Eur J Clin Microbiol Infect Dis (2016) 35:299–303
DOI 10.1007/s10096-015-2545-0

ORIGINAL ARTICLE

A retrospective research of HIV-negative cryptococcal meningoencephalitis patients with acute/subacute onset

H. Zheng[1] · Q. Chen[1] · Z. Xie[1] · D. Wang[1] · M. Li[2] · X. Zhang[1] · Y. Man[1] · J. Lao[3] · N. Chen[3] · L. Zhou[1]

Received: 21 October 2015 / Accepted: 7 December 2015 / Published online: 20 January 2016

Abstract Cryptococcal meningoencephalitis (CM) may present as an acute, subacute, or chronic infection. It manifests as a chronic process in over 75 % of cases, but, sometimes, it presents with a more acute onset, mostly in HIV-associated patients. Until now, there has been no study performed on the clinical features of HIV-negative CM patients with acute/subacute onset. We collected 106 HIV-negative patients diagnosed with CM in our hospital during a 15-year period, analyzed their epidemiological and clinical features, as well as the outcomes, and explored the independent prognosis factors and the factors related to the survival time among them. We found that impaired consciousness (23.4 % vs. 3.4 %, $p=0.017$) was more common in CM patients with acute/subacute onset, while decreased cerebrospinal fluid (CSF) glucose (51.9 % vs. 75.9 %, $p=0.026$) was less common. The ratio of CSF glucose/blood glucose [odds ratio (OR) 0.04, 95 % confidence interval (CI) 0.004–0.262, $p=0.02$], impaired consciousness (OR 5.09, 95 % CI 1.477–17.522, $p=0.01$), and hospitalization length (OR 0.98, 95 % CI 0.977–0.999, $p=0.04$) were indicated to be not only independent prognosis factors in HIV-negative CM patients with acute/subacute onset, but also factors significantly related to the survival time. The results of our study demonstrated that the contact history and potential history risk factors would not affect the onset process of HIV-negative CM patients, and the mortality, hospitalization length, and survival time has not been related to the onset process. However, the ratio of CSF glucose/blood glucose, consciousness level, and hospitalization length of the HIV-negative CM patients with acute/subacute onset should be of greater focus in the clinical work.

Abbreviations

CM	Cryptococcal meningoencephalitis
CNS	Central nervous system
CSF	Cerebrospinal fluid
SLE	Systemic lupus erythematosus
AmBd	Amphotericin B deoxycholate
5-FC	5-Fluorocytosine
FCZ	Fluconazole
OR	Odds ratio
CI	Confidence interval
SD	Standard deviation

Introduction

Meningitis can be categorized as acute, subacute, and chronic onset, based on its duration of symptoms. Chronic meningitis is commonly defined as inflammation evolving during weeks to months, while acute meningitis rarely persists more than a few weeks [1].

Cryptococcal meningoencephalitis (CM) is always included in the differential diagnosis of chronic or subacute meningoencephalitis, since 75 % of CM patients present with symptoms that develop insidiously over 2 to 4 weeks [1, 2]. There are some CM happening acutely or subacutely reported

✉ L. Zhou
zhouliang_1963@126.com

[1] Department of Neurology, Nanfang Hospital, Southern Medical University, No.1838 North Guangzhou Avenue, Guangzhou City, Guangdong Province, People's Republic of China

[2] Department of Neurology, The Central Hospital of Yongzhou, Yongzhou City, Hunan Province, People's Republic of China

[3] Medical Records Room, Nanfang Hospital, Southern Medical University, Guangzhou City, Guangdong Province, People's Republic of China

previously, but nearly all of them are HIV-associated [3–8]. Until now, there has been no study performed on HIV-negative CM patients with acute/subacute onset.

In this study, we defined the HIV-negative CM patients as having no more than a month of symptoms as acute/subacute onset. After comparing their epidemiological and clinical features, as well as outcomes, with those of patients with chronic onset, we explored the independent prognosis factors and the factors related to the survival time in HIV-negative CM patients with acute/subacute onset for the first time.

Materials and methods

Data source and study population

There were 106 HIV-negative patients diagnosed with CM from Nanfang Hospital between July 1, 1998 and June 30, 2013, and they were all included in this study. The patients' medical records were reviewed to extract demographic and clinical features, including potential risk factors, symptoms, and cerebrospinal fluid (CSF) analysis before antifungal therapy. Furthermore, the prognosis factors and factors associated with the survival time of HIV-negative CM patients with acute/subacute onset were analyzed. All patients or their family members signed a written consent in accordance with the ethical committee standards during their hospital stay or outpatient follow-up.

Study criteria

CM was defined by the following criteria from Bestard and Siddiqi [9]: "(1) isolation of cryptococcus from previous or current cerebrospinal fluid cultures, followed by a positive CSF cryptococcal antibody, positive CSF India ink staining, or positive CSF Aley new blue dye staining and clinical features of meningoencephalitis; or (2) isolation of cryptococcus in blood culture with clinical presentations of meningoencephalitis and typical CSF features."

"With potential risk factors" was defined as when CM patients have HIV infection, malignancies, cirrhosis, organ transplantation, end-stage renal failure, autoimmune disorder, diabetes mellitus, idiopathic CH4 T-cell lymphopenia, sarcoidosis, chronic usage of corticosteroids or other immunosuppressive therapy, systemic lupus erythematosus (SLE) or other systemic autoimmune diseases, chronic kidney diseases, mycosis infection of other systems, drug addiction, etc. [10–12].

Therapy

Once patients were diagnosed with CM, intravenous administration of amphotericin B deoxycholate (AmBd) was given at 0.1 mg/kg on the first day, 0.5 mg/kg on the second day, and was increased to 1 mg/kg per day from the third day onwards, together with 100 mg/kg 5-fluorocytosine (5-FC) and 400 mg fluconazole (FCZ) per day orally, known as the induction therapy. After 4–6 weeks of induction therapy, we stopped AmBd when there was no cryptococcus found in at least three sequential CSF examinations by microscopy. FCZ and 5-FC were used continuously for 6–9 more months. Patients with persistent high CSF pressure received lumber punctures every 2–3 days.

Data analysis

For the comparison of continuous variables, such as age, CSF analysis before antifungal therapy, hospitalization length, and survival time, an independent samples *t*-test was performed. The Chi-square test was used to compare the categorical variables, including gender, bird/bird dropping contact history, potential risk factors, symptoms, and outcome status, between HIV-negative CM patients with acute/subacute onset and those with chronic onset. Multivariate analysis was performed for detection of the factors contributing to the prognosis in HIV-negative CM patients with acute/subacute onset. Furthermore, the Cox regression model was used to evaluate the factors related to the survival length among them. Statistical significance was defined as $p < 0.05$ and the data were analyzed using SPSS 16.0 software (SPSS, Chicago, IL, USA).

Results

We reviewed the data of 106 HIV-negative patients diagnosed with CM in our hospital during a 15-year period (July, 1998 to June, 2013) and found 77 patients who presented with acute/subacute onset (no more than a month) of symptoms. The mean age of these patients was 37.58 ± 16.79 years (range: 11 months to 81 years). Similar to the results obtained from the whole population [12], male predominance was also found in the patients with acute/subacute onset (54 male, 70.1 %; 23 female, 29.9 %; overall male:female ratio 2.3:1). There was no difference in the potential risk factors between CM patients with acute/subacute and those with chronic onset (Table 1).

Compared with the HIV-negative CM patients with chronic onset, nonspecific symptoms, including headache (74.0 % vs. 79.3 %) and fever (61.0 % vs. 65.5 %) were less common in acute/subacute onset CM patients (Table 2). While specific symptoms, such as ataxia (3.9 % vs. 3.4 %), impaired consciousness (23.4 % vs.3.4 %), dizziness (2.6 % vs. 0.0 %), and psychosis (3.9 %vs. 3.4 %) were more common, only impaired consciousness showed a statistical difference (Table 2). The CSF analysis of all 106 patients showed that increased CSF pressure (81.6 % vs. 86.2 %, $p = 0.774$), decreased CSF glucose (51.9 % vs. 75.9 %, $p = 0.026$), and increased CSF protein level (70.1 % vs. 78.6 %, $p = 0.392$) were

Table 1 Demographic characteristics, contact history, and risk factors of HIV-negative CM patients with different onset process

	≤30 days	>30 days	*p*-Value
Demographic characteristics			
Age (years), mean ± SD	37.58 ± 16.67	36.58 ± 20.88	0.798
Contact history, no. (%)	3 (3.9)	2 (6.9)	0.516
Gender			
Male, no. (%)	54 (70.1)	21 (72.4)	0.818
Female, no. (%)	23 (29.9)	8 (27.6)	
Risk factors			
Use of corticosteroids and/or immunosuppressants, no. (%)	14 (18.2)	5 (17.2)	0.910
History of SLE or other autoimmune diseases, no. (%)	9 (11.7)	3 (10.3)	1.000
History of kidney diseases, no. (%)	2 (2.6)	2 (6.9)	0.301
History of hematopathy, no. (%)	2 (2.6)	0 (0.0)	1.000
History of DM, no. (%)	5 (6.5)	0 (0.0)	0.320
History of TB, no. (%)	4 (5.2)	2 (6.9)	0.664
History of malignant cancer, no. (%)	1 (1.3)	0 (0.0)	1.000
History of organ transplantation, no. (%)	1 (1.3)	0 (0.0)	1.000

less prevalent in CM patients with acute/subacute onset, but they were prone to have a decreased ratio of CSF glucose/blood glucose (88.2 % vs. 80.8 %, $p = 0.340$) (Table 2).

Evaluating the CM patients demonstrated that those with acute/subacute onset were more inclined to die (48.6 % vs. 27.6 %, $p = 0.052$), but no statistical difference was found. There is no difference in both the hospitalization length and survival time between CM patients with and without acute/subacute onset (Table 2).

As reported in previous studies, there are five major prognosis factors: older than 55 years, a CSF opening pressure greater than or equal to 250mmH_2O, a decreased ratio of CSF glucose/blood glucose, consciousness level, and the duration of intensive care unit stay [12–17]. We chose age, ratio of CSF glucose/blood glucose, consciousness level, CSF pressure, CSF glucose, CSF protein, and hospitalization length to explore the prognosis factors in CM patients with acute/subacute onset. In our multivariate analysis, the ratio of CSF glucose/blood glucose [odds ratio (OR) 0.04, 95 % confidence interval (CI) 0.004–0.262, $p = 0.02$], impaired consciousness (OR 5.09, 95 % CI 1.477–17.522, $p = 0.01$), and hospitalization length (OR 0.98, 95 % CI 0.977–0.999, $p = 0.04$) were independently significant with regards to prognosis (Table 3).

Table 2 Clinical features and outcome of HIV-negative CM patients with different onset process

	≤30 days	>30 days	*p*-Value
Symptoms			
Headache, no. (%)	57 (74.0)	24 (79.3)	0.573
Fever, no. (%)	47 (61.0)	20 (65.5)	0.672
Seizure, no. (%)	4 (5.2)	4 (13.8)	0.210
Dizziness, no. (%)	2 (2.6)	0 (0.0)	1.000
Ataxia, no. (%)	3 (3.9)	1 (3.4)	1.000
Impaired consciousness, no. (%)	18 (23.4)	1 (3.4)	**0.017**
Psychosis, no. (%)	3 (3.9)	1 (3.4)	1.000
CSF, mean ± SD			
Decreased ratio of CSF glucose/blood glucose, no. (%)	67 (88.2)	21 (80.8)	0.340
Increased CSF pressure (mmH2O), no. (%)	62 (81.6)	25 (86.2)	0.774
Decreased CSF glucose, no. (%)	40 (51.9)	22 (75.9)	**0.026**
Increased CSF protein (g/L), no. (%)	54 (70.1)	22 (78.6)	0.392
Outcome			
Death, no. (%)	36 (48.6)	8 (27.6)	0.052
Hospitalization length (days), mean ± SD	49.41 ± 56.96	60.31 ± 48.69	0.364
Survival time (months), mean ± SD	25.86 ± 41.25	32.42 ± 47.96	0.366

Table 3 Multivariate conditional logistic analysis of prognosis factors related to HIV-negative CM patients with acute/subacute onset

Prognosis factor	Multivariate analysis		
	OR	95 % CI	*p*-Value
Age	1.08	0.9391–2.983	0.88
Ratio of CSF glucose/blood glucose	0.04	0.004–0.262	**0.02**
CSF glucose	2.04	0.893–4.672	0.09
CSF pressure	1.02	0.992–1.052	0.16
CSF protein	2.01	0.322–12.559	0.46
Impaired consciousness	5.09	1.477–17.522	**0.01**
Hospitalization length	0.98	0.977–0.999	**0.04**

Cox regression analysis of our study indicated that the ratio of CSF glucose/blood glucose ($p = 0.019$, 95 % CI 0.006–0.631, OR 0.059), impaired consciousness ($p < 0.001$, 95 % CI 0.109–0.534, OR 0.241), and hospitalization length ($p < 0.001$, 95 % CI 0.963–0.987, OR 0.975) were the factors significantly related to the survival time in HIV-negative CM patients with acute/subacute onset (Table 4).

Discussion

CM affects individuals with impaired cell-mediated immunity (such as HIV infection), malignancies, organ transplant recipients, users of chronic corticosteroids or other immunosuppressive regimens, as well as individuals with a competent immune system [11, 18, 19]. Being present in more than 90 % cases of immunocompromised patients, particularly those with AIDS with a more acute course, CM mostly manifests as a subacute or chronic process in HIV-negative patients [2, 20]. In this study, we focus on the HIV-negative CM patients with acute/subacute onset. We analyzed their epidemiological and clinical features, and the outcomes among HIV-negative CM patients, and explored the independent prognosis factors and the factors related to the survival time of patients with acute/subacute onset for the first time.

There is no difference between age, contact history, potential risk factors, mortality, hospitalization length, and survival time between HIV-negative CM patients with acute/subacute onset and those with chronic onset. This result indicated that contact history and potential history risk factors (such as history of use of corticosteroids and/or immunosuppressants, history of SLE or other autoimmune diseases, history of kidney diseases, history of hematopathy, history of diabetes mellitus, history of tuberculosis, history of malignant cancer, or history of organ transplantation) did not affect the onset process of HIV-negative CM patients, regardless of their gender or age. Furthermore, the mortality, hospitalization length, and survival time of the HIV-negative CM patients did not relate to the onset process of their symptoms.

Table 4 Cox regression analysis of factors related to survival length in HIV-negative CM patients with acute/subacute onset

Risk factors	*p*-Value	OR	95 % CI
Age	0.311	0.988	0.964–1.012
Ratio of CSF glucose/blood glucose	**0.019**	0.059	0.006–0.631
CSF pressure	0.332	0.997	0.991–1.003
CSF protein	0.334	0.674	0.298–1.525
Impaired consciousness	**<0.001**	0.241	0.109–0.534
Hospitalization length	**<0.001**	0.975	0.963–0.987

Similar to previous studies in China [11, 12], nonspecific symptoms, such as headache and fever, were the most common symptoms in HIV-negative CM patients with acute/subacute onset. Impaired consciousness, one of the most common clinical manifestations of central nervous system (CNS) infection [21], is the only symptom having a statistical difference between HIV-negative CM patients with acute/subacute onset and those with chronic onset. It is probably because consciousness level, which was strongly associated with therapeutic effect and prognosis, caused more attention among patients and clinical workers than other specific symptoms [15, 16].

Compared to patients with chronic onset, fewer patients with acute/subacute onset had increased CSF pressure (>200 mmH2O), decreased CSF glucose (<2.25 mmol/L), and increased CSF protein (>0.45 g/L). This result indicated that the abnormal CSF analysis was probably directly related to the length of time symptoms persisted.

Unlike previous studies [13, 14], we carried out multivariate analysis on age, CSF analysis, consciousness level, and hospitalization length to find the prognosis factors related to the HIV-negative CM patients with acute/subacute onset and found that the ratio of CSF glucose/blood glucose, impaired consciousness, and hospitalization length were associated with the prognosis. Similar to what we previously reported [12], in patients (inclusive of both HIV-negative and HIV-positive patients), decreased ratio of CSF glucose/blood glucose was an independent prognosis factor: the ratio of CSF glucose/blood glucose of patients who died was 0.04 times that of those who survived. Similar to what Darzé et al. [15] found previously, patients with impaired consciousness were 5.09-fold more likely to die over those without, and impaired consciousness was, therefore, another prognosis factor. In addition, the hospitalization length of patients who died was 0.98 times shorter than that of those who survived, showing that professional care was important to CM patients. This result was consistent to what Chen et al. [13] indicated in 2015. On our Cox regression analysis, these three prognosis factors were also significantly related to the survival time of HIV-negative CM patients with acute/subacute onset. These results demonstrated that the ratio of CSF glucose/blood

glucose, consciousness level, and hospitalization length of the HIV-negative CM patients with acute/subacute onset should receive greater focus, in the hope to decrease mortality.

Although we focused on the onset progress of HIV-negative CM patients and explored the independent prognosis factors and the factors related to the survival time of HIV-negative CM patients with acute/subacute onset, there were some limitations to this approach. A larger sample size may allow more prognosis factors to be detected. A better method of communication to avoid lost cases due to any inconveniences in maintaining contact should be accounted for in future studies. Furthermore, a multicenter study should be performed for a more detailed study.

Acknowledgments A very special thank you is given to Tejash Patel (University of North Carolina, USA) for the contribution to the language of this article.

Author contributions LZ conceived the design for this study and HZ drafted the manuscript. LZ revised the manuscript in detail. HZ, QC, and ZSX collected the data. HZ and DMW performed the statistical analysis. MYL, YM, XMZ, JYL, and NFC made significant contributions to this work by providing assistance and helped in the data collection, data handling, and analysis. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Zunt JR, Baldwin KJ (2012) Chronic and subacute meningitis. Continuum (Minneap Minn) 18(6 Infectious Disease):1290–1318
2. Negroni R (2012) Cryptococcosis. Clin Dermatol 30(6):599–609
3. Chimalizeni Y, Tickell D, Connell T (2010) Evidence behind the WHO guidelines: hospital care for children: what is the most appropriate anti-fungal treatment for acute cryptococcal meningitis in children with HIV? J Trop Pediatr 56(1):4–12
4. Malessa R, Krams M, Hengge U, Weiller C, Reinhardt V, Volbracht L, Rauhut F, Brockmeyer NH (1994) Elevation of intracranial pressure in acute AIDS-related cryptococcal meningitis. Clin Investig 72(12):1020–1026
5. Pappas PG, Bustamante B, Ticona E, Hamill RJ, Johnson PC, Reboli A, Aberg J, Hasbun R, Hsu HH (2004) Recombinant interferon- gamma 1b as adjunctive therapy for AIDS-related acute cryptococcal meningitis. J Infect Dis 189(12):2185–2191
6. Saag MS, Powderly WG, Cloud GA, Robinson P, Grieco MH, Sharkey PK, Thompson SE, Sugar AM, Tuazon CU, Fisher JF, Hyslop N, Jacobson JM, Hafner R, Dismukes WE (1992) Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. N Engl J Med 326(2):83–89
7. Sloan D, Dlamini S, Paul N, Dedicoat M (2008) Treatment of acute cryptococcal meningitis in HIV infected adults, with an emphasis on resource-limited settings. Cochrane Database Syst Rev 4: CD005647
8. Witt MD, Lewis RJ, Larsen RA, Milefchik EN, Leal MA, Haubrich RH, Richie JA, Edwards JE Jr, Ghannoum MA (1996) Identification of patients with acute AIDS-associated cryptococcal meningitis who can be effectively treated with fluconazole: the role of antifungal susceptibility testing. Clin Infect Dis 22(2):322–328
9. Bestard J, Siddiqi ZA (2010) Cryptococcal meningoencephalitis in immunocompetent patients: changing trends in Canada. Neurology 74(15):1233–1235
10. Kwon-Chung K, Bennett JE (1992) Medical mycology. Lea & Febiger, Philadelphia
11. Yuchong C, Fubin C, Jianghan C, Fenglian W, Nan X, Minghui Y, Yalin S, Zhizhong Z (2012) Cryptococcosis in China (1985–2010): review of cases from Chinese database. Mycopathologia 173(5–6): 329–335
12. Zheng H, Li M, Luo Y, Wang D, Yang J, Chen Q, Lao J, Chen N, Yang M, Wang Q (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(1):77
13. Chen CH, Sy HN, Lin LJ, Yen HC, Wang SH, Chen WL, Chen YM, Chang YJ (2015) Epidemiological characterization and prognostic factors in patients with confirmed cerebral cryptococcosis in central Taiwan. J Venom Anim Toxins Incl Trop Dis 21:12
14. Brizendine KD, Baddley JW, Pappas PG (2013) Predictors of mortality and differences in clinical features among patients with Cryptococcosis according to immune status. PLoS One 8(3): e60431
15. Darzé C, Lucena R, Gomes I, Melo A (1999) Prognosis factors in cryptococcal meningoencephalitis. Arq Neuropsiquiatr 57(3A): 649–652
16. Lu CH, Chang WN, Chang HW, Chuang YC (1999) The prognostic factors of cryptococcal meningitis in HIV-negative patients. J Hosp Infect 42(4):313–320
17. Majumder S, Mandal SK, Bandyopadhyay D (2011) Prognostic markers in AIDS-related cryptococcal meningitis. J Assoc Physicians India 59:152–154
18. Lui G, Lee N, Ip M, Choi KW, Tso YK, Lam E, Chau S, Lai R, Cockram CS (2006) Cryptococcosis in apparently immunocompetent patients. QJM 99(3):143–151
19. Nigam C, Gahlot R, Kumar V, Chakravarty J, Tilak R (2012) Central nervous system cryptococcosis among a cohort of HIV infected patients from a University Hospital of North India. J Clin Diagn Res 6(8):1385–1387
20. Liao CH, Chi CY, Wang YJ, Tseng SW, Chou CH, Ho CM, Lin PC, Ho MW, Wang JH (2012) Different presentations and outcomes between HIV-infected and HIV-uninfected patients with Cryptococcal meningitis. J Microbiol Immunol Infect 45(4):296–304
21. Young GB, Ropper AH, Bolton CF (1998) Coma and impaired consciousness: a clinical perspective. McGraw-Hill, New York