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ORIGINAL ARTICLE

Magnetic resonance imaging study of cryptococcal neuroradiological lesions in HIV-negative cryptococcal meningitis

Y. Zhong[1] · Z. Zhou[1] · X. Fang[1] · F. Peng[2] · W. Zhang[1]

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Abstract Magnetic resonance (MR) scanning has become an important diagnostic and management tool in cryptococcal meningitis (CM). However, there are only isolated case reports documenting neuroradiological findings in human immunodeficiency virus (HIV)-negative patients with CM and none has clearly addressed the relationship between cerebral lesions on magnetic resonance imaging (MRI) and prognosis. The MR brain images available from 114 HIV-negative patients with CM were retrospectively analysed. Patients were divided into Group I with one or more CM-related lesions and Group II without CM-related lesions. Initial clinical and biochemical markers and prognosis were collected and compared between the two groups. In the present study, the most common pattern of CM-related lesions by MRI was radiological meningitis, following by Virchow–Robin (VR) dilatation, hydrocephalus, intracerebral nodules and pseudocysts, which was different from previous studies reporting that the main MR findings of cerebral cryptococcosis in HIV-infected patients include dilated VR spaces, masses and pseudocysts. Compared to the patients without CM-related lesions, patients with CM-related lesions presented with a higher percentage of male patients, a higher frequency of altered mental status, a higher positive rate of *Cryptococcus* culture in cerebrospinal fluid (CSF) and a lower ratio of CSF glucose/blood glucose. Poor outcomes were more frequent in patients with presence of CM-related lesions compared to patients without CM-related lesions. In conclusion, the main pattern of cryptococcosis-related lesions on MR scanning differ between non-HIV- and HIV-positive patients with CM. The presence of CM-related lesions was significantly associated with predictors for poor outcome. Neuroimaging on MR scanning is a useful tool to evaluate the initial severity and prognosis of CM without HIV infection.

✉ F. Peng
pfh93@163.com

✉ W. Zhang
weixizhang@qq.com

[1] Department of Neurology, The First Affiliated Hospital of Sun Yat-Sen University, No. 58, Zhongshan Road II, Guangzhou, Guangdong Province 510080, People's Republic of China

[2] Department of Neurology, The Third Affiliated Hospital of Sun Yat-Sen University, No. 600, Tianhe Road, Guangzhou, Guangdong Province, People's Republic of China

Introduction

Cryptococcal meningitis (CM) is caused by *Cryptococcus neoformans*, which is an encapsulated yeast and ubiquitous in soil and avian guano [1, 2]. CM is a serious infection of the central nervous system (CNS) and is mostly found in patients with human immunodeficiency virus (HIV) infection throughout the world. However, most cryptococcosis cases in China have been reported in patients that were not HIV-infected [3, 4]. Antifungal therapy, so far, has successfully decreased the overall mortality rate of CM. However, neurologic sequelae among survivors demonstrate that the prognosis of CM is far from being satisfactory [5].

Magnetic resonance imaging (MRI) scans have been found to be more sensitive than computed tomography (CT) for detecting abnormalities in cerebral cryptococcosis [6–9]. CM-related lesions in brain scan imaging include dilated perivascular spaces, masses, pseudocysts, cryptococcomas, basal meningitis and hydrocephalus [8, 10–13]. In HIV-positive patients, radiological studies involving cerebral cryptococcosis have been numerous. In a study consisting of 62 cases, the results indicated that cryptococcosis-related lesions

are associated with the initial disease severity of cryptococcal meningoencephalitis in HIV-infected patients [8]. Another study including 87 HIV-positive patients indicated that the degree of cerebral involvement reflected by the presence of MRI abnormalities is associated with visual loss secondary to CM [14]. The radiographic appearance of CNS cryptococcosis may vary among groups with different types of immunosuppression and underlying diseases [15]. Evidence is based on case reports or comorbidity with HIV infection. So far, only case reports that focus on neuroradiological features in HIV-negative CM patients have been published, and none has clearly assessed the relationship between CM-related lesions and disease severity. Hence, the goal of our study was to specifically investigate the potential utility of neuroimaging to evaluate the initial severity and prognosis of HIV-negative CM.

Methods

Patient enrollment

A retrospective study of patients with CM was performed at the Third Affiliated Hospital of Sun Yat-Sen University from 2002 to 2014. CM was defined as isolation of *C. neoformans* in one or more cerebrospinal fluid (CSF) cultures or a positive CSF India ink stain and clinical features of meningitis. All enrolled patients had been in the hospital for the first onset of CM. As a criterion for inclusion in our study, all patients tested negative for anti-HIV antibodies. Patients were excluded from our study if they had received antifungal therapy prior to admission. Written informed consent was in accordance with the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University and in compliance with the Declaration of Helsinki.

Clinical symptoms and laboratory studies

A standardised case collection form was used to record clinical, biological and mycological data at baseline. Initial severity was evaluated according to the presence of neurological abnormalities and low ratio of CSF glucose/blood glucose. Neurological abnormalities were defined by the existence of abnormal mental status, seizures and/or neurological defects.

Treatment strategies and prognosis

Antifungal therapy was started as soon as the diagnosis of CM was microbiologically confirmed. The induction treatment included amphotericin B, lipid amphotericin B infusion or oral fluconazole (either with or without combination of flucytosine), followed by fluconazole as the maintenance treatment. Prognosis was assessed by using the Glasgow Outcome Scale [16] as follows: score 1 = death; score 2 = persistent vegetative state; score 3 = severe disability; score 4 = moderate disability; score 5 = good recovery. Patients with a score of 1–3 were further classified into an 'unsatisfactory group,' whereas those with a score of 4 or 5 were classified into a 'satisfactory group.'

Radiological investigations

During the initial 2 weeks after admission, all selected patients underwent MRI scanning. Neuroimaging was performed according to local practice and analysed by a blinded neuroradiologist. Brain lesions were recorded following a preestablished checklist. Lesions that were presumed to be cryptococcosis-related were analysed according to several literatures on brain cryptococcal lesions. CM-related lesions were defined by one of the following criteria: dilated Virchow–Robin (VR) space, pseudocyst(s), intracerebral nodule or mass(es), meningeal enhancement, hydrocephalus and hyper-intensity of the white matter. The CM-related lesions were divided into Group I when one or more CM-related lesions were observed and Group II when no CM-related lesions were presented.

Statistical analysis

Continuous data were presented as the median (interquartile range). The association between the presence of cryptococcosis-related lesions at baseline and initial severity parameters with the subsequent outcomes was analysed using the results obtained from MR scanning. The Mann–Whitney *U*-test was performed on continuous non-normal data and Chi-square or Fisher's exact tests were performed to assess the association between discrete variables. Kaplan–Meier analysis was used to obtain survival curves. A p-value of <0.05 was considered statistically significant. All analyses were two-sided and performed using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic data

In this study, 114 patients with CM were identified. Among the 114 patients, 87 were male. All enrolled patients were tested negative for anti-HIV antibodies. Over half of all patients suffered from underlying conditions (Table 1). The most common underlying disease was diabetes mellitus, followed by liver cirrhosis, chronic renal failure, rheumatologic disease and glucocorticoids use. The first notified abnormal neurological symptoms was, in order of frequency: visual symptoms (18.42%), abnormal mental status (14.91%), auditory symptoms (10.53%)

Table 1 Patient characteristics

	Group I	Group II	Total no.	*p*-Value
Gender	79	35	114	NA
Male	65/79 (82.29%)	22/35 (62.86%)	87 (76.32%)	0.024[a]
Age	40.92 (12.99)	39.65 (13.99)	40.57 (13.22)	0.65
Visual symptoms	14/79 (17.72%)	7/35 (20.00%)	21 (18.42%)	0.772
Auditory symptoms	9/79 (11.39%)	3/35 (8.57%)	12 (10.53%)	0.651
Seizures	6/79 (7.59%)	3/35 (8.57%)	9 (7.89%)	0.873
Abnormal mental status	16/79 (20.25%)	1/35 (2.86%)	17 (14.91%)	0.016[a]
No. with underlying disease	43/79 (54.43%)	15/35 (42.86%)	58 (50.88%)	0.113
Extraneural involvement	14/79 (17.72%)	3/35 (8.57%)	17 (14.91%)	0.206
Cryptococcaemia	17/79 (21.52%)	4/35 (11.43%)	21 (18.42%)	0.2

Group I: patients with one or more CM-related lesions; Group II: patients without CM-related lesions

The results are given as median (interquartile range) or *n* (%)

[a] $p < 0.05$

and seizures (7.89%). The average amount of time between the onset of symptoms and hospitalisation was 23.6 days.

Radiological findings at baseline

MR brain images were analysed from 114 HIV-negative patients with CM, as shown in Table 2. The median interval between the onset of symptoms and initial neuroimaging was 22 days (15–31). Fifteen patients (13.16%) presented with normal brain image at baseline MRI. Out of a total of 114 patients, CM-related lesions were observed in 79 (69.30%) of the 114 patients. The most commonly observed cryptococcosis-related lesions were meningitis (62.28%), followed by VR dilatation (39.47%), hydrocephalus (33.33%), masses (30.70%) and pseudocysts (15.79%). Masses were mainly located in the basal ganglia, white matter of lateral ventricle, cerebellum and pons. Post-gadolinium MRI sequences showed remarkable meningeal enhancement and ring enhancement of some mass lesions, as shown in Fig. 1. In addition, enhancement was observed on the cysts or surrounding parenchyma after contrast medium injection (Fig. 1). Other lesions, including cerebral atrophy, aspecific hypodensities and lacunar infarction, were found in non-HIV patients with CM.

Relationship between baseline clinical and radiological characteristics of patients with CM

Patients were divided into two groups according to the presence or absence of CM-related lesions. We then investigated whether the presence of CM-related lesions was associated with initial clinical features and laboratory data. A higher frequency (82.29%, $p = 0.024$) of males was found in patients with CM-related lesions compared with those who with an absence of CM-related lesions (62.86%). There was no significant difference in underlying disease between the two groups. Patients with CM-related lesions had a higher incidence of altered consciousness in the early stage of the disease compared with those who did not show CM-related lesions (20.25% vs. 2.86%, respectively, $p = 0.016$). No significant differences were found in other abnormal neurology, including cranial nerves palsies and seizures. When CSF characteristics were compared between patients with or without CM-related lesions (Table 3), a significantly lower ratio of CSF glucose/blood glucose at baseline was found in patients with CM-related lesions (0.19 vs. 0.32, respectively, $p = 0.012$). In addition, CM-related lesions were associated with a higher percentage of positive results for *Cryptococcus* culture in the CSF (65.82% vs. 28.57%, respectively, $p = 0.022$).

Table 2 Initial findings of MR brain images collected from 114 non-HIV-infected patients with CM

Results of brain imaging	*n*	%
Normal	15	13.16%
CM-related lesions	79	69.30%
VR dilatation	45	39.47%
Pseudocysts/cryptococcomas	18	15.79%
Intracerebral nodule(s)/mass(es)	35	30.70%
Radiological meningitis	71	62.28%
Hydrocephalus	38	33.33%
Other lesions		
Cerebral atrophy	7	6.14%
Aspecific hypodensities	13	11.40%
Lacunar infarction	5	4.39%

The results are given as *n* (%)

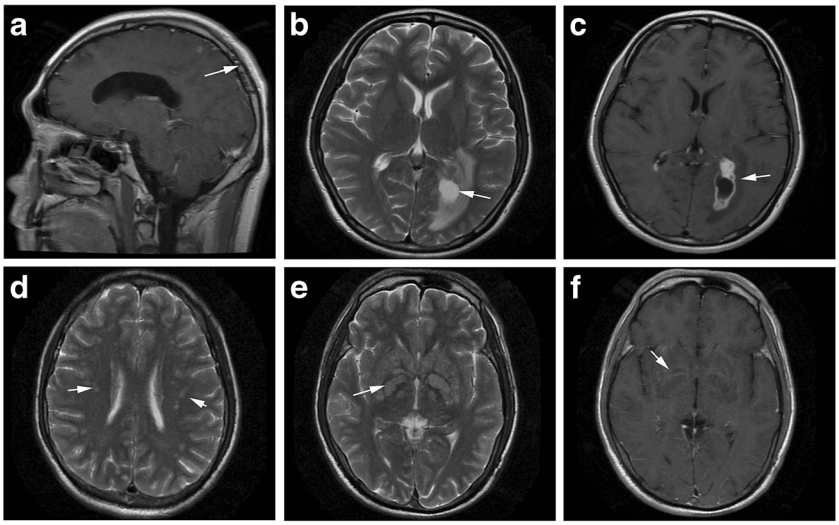

Fig. 1 Representative magnetic resonance images of abnormal radiologic findings in non-HIV patients with cryptococcal meningitis. **a** Sagittal T1-weighted post-gadolinium contrast enhancement showing obvious nodular meningeal enhancement. **b** Axial T2-weighted image showing a mass lesion in the region of white matter of the left lateral ventricle trigone. **c** Post-gadolinium magnetic resonance imaging (MRI) sequences showing remarkable ring enhancement of the mass lesion. **d** Axial T2-weighted image showing multiple dilated hyperintense Virchow–Robin spaces in the bilateral centrum semiovale. **e** Axial T2 sequence showing bilateral pseudocysts in the region of basal ganglia. Pseudocysts are thick walled and septated with a proteinaceous content. **f** Post-gadolinium MRI sequences displaying enhancement of the cysts or surrounding parenchyma

Relationship between baseline radiological characteristics and prognosis of patients with CM

No significant differences were observed in the therapeutic regimen between the presence and absence of CM-related lesions. The patient outcomes are shown in Table 4. Of 79 patients who presented with presence of CM-related lesions, nine died and 70 survived. Eight patients were lost to follow-up. Thirty-two patients were classified in the group of poor prognosis. Of the other 35 CM patients without CM-related lesions, 26 had a good prognosis, whereas for the other eight, the prognosis was poor. Poor outcomes were more frequently found in patients with CM-related lesions compared to patients without CM-related lesions ($p = 0.033$). The Kaplan–Meier survival curve analysis is shown in Fig. 2. No significant differences in mortality hazards were found between patients with or without CM-related lesions.

Discussion

The present study is, by far, the largest study to analyse the radiological appearances of CM in non-HIV patients. We further investigated brain lesions associated with CM in relation to initial severity and prognosis of HIV-negative CM.

In this study, we demonstrated that the most common pattern of CM-related lesions by MRI in patients without HIV infection was radiological meningitis, which was different from that in HIV-infected patients as previously described [17, 18]. The primary MR findings of cerebral cryptococcosis in HIV-infected patients are dilated VR spaces, masses and pseudocysts [17, 18]. Radiological meningitis and hydrocephalus are relatively less frequent in CM co-infected with HIV [8]. These differences were in accordance with a previous study reporting that the radiographic features of CNS cryptococcosis can vary among groups with different types of

Table 3 CSF features

	Group I	Group II	*p*-Value
CSF protein	0.93 (0.58)	0.96 (1.34)	NS
CSF glucose	1.61 (1.05)	1.93 (1.26)	NS
Ratio of CSF glucose/blood glucose	0.19 (0.10)	0.32 (0.22)	0.012[a]
CSF culture positive	52/79 (65.82%)	10/35 (28.57%)	0.022[a]

CSF: cerebrospinal fluid; Group I: patients with one or more CM-related lesions; Group II: patients without CM-related lesions

The results are given as median (interquartile range) or *n* (%)

[a] $p < 0.05$

Table 4 Patient prognosis according to the Glasgow Outcome Scale

Glasgow Outcome Scale	Group I	Group II	*p*-Value
1	9/71 (12.68%)	3/34 (8.82%)	0.562
2	3/71 (4.23%)	1/34 (2.94%)	0.748
3	20/71 (28.17%)	4/34 (11.76%)	0.053
4	11/71 (15.49%)	11/34 (32.35%)	0.047
5	28/71 (39.44%)	15/34 (44.12%)	0.461
Satisfactory outcomes	39/71 (54.93%)	26/34 (76.47%)	0.033[a]
Unsatisfactory outcomes	32/71 (45.07%)	8/34 (23.53%)	0.033[a]
Lost to follow-up	8/79 (10.13%)	1/35 (2.86%)	0.184

Group I: patients with one or more CM-related lesions; Group II: patients without CM-related lesions

The results are given as *n* (%)

[a] $p < 0.05$

immunosuppression [9]. Dilated VR spaces, as a manifestation of cryptococcosis in acquired immunodeficiency syndrome (AIDS) patients, was also commonly observed in CM patients without HIV, supporting that VR dilatation is not specific to CM with AIDS and can also be found in other conditions [17, 18]. In our study, we showed that, among the patients without HIV infection, 13.16% had a normal MR scan, whereas approximately half of the patients with HIV infection presented with a normal MR scan [19]. In addition, it has been reported that the meningeal enhancement on MRI was minimal or absent in cases of CM with AIDS [13]. In our series, however, it was found that enhancement of meninges and some mass lesions on MRI was significant. Contrast enhancement of the lesions is considered as evidence of breakdown of the blood–brain barrier and inflammatory reaction [20]. The impaired cell-mediated immunity in patients with AIDS may account for the differences in contrast enhancement [13, 21].

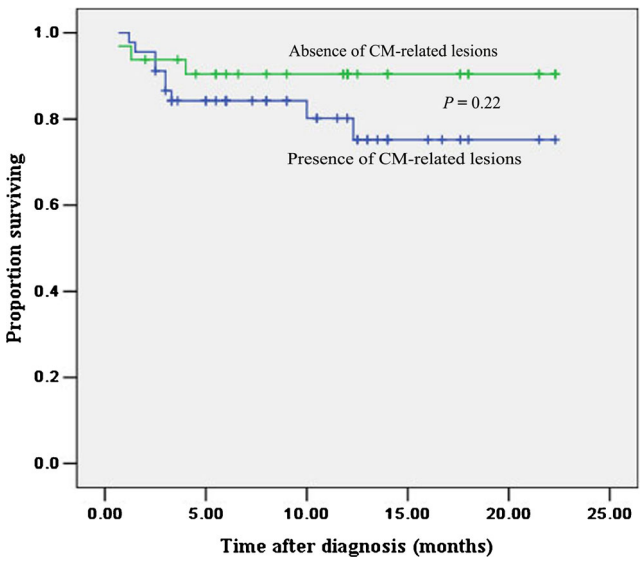

Fig. 2 Kaplan–Meier survival curves, as related to CM-related lesions on MR images, among HIV-negative patients with cryptococcal meningitis

The main findings of this study were related to certain differences between CM patients with or without CM-related lesions on MR images. In this study, CM was predominant in males, which was consistent with previous studies on sex difference, with more male patients developing clinical cryptococcosis [22, 23]. The presence compared to absence of cryptococcosis-related lesions had been observed in a significantly higher percentage of male patients. The reason for this difference was not entirely understood; however, it may be due to the fact that the male immune system is less efficient in controlling *Cryptococcus neoformans* infection [24]. In the current study, the higher frequency of abnormal mental status in patients with CM-related lesions was in accordance with previous studies among non-AIDS patients with CM, which indicate that patients who presented with a normal mental status had a better prognosis [9, 25]. In addition, a study in a large cohort of CM patients with AIDS demonstrated that abnormal mental status was associated with death during treatment [26]. This suggests that the mental status of the patient at the time of admission is a useful pretreatment predictor in the general assessment of prognosis.. Further, the higher positive rate of *Cryptococcus* cultures in CSF in patients with CM-related lesions implied that patients with CM-related lesions had a higher burden of organisms compared to patients without CM-related lesions. According to a study conducted by Diamond and Bennett, a higher burden of organisms evaluated by India ink examinations correlated with failure or relapse of CM [27]. Low CSF glucose levels usually indicate a high *Cryptococcus* titre and a poor host immunity state [28]. The CSF glucose/blood glucose ratio, which was significantly lower in patients with CM-related lesions compared to patients without CM-related lesions in the present study, has been shown to be a significant adverse prognostic factor for CM and other forms of meningitis. Moreover, the CSF glucose/blood glucose ratio in patients with suspected meningitis had been recommended as part of the guidelines for the management of meningitis in Japan [29–31]. Taken together, CM-related lesions as identified on MR images indicated poor inflammatory reactions and were associated with pretreatment predictors of poor prognosis for non-HIV patients with CM.

The therapeutic results of all patients showed a mortality rate of 11.4% (12/105) and about 50% of survivors had moderate to severe neurological deficits. The mortality rate in our series was consistent with previous studies revealing that the overall mortality in HIV-negative patients varied from 9 to 31% [32, 33]. The mortality of CM was not different in patients with or without CM-related lesions. However, a higher frequency of unsatisfied outcomes was observed in patients with CM-related lesions, which could be explained by the above-mentioned results that CM-related lesions as identified on MR images correlated with risk prognostic factors.

In summary, our study demonstrated that the primary pattern of cryptococcosis-related lesions recorded by MR in non-HIV patients with CM is different from that in HIV-positive patients. The presence of CM-related lesions was significantly associated with risk prognostic factors, including altered mental status, decreased CSF glucose/blood glucose ratio and high burden of organisms. Neuroimaging on MRI scans may be considered as a useful tool to evaluate the initial severity and prognosis of CM developed in HIV-negative patients.

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Authors' contributions W-XZ and F-HP participated in the design of the study. Y-HZ drafted the manuscript. ZZ and F-HP participated in collecting the clinical data. X-BF participated in the statistical analysis. All authors edited the manuscript and read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethics approval Ethical approval was provided by the Third Affiliated Hospital of Sun Yat-Sen University.

References

1. Dromer F, Mathoulin-Pélissier S, Launay O et al (2007) Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. PLoS Med 4:e21
2. Lee IR, Yang L, Sebetso G et al (2013) Characterization of the complete uric acid degradation pathway in the fungal pathogen *Cryptococcus neoformans*. PLoS One 8:e64292
3. Bicanic T, Harrison TS (2005) Cryptococcal meningitis. Br Med Bull 72:99–118
4. Fang W, Fa Z, Liao W (2015) Epidemiology of *Cryptococcus* and cryptococcosis in China. Fungal Genet Biol 78:7–15
5. Liliang PC, Liang CL, Chang WN et al (2003) Shunt surgery for hydrocephalus complicating cryptococcal meningitis in human immunodeficiency virus-negative patients. Clin Infect Dis 37:673–678
6. Popovich MJ, Arthur RH, Helmer E (1990) CT of intracranial cryptococcosis. AJR Am J Roentgenol 154:603–606
7. Tien RD, Chu PK, Hesselink JR et al (1991) Intracranial cryptococcosis in immunocompromised patients: CT and MR findings in 29 cases. AJNR Am J Neuroradiol 12:283–289
8. Charlier C, Dromer F, Lévêque C et al (2008) Cryptococcal neuroradiological lesions correlate with severity during cryptococcal meningoencephalitis in HIV-positive patients in the HAART era. PLoS One 3:e1950
9. Mitchell TG, Perfect JR (1995) Cryptococcosis in the era of AIDS—100 years after the discovery of *Cryptococcus neoformans*. Clin Microbiol Rev 8:515–548
10. Sahraian MA, Motamedi M, Azimi AR et al (2007) Bilateral pulvinar thalamic calcification in a patient with chronic cryptococcal meningitis. Eur J Neurol 14:e1–e2
11. Awasthi M, Patankar T, Shah P et al (2001) Cerebral cryptococcosis: atypical appearances on CT. Br J Radiol 74:83–85
12. Arnder L, Castillo M, Heinz ER et al (1996) Unusual pattern of enhancement in cryptococcal meningitis: in vivo findings with postmortem correlation. J Comput Assist Tomogr 20:1023–1026
13. Miszkiel KA, Hall-Craggs MA, Miller RF et al (1996) The spectrum of MRI findings in CNS cryptococcosis in AIDS. Clin Radiol 51:842–850
14. Loyse A, Moodley A, Rich P et al (2015) Neurological, visual, and MRI brain scan findings in 87 South African patients with HIV-associated cryptococcal meningoencephalitis. J Infect 70:668–675
15. Kumari R, Raval M, Dhun A (2010) Cryptococcal choroid plexitis: rare imaging findings of central nervous system cryptococcal infection in an immunocompetent individual. Br J Radiol 83:e14–e17
16. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet 1:480–484
17. Andreula CF, Burdi N, Carella A (1993) CNS cryptococcosis in AIDS: spectrum of MR findings. J Comput Assist Tomogr 17:438–441
18. Mathews VP, Alo PL, Glass JD et al (1992) AIDS-related CNS cryptococcosis: radiologic-pathologic correlation. AJNR Am J Neuroradiol 13:1477–1486
19. Powderly WG (1993) Cryptococcal meningitis and AIDS. Clin Infect Dis 17:837–842
20. Zuger A, Louie E, Holzman RS et al (1986) Cryptococcal disease in patients with the acquired immunodeficiency syndrome. Diagnostic features and outcome of treatment. Ann Intern Med 104:234–240
21. Kovoor JME, Mahadevan A, Narayan JP et al (2002) Cryptococcal choroid plexitis as a mass lesion: MR imaging and histopathologic correlation. AJNR Am J Neuroradiol 23:273–276
22. Mirza SA, Phelan M, Rimland D et al (2003) The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992–2000. Clin Infect Dis 36:789–794
23. Tay ST, Rohani MY, Hoo TS et al (2010) Epidemiology of cryptococcosis in Malaysia. Mycoses 53:509–514
24. McClelland EE, Hobbs LM, Rivera J et al (2013) The role of host gender in the pathogenesis of *Cryptococcus neoformans* infections. PLoS One 8:e63632
25. Darzé C, Lucena R, Gomes I et al (1999) Prognosis factors in cryptococcal meningoencephalitis. Arq Neuropsiquiatr 57:649–652
26. Larsen RA, Leal MA, Chan LS (1990) Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS. A randomized trial. Ann Intern Med 113:183–187
27. Diamond RD, Bennett JE (1974) Prognostic factors in cryptococcal meningitis. A study in 111 cases. Ann Intern Med 80:176–181
28. Zheng H, Li M, Luo Y et al (2015) A retrospective study of contributing factors for prognosis and survival length of cryptococcal meningoencephalitis in Southern part of China (1998–2013). BMC Infect Dis 15:77
29. Jakka SR, Veena S, Atmakuri RM et al (2006) Characteristic abnormalities in cerebrospinal fluid biochemistry in children with cerebral malaria compared to viral encephalitis. Cerebrospinal Fluid Res 3:8
30. Nakayama T (2013) Clinical practice guidelines of the Societas Neurologica Japonica. Rinsho Shinkeigaku 53:1342
31. Tamune H, Takeya H, Suzuki W et al (2014) Cerebrospinal fluid/blood glucose ratio as an indicator for bacterial meningitis. Am J Emerg Med 32:263–266
32. Moosa MYS, Coovadia YM (1997) Cryptococcal meningitis in Durban, South Africa: a comparison of clinical features, laboratory findings, and outcome for human immunodeficiency virus (HIV)-positive and HIV-negative patients. Clin Infect Dis 24:131–134
33. Kiertiburanakul S, Wirojtananugoon S, Pracharktam R et al (2006) Cryptococcosis in human immunodeficiency virus-negative patients. Int J Infect Dis 10:72–78