Fluorocitosine.

competent individuals, subsequent dissemination can occur. Amphotericin B and fluconazole are the most common antifungal agents used in the treatment of cryptococcosis. In light of the potential risk of amphotericin B toxicity, therapy with fluconazol in immunocompentent children is recommended.[24–26] For all imunocompromised patients, a work-up for extrapulmonary disease is indicated, including a lumbar puncture to exclude CNS infection. In these cases, the type and duration of therapy should be guided by the immune status of the host and the extent of disease.[26]

BRAZILIAN EXPERIENCE WTH PAEDIATRIC CASES OF CRYPTOCOCCOSIS

This experience is based upon an analysis of 32 cryptococcosis cases reported in children (Table 1) supplemented by 21 new cases from southern Brazil (Porto Alegre ($n = 10$)) and northern Brazil (Pará ($n = 11$)) that were diagnosed by the Mycology Laboratory of Santa Casa Complexo Hospitalar – Porto Alegre, RS, Brazil (Table 2).

In the literature ($n = 32$), 17 patients were boys and 15 were girls aged 1–13 years (average 7.6 years).[10,13,17,27–30] In the new cases ($n = 21$) 11 patients were boys and 10 were girls aged 0–16 years (average 7.8 years). Only 3% of the cases in the reported literature and 9.5% of the new patients were younger than 2 years, which is consistent with the report of Goldman et al (2001)[31] that showed serologic evidence of disease acquisition occurring after the second year of life. In another international study, the cryptococcosis infection also occurred more frequently in middle childhood (6–12 years), rarely appearing during the first 2 years.[32] This could be explained by the increase of the mobility and independence of children resulting in increased environmental exposure.[31]

The most common presenting symptoms and signs from the Brazilian cases (Table 1) were headache, fever, vomiting, neck pain and stiffness (93.7% – 30/32 cases), similar to those described in literature.[3,18,19] Hydrocephalus was observed in one child from Pará, and in six cases from the literature.[13,29] In fact, CNS is the most commonly involved site in cryptococcosis infection due to the tissue tropism of the agent, which can find an ideal habitat that provides for its nutritional requirements from the cerebrospinal fluid (CSF) and tissue of the basal ganglia.[18,33] Thus, meningitis is the predominant clinical presentation with fever, vomiting and headache as the most common symptoms.[18,33] Pulmonary cryptococcosis without dissemination is an unusual presentation of cryptococcal infection in immunossupressed children.[34,35] Herein, none of the patients suffered from the respiratory disease without involvement of other systems; all of the cases had CNS involvement.

In relation to the aetiological agent and diagnostic method used, in 2002, Correa et al.[13] reported nine cases diagnosed in cerebrospinal fluid (CSF) as *C. gattii*; in those, eight were also diagnosed with positive antigen. In 1987, Fontana et al.[27] isolated *C. neoformans* in the CSF in all patients ($n = 3$) as well as in a tracheal aspirate in one case. In 1997, Py et al.[28] reported that from all five cases, none was diagnosed by culture, three only by direct examination of the CSF, only one by antigen detection and one by both tests. In 1994, Rozembaum et al.[29] isolated *C. neoformans* in the two cases reported: one in the CSF and the other in blood as well. In 2004, Pasqualotto et al.[30] reported one case in a child, diagnosed as *C. neoformans* (Table 3).

In contrast, in the new cases studied, 90.5% were positive on direct examination of the CSF, *C. neoformans* was identified in 47.6% of the children and *C. gattii* in 33.3%. Interestingly, from the 11 cases from northern Brazil, 10 were due to *C. gattii* in contrast to cases in the south, where nine of the 10 cases were attributed to *C. neoformans* (Table 4). In most countries where cryptococcosis due to *C. gattii* is endemic, the disease rarely occurs in children.

Table 2
Brazilian children cryptococccosis cases diagnosed in Mycology Laboratory of Santa Casa Hospital, Porto Alegre, RS, Brazil

No.	State	Sex/Age [years]	Clinical features	Underlying Illness	Treatment	Outcome
1	RS	M/12	Headache, vomit, neck pain, ataxia/3 months	None	AmB + 5Fc	Death, 1 month
2	RS	M/9	Headache, vomit, neck pain, weight loss/3 months	AIDS, hemophilia A, chickenpox	AmB + 5Fc	Death, 7 month
3	RS	F/1	Fever, sleepness, irritability, vomit, nuchal rigidity	None	NA	NA
4	RS	F/3m	sudden fontanelle distortion and suture diastasis	Congenital cardiopathy, prematurity, pulmonary dysplasia	AmB	Death, 1 month
5	RS	F/7	Cough, convulsions, blindness, nuchal rigidity	AIDS, broncopneumonia	AmB + 5Fc	Death, 1 month
6	RS	F/12	Headache, vomit, weight loss	AIDS	AmB	Death
7	RS	F/2	Fever, headache, dizziness, right face paresia, cervical linphadenomegaly	Cerebral tumor (anaplasic ependymoma)	Flu	Death, 4 months
8	RS	M/10	Headache, vomit, convulsions/1 month	AIDS	AmB	Death
9	RS	F/7	Headache, vomit	Rhabidomyosarcoma embryonal (botryoid)	AmB	NA
10	RS	M/7	Fever, headaches, vomit, nuchal rigidity, weight loss, intracranial hypertension/1 month	AIDS	AmB + Flu	NA
11	RS	M/13	Fever, headache, vomit, chest pain	Lung transplantation	NA	NA
12	PA	M/16	Fever, convulsion, headache, nuchal rigidity, diploidy, confusion	None	AmB + Flu	NA
13	PA	F/6	Fever, headache, vomit, weight loss, nuchal rigidity, convulsion/40 days	None	AmB	Death
14	PA	M/7	Fever, weight loss, anorexia, vomit, nuchal rigidity, ataxia	AIDS	AmB	NA
15	PA	F/5	Headache, convulsion, nuchal rigidity, vomit/1 month	None	AmB	Death
16	PA	F/6	Fever, headache, irritability/2 years	Typhoid fever	AmB	Improved
17	PA	F/10	Fever, headache, vomit	None	AmB + Flu	Improved
18	PA	M/8	Fever, headache, vomit, hydrocephalus	Pulmonary tuberculosis	AmB	Improved
19	PA	M/12	Fever, headache, vomit	None	Anfo B	Improved
20	PA	M/8	Fever, headache, vomit, photophobia, convulsions, dry cough/3 months	None	AmB + Flu	Improved
21	PA	M/8	Fever, headache, abdominal pain, vomit, nuchal rigidity	None	AmB + Flu	Improved
22	PA	M/12	Fever, headache, vomit, chest pain	None	AmB + Flu	Improved

PA: Pará; RS: Rio Grande do Sul; F: female; M: male; NA: data not avaiable; AIDS: acquired immunodeficiency syndrome; AmB: amphotericin B; Flu: fluconazole; 5-Fc: 5-Fluorocitosine.

Table 3
Etiology and diagnostic methods of Brazilian children cryptococcosis cases reviewed from the literature

No.	Ref.	State	Sex/Age [years]	Diagnostic tests		
				CSF -D	Culture	CSF Ag detection
1	10	PA	M/1	*C sp.*	CSF - *Cryptococcus sp.*	None
2	13	PA	F/8	*C sp.*	CSF- *Cryptococcus sp.*	None
3	13	PA	M/12	*C sp.*	CSF- *Cryptococcus sp.*	None
4	13	PA	F/6	*C sp.*	CSF- *Cryptococcus sp.*	None
5	13	PA	F/11	*C sp.*	CSF- *Cryptococcus sp.*	None
6	13	PA	M/8	*C sp.*	CSF- *Cryptococcus sp.*	None
7	13	PA	M/8	*C sp.*	CSF- *Cryptococcus sp.*	+
8	13	PA	F/13	*C sp.*	CSF- *Cryptococcus sp.*	+
9	13	PA	M/12	*C sp.*	CSF- *Cryptococcus sp.*	None
10	13	PA	M/10	*C sp.*	CSF- *Cryptococcus sp.*	None
11	13	PA	M/11	*C sp.*	CSF- *Cryptococcus sp.*	+
12	13	PA	M/12	*C sp.*	CSF - *C. gattii*	+
13	13	PA	F/8	*C sp.*	CSF - *C. gattii*	+
14	13	PA	F/6	*C sp.*	CSF - *C. gattii*	+
15	13	PA	F/3	*C sp.*	CSF - *C. gattii*	+
16	13	PA	M/5	*C sp.*	CSF - *C. gattii*	None
17	13	PA	M/11	*C sp.*	CSF - *C. gattii*	+
18	13	PA	M/11	*C sp.*	CSF - *C. gattii*	+
19	13	PA	F/8	*C sp.*	CSF - *C. gattii*	+
20	13	PA	F/12	*C sp.*	CSF - *C. gattii*	+
21	17	RS	M/2	*C sp.*	CSF - *C. neoformans*	None
22	27	RS	F/2	*C sp.*	CSF - *C. neoformans*	None
23	27	RS	F/3	*C sp.*	CSF, tracheal fluid - *C. neoformans*	None
24	27	RS	M/9	*C sp.*	CSF - C. neoformans	None
25	28	RJ	M/8	*C sp.*	None	None
26	28	RJ	F/5	*C sp.*	None	None
27	28	RJ	M/7	Negative	None	+
28	28	RJ	F/7	*C sp.*	None	None
29	28	RJ	F/5	*C sp.*	None	+
30	29	RJ	M/3	*C sp.*	CSF and blood - *C. neoformans*	None
31	29	RJ	M/10	*C sp.*	CSF - *C. neoformans*	None
32	30	RS	F/7	*C sp.*	CSF - *C. neoformans* var. *grubii*	None

PA: Pará; RS: Rio Grande do Sul; RJ: Rio de Janeiro; F: female; M: male; CSF: cerebrospinal fluid; D: Direct examination; *C*: *Cryptococcus*; Ag: antigen.

Nevertheless, in the northeastern and northern Brazilian regions, especially in the State of Pará, where cryptococcosis by *C. gattii* is also endemic, the disease in children is relatively frequent as described here.[13]

AIDS was reported in seven cases (22%) in the literature.[28–30] Only four patients did not have an underlying condition,[13,17,27,29] of these were three who were infected by *C. gattii*[13,17,27] and one by *C. neoformans.*[29] In the present cases, AIDS was diagnosed in six children (28%), while 10 (48%) did not have any underlying associated condition (eight from Pará and mostly in children who were infected by *C. gattii*). The association of cryptococcosis and AIDS in Brazil was relatively low in comparison with the

Table 4
Etiology and diagnostic methods of Brazilian children cryptococcosis cases diagnosed in Mycology Laboratory of Santa Casa Hospital, Porto Alegre, RS, Brazil

No.	State	Sex/Age [years]	Diagnostic tests		
			Direct examination	Culture	Ag detection
1	RS	M/12	CSF- *C.* sp.	CSF - *C. neoformans* (A)	None
2	RS	M/9	CSF- *C.* sp.	CSF - C. neoformans (A)	None
3	RS	F/1	CSF- *C.* sp.	CSF - C. neoformans (A)	None
4	RS	F/3m	CSF- *C.* sp.	CSF - C. neoformans	CSF and blood +
5	RS	F/7	None	ISO - urine - *C. neoformans*	Blood and CSF +
6	RS	F/12	CSF and urine - *C.*sp.	CSF and urine - *C. neoformans*	Blood and CSF +
7	RS	F/2	None	CSF - *C. neoformans*	CSF +
8	RS	M/10	CSF- *C. sp.*	CSF and Blood - *C. neoformans*	CSF +
9	RS	F/7	Lung biopsie- *C. sp.*	None	Blood +
10	RS	M/7	CSF- *C. sp.*	CSF - *C. neoformans*	Blood, CSF and urine +
11	RS	M/13	Lung biopsie- C. sp.	Lung biopsie - *C. neoformans*	None
12	PA	M/16	CSF- *C. sp.*	CSF - *C. gattii*	CSF +
13	PA	F/6	CSF- *C. sp.*	CSF - *Cryptococcus sp.*	CSF +
14	PA	M/7	CSF- *C. sp.*	CSF - *C. gattii*	None
15	PA	F/5	CSF- *C. sp.*	CSF - *C. gattii*	CSF +
16	PA	F/6	CSF- *C. sp.*	CSF - *C. gattii*	None
17	PA	F/10	CSF- *C. sp.*	CSF - *Cryptococcus sp.*	CSF +
18	PA	M/8	CSF- *C. sp.*	CSF - *C. gattii*	CSF +
19	PA	M/12	CSF- *C. sp.*	CSF - *C. gattii*	CSF +
20	PA	M/8	CSF- *C. sp.*	CSF - *C. gattii*	CSF +
21	PA	M/8	CSF- *C. sp.*	CSF - *C. neoformans*	CSF +
22	PA	M/12	CSF- *C. sp.*	CSF - *Cryptococcus sp.*	CSF +

RS: Rio Grande do Sul; PA: Pará; F: female; M: male; CSF: cerebrospinal fluid; *C*: *Cryptococcus*; Ag: antigen.

worldwide literature, which shows that 7–10% of patients with AIDS are affected by cryptococcosis, and AIDS-associated cryptococcosis accounts for 50% of all cryptococcal infections reported.[32] This limited co-infection of AIDS and cryptococcosis in the present series can be explained by the fact that *C. gattii*, which was frequently isolated from healthy children without underlying disease from Pará (an endemic area), is a common agent that infects immunocompetent hosts.[22]

Although the treatment used was amphotericin B as monotherapy medication (10/21–present cases, 9/32 – literature) or associated with fluconazole and/or 5-flucytosine (9/21 – present cases, 21/32 – literature), the case fatality rate (12/32 (37.5%) – literature vs. 9/21 (42.8%) present series) was high. The poor prognosis is attributed to the severity of the infection with the involvement of the CNS, resulting in therapeutic failure. This conclusion is supported by Abadi et al.[32] which showed a higher mortality rate in children who had evidence of disseminated cryptococcosis. In fact, the success of treatment with amphotericin B and flucytosine was described in AIDS children with an early diagnosis and therapy of cryptococcal meningitis.[6,25,33–36]

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