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ORIGINAL ARTICLE

Clinical characteristics and prognosis of pediatric cryptococcosis in Beijing Children's Hospital, 2002–2014

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Abstract Cryptococcosis is a rare pediatric disease. The aim of the study is to describe clinical characteristics and prognosis of pediatric cryptococcosis from 2002 to 2014 in Beijing Children's Hospital. A total of 53 cases of cryptococcosis were identified, 69.8% of which were males. The mean age was 7 years. Forty-one (77.4%) patients had no underlying conditions. Fever, headache, and vomiting were the most common symptoms. The most common sites were the central nervous system (CNS), followed by the lungs. Most patients received a combination of amphotericin B and fluconazole with or without flucytosine as their initial regimen. Twenty-seven patients received a follow-up and six patients (22.2%) had died. The factors associated with neurological complications or death were headache ($P = 0.008$), seizures ($P = 0.006$), visual impairment ($P = 0.011$), neck stiffness ($P = 0.008$), low erythrocyte sedimentation rate (ESR) ($P = 0.024$), and a cerebral spinal fluid (CSF) cryptococcal antigen titer ≥ 1:1024 ($P = 0.038$).

Conclusions: The majority of cryptococcosis cases in China occurred in children without underlying conditions, causing multiple organ damage. The CNS was the most common site. Patients who had headaches, seizures, or high CSF antigen titers experienced neurological complications or died.

What is known:
• *Cryptococcosis is a rare cause of infection in children.*

What is new:
• *This review gives a brief overview over pediatric cryptococcosis in China*

Keywords Cryptococcosis · Pediatrics · Clinical characteristics · Prognosis

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Abbreviations

5-FC	5-Flucytosine
AIDS	Acquired immune deficiency syndrome
AmB	Amphotericin B deoxycholate
CM	Cryptococcal meningitis
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
ESR	Erythrocyte sedimentation rate
Flu	Fluconazole
HIV	Human immunodeficiency virus
MBL	Mannose-binding lectin
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
VOR	Voriconazole
WBC	White blood cell
XLA	X-linked agammaglobulinemia

Introduction

Cryptococcosis is an invasive mycotic infection caused by the *Cryptococcus* species, an encapsulated, yeast-like fungus with the ability to infect a number of sites, and primarily results in meningitis with significant morbidity and mortality [30]. It is often reported to develop in immunocompromised hosts, specifically adult patients with AIDS. However, the majority of cryptococcosis cases in China are reported to have occurred in immunocompetent hosts [7].

Many large-scale studies have been conducted in adult patients with cryptococcosis, but there are limited studies focusing on pediatric populations. To our knowledge, fewer than 1000 cases of pediatric cryptococcal infection have been reported in English-language studies [1, 11, 14, 16, 18, 20, 22, 25, 34, 36], most of which occurred in non-HIV-infected but immunocompromised hosts. The clinical characteristics of pediatric patients with cryptococcosis differ between reports. Accordingly, we conducted a retrospective study to investigate the clinical manifestations and outcomes of pediatric cryptococcosis at Beijing Children's Hospital.

Materials and methods

Study design

We reviewed data from children (younger than 18 year old) confirmed cryptococcosis who admitted to Beijing Children's Hospital (a 970-bed tertiary health care hospital) between January 2002 and September 2014 in this retrospective study.

We reviewed patient records for demographic data, clinical manifestations, and laboratory findings from the Medical Records and Statistics Room. All imaging studies were reviewed by a single radiologist and the initial treatment.

Case definition

Cryptococcosis cases were defined by (1) positive culture of *Cryptococcus* from a normally sterile site, (2) a positive India ink staining of cerebrospinal fluid (CSF), (3) positive cryptococcal antigen in CSF and/or in the blood, and (4) a pathological diagnosis. Disseminated cryptococcosis was defined when at least two noncontiguous organs were affected [31].

Cryptococcal antigen assay: The Immy Latex-Crypto Antigens (Immuno-Mycologics, Inc.) were used to perform the antigen assay.

Long-term outcomes

Long-term prognosis was assessed in April 2015 by contacting the families by telephone. Following items were asked: outcome: dead or alive; symptoms: (1) headache, (2) nausea and vomiting, (3) sight, (4), hearing, and (5) epilepsy; dysthymic disorders: (1) irritability, (2) anxious, and (3) depression; dyskinesia: (1) limb paralysis, (2) facial paralysis, (3) ataxia, and (4) dysphonia. Patients who had neurological complications (blindness and personality changes, e.g., irritability) or had passed away were categorized as having a poor status; all others were determined to be in good status.

Statistical analysis

Mean and standard deviations (SDs) are shown when distributions were confirmed normal; median and interquartile range (IQRs) are reported otherwise. The categorical variables were compared using the Chi-square test or Fischer's exact test, as appropriate. Continuous variables within two groups were compared using the independent t test for parametric data and the Mann-Whitney U test for non-parametric data. P values < 0.05 were considered statistically significant. All of the statistical analyses were conducted using Statistical Product and Service Solutions (SPSS), version 19.0 (IBM, NY, USA).

Results

Demographic data and underlying conditions

A total of 53 hospitalized children were diagnosed with cryptococcosis during the 13.75-year study period. The cases originated from 11 provinces in the mainland, mostly from North China and Central China (Fig. 1). The temporal trend over the years was shown in Fig. 2. Table 1 describes the demographic characteristics of the sample. All of the children were Han

	Provinces	N	%
1	Hebei	22	41.5
2	Henan	8	15.1
3	Shandong	6	11.3
4	Shanxi	4	5.7
5	Jiangxi	3	5.7
6	Hunan	3	5.7
7	Guizhou	3	5.7
8	Anhui	1	1.9
9	Hubei	1	1.9
10	Chongqing	1	1.9
11	Yunnan	1	1.9

Fig. 1 Map of mainland China showing the provinces in which cryptococcosis was diagnosed from 2002 to 2014

Chinese, and 37 (69.8%) were male. The average age was 7 years, with only two patients being younger than 2 years. Additionally, 19 (35.8%) cases had a history of exposure to poultry, including 11 who were exposed to pigeons and 8 to chickens. The underlying conditions included in the analysis are presented in Table 1; however, 77.4% (41) of the patients had no underlying disease.

Organ involvement and clinical manifestations

The most commonly affected organs were the central nervous system (CNS) (42 cases; 79.2%) and lungs (28 cases; 52.8%). Compared with patients with cryptococcal meningitis (CM), non-CM patients were more likely to present from January to March (63.6 vs. 9.5%) (Table 1). Other involved sites included the lymph nodes (24 cases; 45.2%) (17 abdominal, 16 pulmonary, and two cervical), liver (9 cases; 17.0%), spleen (9 cases; 17.0%), and kidneys (2 cases; 3.8%), and the skin, skeleton, and costal cartilage were involved in one case each (1.9%). Disseminated cryptococcosis was identified in 25 (47.2%) patients.

The time to diagnosis ranged from 2 days to 20 months, with an average of 35 days. The common clinical manifestations were as follows: fever, in 53 cases (100%); headache, 33 (62.3%); vomiting, 30 (56.6%); confusion, 19 (35.8%); and cough, 19 (35.8%), as shown in Table 2. Fever and headache were the predominant symptoms. Four of 42 (9.5%) CM cases did not show any neurological symptoms, and 9 of 28 (31.2%) patients with pulmonary disease had no respiratory symptoms.

Laboratory examinations

The median white blood cell (WBC) count at presentation on the peripheral smear was 11,700 (interquartile range, 9000–16,000) cells per mm^3, with a median neutrophil percentage of 69%. The average eosinophil count was 1870 (± 1500) cells

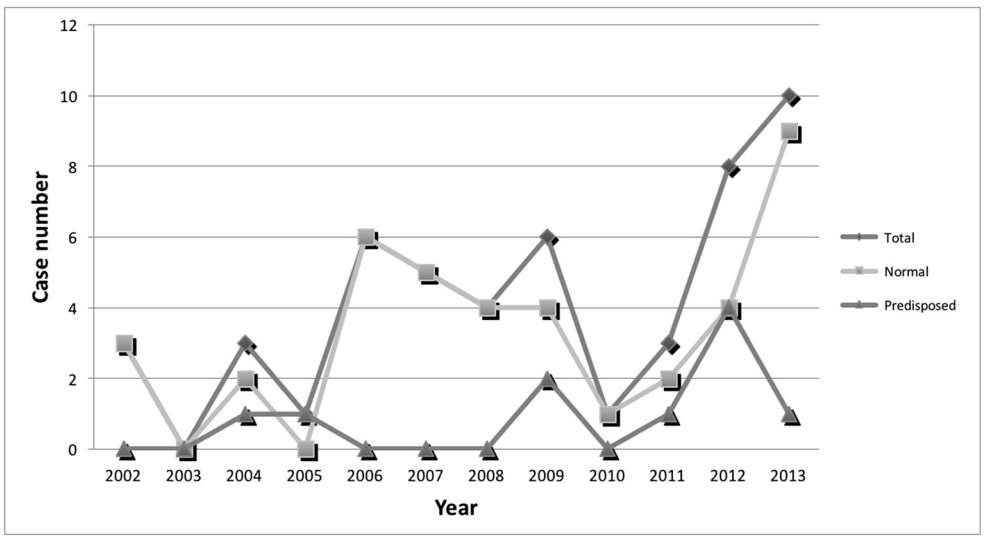

Fig. 2 Temporal trend of cryptococcosis in children, 2002–2013

Table 1 Characteristics of hospitalized patients with cryptococcosis ($N = 53$)

Item	Overall ($N = 53$) (%)	CM ($n = 42$) (%)	Non-CM ($n = 11$) (%)	P
Male gender	37 (68.9)	29 (69.0)	8 (72.7)	1
Age (year, range)	7 (1–17)	7 (1–15)	7 (2–17)	0.829
< 2 years old	2 (3.8)	2 (4.8)	0 (0)	
2–5 years old	19 (35.8)	14 (33.3)	5 (45.5)	
> 5 years old	32 (60.4)	26 (61.9)	6 (54.5)	
Rural residence	40 (75.5)	34 (81.0)	6 (54.5)	0.112
Poultry exposure	19 (35.8)	17 (40.5)	2 (18.2)	0.290
Underlying conditions	12 (22.6)	11 (26.2)	1 (9.1)	0.421
HIV infection	1	1	0	
Nephritic syndrome	2	2	0	
XLA[a]	1	1	0	
ALL[b]	1	0	1	
JRA[c]	1	1	0	
HBV carrier	1	1	0	
Allergic purpura	1	1	0	
Tuberculosis	1	1	0	
ASD[d]	1	1	0	
PAS[e]	1	1	0	
Empyema	1	1	0	
Date of illness onset				0.001*
Jan–Mar	11 (20.8)	4 (9.5)	7 (63.6)	
Apr–Jun	12 (22.6)	10 (23.8)	2 (18.2)	
Jul–Sept	20 (37.7)	18 (42.9)	2 (18.2)	
Oct–Dec	10 (18.9)	10 (23.8)	0 (0)	
Time to diagnosis (days)	35 (21–53)	30 (19–56)	52 ± 32	0.111
< 2 weeks	7 (13.2)	7 (16.7)	0	
2 weeks-2 months	37 (69.8)	28 (66.7)	9 (81.8)	
> 2 months	9 (17.0)	7 (16.7)	2 (18.2)	

*$P < 0.05$

[a] *XLA* X-linked agammaglobulinemia

[b] *ALL* acute lymphoblastic leukemia

[c] *JRA* juvenile rheumatoid arthritis

[d] *ASD* atrial septal defect

[e] *PAS* pulmonary artery sling

per mm^3 (normal range, 50–500 cells per mm^3), with an elevated eosinophil count in 27/45 (60.0%) of the patients: 17 (37.8%) were mildly elevated (500 to 1500 cells per mm^3), 9 (22.2%) were moderately elevated (1500 to 5000 cells per mm^3), and 1 (2.2%) was severely elevated (greater than 5000 cells per mm^3). The median C-reactive protein (CRP) level was 32 (interquartile range, 8–64) mg/L (normal range, < 8 mg/L), and CRP was elevated in 38 (71.7%) of the patients. The average erythrocyte sedimentation rate (ESR) was 46.5 mm/h (± 30.2 mm/h) (normal range, < 20 mm/h), and ESR was elevated in 47 (88.9%) patients. Immunoglobulin levels were obtained in 42 (79.2%) patients. IgA and IgG were all within the normal range, with the exception of a patient with X-linked agammaglobulinemia (XLA), in whom they were significantly decreased. Lymphocyte subsets were determined in 41 (77.4%) patients. CD4% was 35% (interquartile range, 28–38%) (normal range, 27–57). All $CD4^+$ lymphocyte counts were more than 500 cells/μL, except for in the one HIV-infected patient, in whom the count was 241 cells/μL.

Pathogen findings

The blood culture was positive in 53.3% (16/30) of the patients. The serum latex agglutination test was positive for

Table 2 Clinical characteristics of the 53 children with cryptococcosis

Characteristic	Number	%
Fever	53	100.0
CNS symptoms		
Headache	33	62.3
Vomiting	30	56.6
Confusion	19	35.8
Seizure	13	24.5
Impaired vision	10	18.9
Limb weakness	6	11.3
Ptosis/eye movement disorder	4	7.5
Facial paralysis	4	7.5
Tinnitus	2	3.8
Respiratory symptoms		
Cough	19	35.8
Thoracalgia	2	3.8
Dyspnea	1	1.9
Abdominal pain	7	13.2
Abdominal distension	1	1.9
Jaundice	1	1.9
Facial herpes	1	1.9
Swollen right ankle	1	1.9
Chest wall mass	1	1.9

Table 3 Imaging and ultrasound findings of cryptococcosis cases

Examination	Number	%
Cranial CT	35	
Atrophy	18	51.4
Low density	14	40.0
Hydrocephalus	8	22.9
Subdural effusion	3	8.6
Bilateral basal ganglia calcification	1	2.9
Cranial MRI	24	
Virchow-Robin spaces	15	62.5
Gelatinous pseudocyst	8	33.3
Multiple miliary nodules enhancement	5/13	38.5
Leptomeningeal enhancement	7/13	53.8
MRV:transverse/sigmoid sinus stenosis	16/18	88.9
MRA: arterial narrowing	6/17	35.3
Chest CT/X-ray	53	
Multiple nodules	5	9.4
Miliary pattern	7	13.2
Patchy shadows	9	17.0
Reticular opacities	7	13.2
Thin-walled cavity	1	1.9
Lymphadenopathy	16	30.2
Slight pleural effusion	3	5.7
Abdominal ultrasound	53	
Multiple lymph nodes	17	32.1
Liver: multiple hypoechoic lesions	9	17.0
Spleen: multiple hypoechoic lesions	9	17.0
Kidney: multiple hypoechoic lesions	2	3.8

Cryptococcus in 36/42 (85.7%) patients, with titers ranging from 1:8 to > 1:1024. Of the 42 CM patients, CSF cultures, India Ink staining, and antigen tests were positive in 82.9% (34/41), 85.7% (36/42), and 82.4% (28/34), respectively.

Other positive culture sites included bone, sputum, and soft tissue abscess. Histologic examinations showed cryptococcosis in abdominal lymph nodes (three cases), mediastinal lymph nodes (three cases), cervical lymph nodes (two cases), the liver (two cases), marrow (one case), and skin (one case).

Radiological findings

The abnormalities found through imaging and ultrasounds are listed in Table 3. The typical abnormalities on chest CT/X-ray and cranial magnetic resonance imaging (MRI) are shown in Fig. 3. The chest CT/X-ray showed no obvious pulmonary lobes, segmental tendency of nodules, or patchy shadows. Cases of disseminated cryptococcosis had a higher likelihood of miliary lung disease and lymphadenopathy than non-disseminated cases (28 vs. 0% and 52 vs. 11%, respectively, $P < 0.01$).

Treatment and outcomes

The median length of hospital stay was 31 (interquartile range, 18–53) days. Fifty-one patients received treatment, one patient refused therapy without treatment, and the one HIV-infected patient transferred to a specialized infectious disease hospital with unknown therapy. The initial treatments were classified as follows: amphotericin B (AmB) combined with fluconazole (Flu) ± 5-fluorocytosine (5-FC) in 29 patients (56.9%); Flu ± 5-FC in 10 patients (19.6%); AmB ± 5-FC in 11 cases (21.5%); and voriconazole (VOR) alone for 1 child with osteomyelitis (Table 4).

Twenty-seven (50.9%) patients were followed by phone after discharge. The median follow-up time after first admission was 994 days (range 221–4413). Six patients (22.2%) died, all of whom had CM. Twenty-one (77.8%) patients survived, including 1 case that had blindness, tic disorder, and irritability; one case that had blindness and irritability; other cases did well at their ages and did not have symptoms or sequelae. The HIV-infected patient had good outcomes.

Our analysis showed that lymph node involvement was associated with good patient outcomes ($P = 0.033$) and that headache ($P = 0.008$), seizures ($P = 0.006$), visual impairment ($P = 0.011$), neck stiffness ($P = 0.008$), low ESRs ($P = 0.024$), and high (≥ 1:1024) CSF antigen titers ($P = 0.038$) were associated with poor patient status (Table 5).

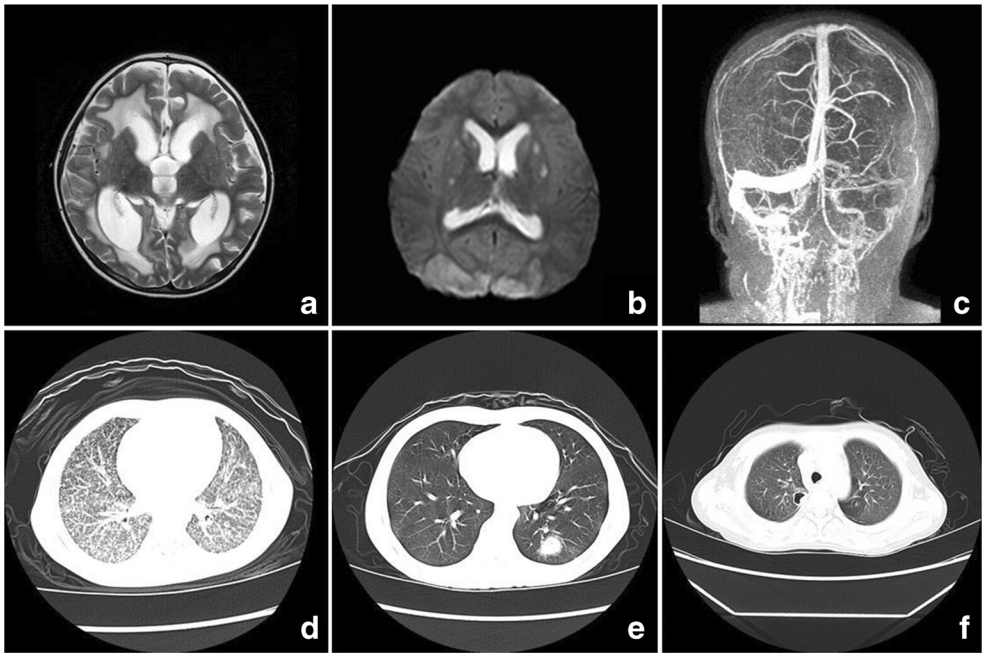

Fig. 3 Imaging findings of pediatric cryptococcosis cases. **a** A 3-year-old boy who presented with fever and headache for one month. MRI axial T2-weighted image: presented clustered tiny foci that were hyperintense in T2-weighted images, dilated Virchow-Robin spaces (*VRS*) in the basal ganglia region, and hydrocephalus with encephaledema. **b** A 5-year-old boy who presented with fever and headache for 15 days. Cranial MRI axial DWI-weighted image: multiple patchy hyperintensities of gelatinous pseudocyst with multiple patchy hyperintensities on T1-, T2-, and DWI-weighted images in the basal ganglia region. **c** A 6-year-old girl who was admitted with headache and seizures for 20 days. Magnetic resonance venography (*MRV*): left transverse sinus and sigmoid sinus stenosis. **d** A 5-year-old boy who presented with fever and cough for 1 month. CT scan: innumerable small bilateral pulmonary nodules consistent with a miliary pattern. **e** A 10-year-old girl who was admitted with headache for 15 days and cough for 7 days. CT scan: a nodule in left interior lung lobe with halo sign. **f** A 14-year-old HIV-infected boy who presented with headache for one month and fever and cough after admission. CT scan: a subpleural thin-walled cavity inside the right upper lung, the inner wall was smooth, with surrounding ground-glass opacity

Discussion

Our study provided an analysis of pediatric cryptococcosis cases in China. Cryptococcosis is a rare pediatric disease worldwide, accounting for only 0.9–2% of cases [22].

In this study, there was a predominance of the male gender (68.9%), similar to in previous reports [16]. The average age of our patients was 7 year old, and only two patients were younger than 2 years. This age distribution can be explained by the increased environmental exposures with age [9]. We found non-CM cases are more likely to occur from January to March and CM cases are more likely to occur in summer and autumn (July–December). Some articles mentioned about half of the CM cases occurred in summer (June–August) in children [11, 12]. The

Table 4 Treatment and prognosis of CM and non-CM in children

Treatment	Total			CM			Non-CM		
	Number	Good status	Poor status	Number	Good status	Poor status	Number	Good status	Poor status
Flu ± 5-FC	10	2	1	6	0	1	4	2	0
AmB ± 5-FC	11	6	0	9	5	0	2	1	0
AmB + Flu ± 5-FC	29	9	6	25	7	6	4	2	0
VOR	1	1	0	0	0	0	1	1	0
Unknown[a]	1	1	0	1	1	0	0	0	0
Without treatment[b]	1	0	1	1	0	1	0	0	0
Total	53	19	8	42	13	8	11	6	0

Flu fluconazole, *5-FC* 5-fluorocytosine, *AmB* amphotericin B, *VOR* voriconazole

[a] The HIV-infected patient transferred to a specialized infectious disease hospital with unknown therapy

[b] One patient's guardian refused therapy

Table 5 Factors affected long-term prognosis ($N = 27$)

Item	Good outcome[a] ($n = 19$) (%)	Poor outcome[b] ($n = 8$) (%)	P
Age (years)	8 ± 5	6 ± 3	0.322
Male gender	13 (68.4)	3 (37.5)	0.206
Poultry exposure	7 (36.8)	2(25.0)	0.676
Underlying condition	6(31.6)	3 (37.5)	1
Time to diagnosis (days)	39 ± 30	23 ± 16	0.175
Involved sites			
CNS	13 (68.4)	8 (100)	0.136
Lung	13 (68.4)	2 (25.0)	0.087
Lymph nodes	12 (63.2)	1 (12.5)	0.033*
Dissemination	13 (68.4)	2 (25.0)	0.087
Clinical manifestations			
Respiratory symptoms	8 (42.1)	2 (25.0)	0.666
Headache	9 (47.4)	8 (100)	0.012*
Confusion	4 (21.1)	4 (50.0)	0.183
Seizures	3 (15.8)	6 (75.0)	0.006*
Visual impairment	2 (10.5)	5 (62.5)	0.011*
Neck stiffness	5 (26.3)	7 (87.5)	0.008*
Laboratory results			
WBC (per mm^3)	14.0 ± 7.7	10.4 ± 1.7	0.072
Eosinophil (per mm^3)	1.4 ± 1.5	0.7 ± 0.7	0.303
CRP (mg/L)	67.9 ± 79.8	30.3 ± 33.1	0.246
ESR (mm/h)	32.2 ± 7.8	15.4 ± 6.9	0.024*
Positive blood culture	7/13 (53.8)	3/5 (60.0)	1
CSF			
WBC (cells/μL)	78.6 ± 87.3	34.1 ± 35.7	0.189
Glucose (mmol/L)	2.7 ± 1.0	2.9 ± 2.1	0.730
Protein (mg/L)	673.7 ± 393.1	633.5 ± 627.6	0.857
Antigen titer ≥1:2014	7/12 (58.3)	6/6 (100)	0.038*
Initial therapy	18	7	0.223
Flu ± 5-FC	2 (11.1)	1 (14.3)	
AmB ± 5-FC	6 (33.3)	0(0)	
AmB + Flu ± 5-FC	9 (50.0)	6 (85.7)	
VOR	1 (5.6)	0 (0)	

CNS central nervous system, *WBC* white blood cell, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *CSF* cerebral spinal fluid, *Flu* fluconazole, *5-FC* 5-fluorocytosine, *AmB* amphotericin B, *VOR* voriconazole

*$P < 0.05$

[a] The HIV-infected patient had a good prognosis, but the initial therapy used was unclear

[b] One child who refused treatment later died

reason for this is unclear. Although the effects of climatic factors across the seasons may be an important epidemiologic characteristic of Cryptococcosis [33], the seasonal difference between CM and non-CM has not been reported as far as I know. Our data showed that only 22.6% of patients had underlying conditions, including only one who had HIV infection. Most previous reports worldwide have reported cryptococcosis in individuals with underlying immunocompromising conditions, AIDS in particular [32]. The reported proportions of afflicted children with underlying diseases in different countries were 86% in South Africa [22], 65.9% in Brazil [34], 63.5% in the USA [16], 56% in Taiwan [14], and 53.7% in Colombia [20]. However, the reported proportion of cryptococcosis cases in immunocompromised hosts in China has been low, at only 26.1% of children and 33.1% of adults with CM [11, 21, 38]. Together with previous studies, these studies may indicate that immunosuppression is not the primary risk factor for cryptococcosis in Chinese people. Host genetic factors may contribute to the high prevalence of the apparently healthy cases reported in China. However, "apparently healthy" patients may still have mannose-binding

leptin (MBL) deficiency, which is known to predispose people of Han Chinese ethnicity to CM [28]. Moreover, FCGR2B 232I/T genotypes have been associated with HIV-uninfected Chinese patients compared with healthy controls [13].

Globally, the majority of cases are caused by the *Cryptococcus neoformans var. grubii* subspecies (especially molecular type VNI) [23]. Chen et al. [3] analyzed 129 clinical isolates from China and showed that 93% were VNI, demonstrating significant genetic homogeneity, as cases had the same subgenotype, VNIc. However, this prevalence of VNIc is not unique to China; *C. neoformans* in the Korean clinical population has also been reported to be genetically homogeneous, with a strong majority of VNIc subgenotype (93%). However, the hosts in Korea predominantly had underlying conditions [4]. Therefore, the prevalent strain type alone cannot explain why the majority of infections in China have occurred in apparently healthy persons. Limited data are available regarding the species isolated from pediatric patients [20, 24]. Therefore, further studies on the molecular epidemiology of *Cryptococcus* strains in Chinese children are needed.

Disseminated cryptococcosis occurred in a high proportion of patients (47.2%), with *Cryptococcus* spp. present in numerous sites, most commonly the CNS and lungs. Other sites such as the lymph nodes, spleen, liver, skin, and bone marrow were reported in very few cases [2, 15, 26, 27, 37]. The clinical manifestations of cryptococcosis are not specific, and it could easily be misdiagnosed as tuberculosis.

Diffuse miliary nodules and lymphadenopathy were more common in pediatric patients than in adults. Only 4% of pulmonary cryptococcosis cases in adults showed diffuse miliary nodules, and 5.7% showed lymphadenopathy [6, 19]. Our study illustrated that miliary manifestations and lymphadenopathy were highly prevalent in pediatric cases without underlying disease. These imaging features could lead these cases to be misdiagnosed as tuberculosis.

Our results showed that eosinophilia was prevalent, with 10/45 (22.2%) moderately or severely elevated cases. One article described how eosinophils are immune to *Cryptococcus* spp. [8]. Eosinophils have been shown to be a major source of Th2 cytokine IL-4 during cryptococcal infection. Eosinophil-deficient mice infected with *C. neoformans* had fewer Th2 cells and increased Th1/Th17 cells, in addition to a reduction of inflammatory cells. This again indicates a detrimental role of eosinophils, whereby a Th2 profile is induced in their presence. An interesting clinical observation of an immunocompetent patient with disseminated *C. neoformans* infection and elevated eosinophil levels suggests that *Cryptococcus* is able to induce a Th2 profile that may lead to eosinophilia. [8]. Very few studies have noted elevations in eosinophilia [35].

Given the high rate of loss of outpatient treatment information, we could not fully evaluate the therapeutic regimens and ultimate outcomes. Most patients received a combination of AmB and Flu with or without 5-FC as their initial treatment regimen. Only one patient received VOR. Although VOR may show activity against cryptococcosis, its effectiveness as a first-line agent in children has not been established. In our study, VOR was effective for osteomyelitis. Although treatment guidelines recommend AmB with 5-FC as the induction therapy for cryptococcal meningitis, evidence of treatment in children are still insufficient, especially in non-HIV children. In our clinical work, we add AmB dose gradually, in that way, Amb with fluconazole and 5-FC may be physicians' first choice, especially in severe patients. In addition, some articles mentioned the effectiveness of AmB with fluconazole both in HIV and non-HIV population [38]. In conditions of children who were intolerable of Amb, fluconazone would also be prescribed. In terms of prognosis, in spite of six patients who were treated with AmB + Flu + −5-FC had poor status in this study, therapy selection bias may exist because severe cases were more easily taken this prescription.

The mortality rate in this study was 22.2%, which is similar to the rate identified in Chinese pediatric CM data in Shijiazhuang [11], lower than 39.19% reported in Sichuan province of China and 43% reported in African children with acquired immunodeficiency syndrome [10, 21]. Previous studies have reported that the factors associated with high mortality include cryptococcemia, organ failure or hematologic malignancy, unsuccessful therapy, non-pulmonary infection site, intracranial hypertension, and high serum antigen titers [5, 29]. In our study, patients with headache, seizures, visual impairment, neck stiffness, low ESRs, and high (≥ 1:2014) CSF antigen titers had a poor long-term prognosis. Furthermore, we found that all patients who died had CM.

Epidemiological data on cryptococcosis in children are scarce, and we provided a comparatively large sample of data using a comprehensive clinical analysis. However, this study had some limitations. It was a single-center inpatient-based retrospective study with a high rate of loss to follow-up. Additionally, there was a wide range of follow-up periods. Finally, we did not determine the molecular type of the involved species. As the epidemiology of *Cryptococcus* spp. appears to be changing [17], species classification and further molecular typing would allow for a better understanding of the epidemiology of pediatric cryptococcosis in Chinese children.

Conclusions

The majority of cryptococcosis cases in China occurred in children without underlying conditions. These infections damaged multiple organs, with the central nervous system being the most common involved site. Neurological complications and mortality occurred in patients who had headaches, seizures, and high CSF antigen titers.

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Authors' Contributions All of the authors had access to the full dataset (including the statistical reportsand tables) and take responsibility for the integrity of the data and the accuracy of the data analysis. Gang Liu, Yonghong Yang, Lingyun Guo, Linlin Liu, Yue Liu and Shaoying Li conceived and designed thestudy. Gang Liu, Lingyun Guo, Linlin Liu, Yue Liu and Tianming Chen collected the data and designed the analysis. Gang Liu, Yonghong Yang, Lingyun Guo, Linlin Liu and Yue Liu interpreted the data. Lingyun Guo and Linlin Liu wrote the first draft of the paper. Gang Liu, Lingyun Guo and Linlin Liu reviewed and approved the final report.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and informed consent This study was reviewed and approved by the Ethics Committee of Beijing Children's Hospital Affiliated to Capital Medical University (2017-k-26). Because this is a retrospectively study, we obtained the data of patients from the Medical Records and Statistics Room and we analyzed the data anonymously; thus, informed consent was not required.

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