Clinical Neurology and Neurosurgery 186 (2019) 105539

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Predictors of hospital discharge outcome from the presenting clinical characteristics and the first cerebrospinal fluid analysis among the patients with cryptococcal meningitis

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ARTICLE INFO

Keywords:
Meningitis
Cryptococcus
Outcome

ABSTRACT

Objective: Prognosticators of the outcome of patients with cryptococcal meningitis (CM) at variable follow-up time has been reported. We aimed to identify prognosticators of an outcome on hospital discharge of treated CM.
Patients and methods: The presenting characteristics of CM patients admitted in Songklanagarind Hospital from 2002 to 2017 were retrospectively reviewed. The unfavorable outcome was defined as no improvement or death after starting treatment. The significant differences in clinical presentations between the patients with favorable and unfavorable outcomes were descriptively analyzed. The significant independent predictors from the clinical presentations and the first results of cerebrospinal fluid (CSF) analysis with cut-off values were further defined by multiple logistic regression analysis and shown in adjusted odds ratios ($p < 0.05$).
Results: Sixty-two CM patients were enrolled and 33 (53.2%) of them were females. Their median (IQR) age was 37 (30, 46) years old. HIV serology was positive in 71.0%. Concurrent immunosuppressant use and systemic malignancies were 6.5 and 4.8%, respectively. The median (IQR) days of hospital stay was 18.0 days (12.8, 23.0). Eleven patients had unfavorable outcomes at hospital discharge (8 died, 3 no neurological improvement). Cranial nerve palsy and high CSF protein were dependent predictors for the unfavorable outcome, while high CSF glucose was a protective factor. In addition, CSF protein > 270 mg/dL was an independent predictor for the unfavorable outcome when adjusted for other CSF analysis results (adjusted odds ratio 27.1, 95% confidence interval 1.1–678.5, $p = 0.034$).
Conclusion: Elevated CSF protein was a significant independent predictor for an unfavorable outcome.

1. Introduction

Cryptococcosis is a fungal infection disease caused by *Cryptococcus neoformans/Cryptococcus gattii* species complex (CNG-C). Nowadays, most of the infected patients have an underlying disease that impairs host immunity. Human immune deficiency virus (HIV) infection is a common predisposing risk for acquiring cryptococcal infection. Moreover, the patients with other acquired or treatment-induced low immunity states such as autoimmune disorders, liver cirrhosis, chronic renal failure, diabetes mellitus, and organ transplantation, are also at risk [1–3]. Cryptococcal meningitis (CM) is a fatal form of cryptococcal infection. Intensive surveillance among high-risk patients followed by proper and timely treatment is mandatory. The common presentations of CM are severe headache, nausea, vomiting, and altered sensorium (AS), whereas fever may be subtle or even absent. Markedly elevated intracranial pressure (ICP) is a main pathologic mechanism of CM resulting in devastating neurological sequelae or even death eventually. The significant predictors of unfavorable outcome reported included older age, AS, high opening cerebrospinal fluid (CSF) pressure, high CSF protein, and high CSF cryptococcal antigen titer [4–8]. However, the previous studies reporting the prognosticators of treated CM patients included mostly HIV-infected patients. Moreover, they reported a

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https://doi.org/10.1016/j.clineuro.2019.105539
Received 22 August 2019; Received in revised form 18 September 2019; Accepted 26 September 2019
Available online 27 September 2019
0303-8467/

wide variety of prognosticators because of the variety of definitions of outcomes and duration of follow-up before the final evaluation [5–8]. The current study was aimed to define the predictors of treatment outcome of CM on the date of hospital discharge from the presenting clinical characteristics and the results of first CSF analysis. The outcomes were simply classified as a favorable or unfavorable outcome. We studied the patients who acquired CM with the background of various immune impairments.

2. Materials and methods

2.1. Study subjects and setting

The enrolled subjects were hospitalized patients aged ≥15 who were diagnosed CM from January 2002 to December 2017. The authors used the search terms "B451 Cerebral Cryptococcosis" and "G021 Meningitis in mycoses classified elsewhere" to identify the CM cases from the computerized hospital database. CM was diagnosed by the clinical symptoms and radiological brain images of chronic meningitis in association with a positive result in one of the following investigations: India ink stain for encapsulated yeast cells, serum cryptococcal antigen (S CrAg), and cerebrospinal fluid cryptococcal antigen (CSF CrAg). All of the enrolled CM cases were treated by amphotericin B (0.7 mg/kg/day) for 14 days as induction treatment, followed by oral fluconazole 400 mg/day for another 8 weeks for maintenance treatment. However, by following the guideline of Infectious Diseases Society of America (IDSA) and World Health Organization (WHO) in 2010, the treatment regimen was adapted to be amphotericin B (0.7 mg/kg/day) plus fluconazole 800 mg/day for 14 days, followed by oral fluconazole 800 mg/day for another 8 weeks. Thereafter, 200 mg/day of oral fluconazole was given for long-term prophylaxis against cryptococcal re-infection

The current study was done in Songklanagarind Hospital which is a tertiary medical care and medical teaching hospital at Prince of Songkla University. The hospital is a referral center for complicated cases in all specialties from the primary medical centers in Southern Thailand.

2.2. Data collection

The collected data included general demographic data, underlying diseases, serology of HIV infection, concurrent use of immune-suppressive medicines (e.g. corticosteroids, chemotherapy, and other immune-suppressants), initial neurological signs and symptoms, the results of the first CSF analysis, and the total days of hospital stay. The outcomes were based on the recorded neurological evaluation assessed by the attending physicians on the day of hospital discharge. They were classified as "favorable" when there were at least ≥ 2 scores or grading levels gained from the baseline by one or more of commonly-used neurological evaluation scores following the presenting symptoms (i.e. Glasgow coma score, visual acuity, and visual analogue pain score), and "unfavorable" when there was no improvement or worse in neurological conditions, or all-cause deaths during hospitalization.

2.3. Statistical analysis

Descriptive statistics such as percentage, mean (SD), and median (IQR) were used to demonstrate general demographic data, presenting neurological signs and symptoms, and CSF profiles. Fisher's exact test and rank-sum test were used to identify the parameters with statistically significant differences between CM patients with favorable and unfavorable outcomes. The predictive factors of unfavorable outcome were identified from the initial clinical characteristics and the results of the first CSF analysis by logistic regression analysis and shown in crude and adjusted odds ratios. The level of significance was set at $p < 0.05$. By focusing on the results of the first CSF analysis, we also determined the best cut-off values of the CSF analysis results by receiver operating curve (ROC). The determined cut-off values were further tested for their independent significance in predicting the unfavorable outcome, and were shown in crude and adjusted odds ratios.

2.4. Ethical considerations

The study protocol was reviewed and approved by the Ethics Committee of Faculty of Medicine, Prince of Songkla University, with the registration no. 60-354-14-4. The consent to perform the study was obtained through the approval from the Ethics Committee of Faculty of Medicine, Prince of Songkla University on behalf of all subjects enrolled in this retrospective study. The authors strictly followed the 1964 Declaration of Helsinki and the related good practice guidelines in conducting a research.

3. Results

A total of 62 cases of CM were diagnosed during the study period. Females were slightly more (53.2%) than males. The median (IQR) age was 37 (30, 46) years old. The majority of the enrolled cases had positive HIV serology (71.0%). Fever, headache, nuchal rigidity, nausea, and vomiting, but without focal neurological deficit, that compose the syndrome of meningitis were the common presentations. However, signs of meningeal inflammation presented in only 27.4%. The initial CSF analysis found elevated mean CSF opening pressure along with high CSF protein level and high white blood cell count in all enrolled cases. Encapsulated budding yeast cells were found in half (53.2%) of the cases. CSF CrAg and CSF culture for *Cryptococcus* species. were presented in 66.1% and 64.5%, respectively. All of the positive CSF cultures revealed CNG-C. Concurrent immunosuppressive agents including corticosteroid use and the association with systemic malignancy were found in 11 and 3 cases, respectively. Other systemic illnesses that compromised host immunity were diabetes mellitus, renal insufficiency, and liver cirrhosis which consisted of 10 cases in our series (Table 1). There was no patient with intact immunity found in our series. The median (IQR) days of hospital stay was 18 days (12.8, 23.0). On the date of hospital discharge, 51 patients had favorable outcome, whereas 11 patients acquired unfavorable outcome in which 8 (12.9%) patients died and three patients had no neurological improvement. The causes of death were systemic complications due to the compromised baseline immunity and clinical status i.e. gastrointestinal bleeding (1), septic shock (4), central diabetes insipidus (1), severe hypoxemia (1), whereas increased ICP that resulted in brain herniation was reported in only one case.

Only one of our patients underwent ventriculoperitoneal shunt for reduction of the CSF pressure because the consents were not obtained from the others. The osmotic agents for reduction of the brain edema were not applied in our patients. Instead, the repeated lumbar punctures to temporary reduction of the CSF pressure were performed, and no significant clinical benefit was found (Table1 and 2). In addition, the effect of new treatment regimen following IDSA and WHO recommendations in 2010 on the outcome showed no significant difference.

(84% [new regimen] vs. 81.1% [previous regimen] had favorable outcome; $p = 0.52$) The duration from the onset symptoms to treatment was determined and analyzed for the association with the outcomes, in which we found no significant association (Table1). Although when the durations were classified into sub-acute and chronic onsets, there was no significant predictor identified as well (Table2).

The significant predictors of unfavorable outcomes were CSF protein (crude odds ratio [OR] 1.01, 95% confidence interval [CI] 1.00–1.02, $p = 0.002$) and cranial nerve palsy (crude OR 5.12, 95% CI 0.91–28.76, $p < 0.001$), while CSF glucose showed a significant protective effect (crude OR 0.94, 95% CI 0.81 to 0.99, $p = 0.006$) (Table2). We could not further identify the independent predictors by multivariate logistic regression analysis because of the limited number of

Table 1
Comparison of demographic and presenting clinical characteristics between the cryptococcal meningitis patients with favorable and unfavorable outcomes.

Variable	Overall (N = 62) n (%)	Favorable outcome (N = 51) n (%)	Unfavorable outcome (N = 11) n (%)	P value
Sex				> 0.999
Male	28 (45.2)	23 (45.1)	5 (45.5)	
Female	34 (54.8)	28 (54.9)	6 (54.5)	
Age (years), median (IQR)	37.0 (30.0, 46.0)	36.0 (29.5,42.0)	46.0 (41.5,54.5)	0.014**
Fever	41 (66.1)	37 (74.0)	4 (36.4)	0.03*
Headache	48 (77.4)	43 (91.5)	5 (45.5)	0.002*
Visual changes	5 (8.1)	4 (7.8)	1 (9.1)	> 0.999
Nausea and/or vomiting	46 (74.2)	41 (87.2)	5 (45.5)	0.006*
Seizure[a]	8 (12.9)	7 (14.9)	1 (9.1)	> 0.999
Alteration of consciousness	10 (16.1)	7 (14.9)	3 (27.3)	0.381
Cranial nerve palsy[b]	7 (11.3)	4 (7.8)	3 (27.3)	0.099
Meningeal irritation signs: positive	17 (27.4)	15 (29.4)	2 (18.2)	0.712
Anti-HIV serology: positive	44 (71.0)	39 (76.5)	5 (50.0)	0.124
CSF India ink stain: positive for encapsulated yeast cells	33 (53.2)	28 (59.6)	5 (55.6)	> 0.999
CSF cryptococcal Ag: present	41 (66.1)	35 (72.9)	6 (66.7)	0.700
CSF culture: positive for *Cryptococcus* spp.	40 (64.5)	32 (64.0)	8 (88.9)	0.247
Serum cryptococcal Ag: positive	42 (67.7)	36 (78.3)	6 (66.7)	0.428
Systemic malignancy	3 (4.8)	1 (2.0)	2 (18.2)	0.079
Corticosteroids use	7 (11.3)	6 (11.8)	1 (9.1)	> 0.999
Concurrent immunosuppressive agents use	4 (6.5)	2 (3.9)	2 (18.2)	0.141
Renal insufficiency	4 (6.5)	2 (4.2)	2 (18.2)	0.154
Diabetes mellitus	2 (3.2)	1 (2.1)	1 (9.1)	0.341
Liver cirrhosis	4 (6.5)	0 (0.0)	4 (36.4)	< 0.001*
CSF open pressure (cm H2O), mean (SD)	31.5 (11.7)	31.6 (14.7)	30.6 (15.8)	0.867
CSF glucose (mg/dL), median (IQR)	39.0 (22.0, 48.0)	42.0 (32.0, 48.0)	22.0 (13.0, 30.0)	0.004**
CSF protein (mg/dL), median (IQR)	89.4 (52.9, 138.2)	80.0 (47.5, 111.4)	147.3 (97.7, 328.0)	0.017**
CSF cell count (cell/ mm^3), median (IQR)	20.0 (4.0, 96.5)	19.0 (2.0, 95.8)	48.0 (13.0, 90.0)	0.217
Duration from the onset of symptoms to treatment, median (IQR) (days)	14.0 (5.0, 21.0)	14.0 (5.0, 21.0)	5.0 (2.8, 18.0)	0.256
Modes of the onset				0.357
Acute (0-7 days)	22 (38.6)	17 (34.7)	5 (62.5)	
Sub-acute (8-14 days)	17 (29.8)	16 (32.7)	1 (12.5)	
Chronic (≥ 15 days)	18 (31.6)	16 (32.7)	2 (25)	
Repeated lumbar punctures for reduction of CSF pressure	43 (69.4)	36 (70.6)	7 (63.6)	0.724

[a] All seizure types.
[b] Disorders of all cranial nerves (CN) including CN II (5 cases), and other CNs (2 cases).
* Fisher's exact test, $p < 0.05$.
** Rank sum test, $p < 0.05$.

studied cases.

In order to use the results of the first CSF analysis to predict the outcomes, the best cut-off points of each CSF analysis result determined by ROC curve were: CSF glucose > 36 mg/dL, CSF protein > 270 mg/dL, total white cell count > 45 cells/mm^3, CSF opening pressure > 24 cmH_2O, and CSF CrAg > 1:640. We found that merely the initial CSF protein was the significant independent predictor after adjusting for all other variables of CSF analysis results mentioned (adjusted OR 27.1, 95% CI 1.1–678.5, p = 0.034) (Table 3).

4. Discussion

The common presenting symptoms of CM in the current study were fever, headache, nausea, and vomiting, whereas AS which was common in the previous studies presented in fewer patients (16.13%) [4,5]. This might be due to more severe cases of CM in the previous studies that were performed in HIV endemic areas. The included subjects possibly had markedly lower host immunity at the time of acquiring CM, and therefore, predisposed them to a higher rate of complications and fatal outcome [4]. Although CM is a meningeal infection, it is common to find less proportion of positive meningeal irritation sign like our study (27.42%). Moreover, the number of total white blood cells in CSF was not markedly high, while an elevated opening CSF pressure and elevated level of CSF protein were obviously found. Such findings of CSF analysis in this study agreed with those reported in a previous study [6]. The principal pathogenesis of CM is markedly elevated ICP rather than severe meningeal inflammation that was found in tuberculous meningitis [6]. Therefore, the major presenting symptoms of CM are headache, nausea, vomiting, papilledema, and AS indicating elevated ICP while the CSF pleocytosis is not pronounced. Hence, the mortality and morbidity of CM are directly related to the level of elevated ICP, but not to the severity of meningeal inflammation. Moreover, we considered that the outcomes in our setting were markedly based on the preexisting illnesses and multiple complications of low-immunity patients, but were not based greatly on the regimen of CM treatment.

The dependent factors predicting unfavorable outcome in the current study were elevated CSF protein and cranial nerve palsy, whereas elevated CSF glucose was a protective factor (Table 2). Several earlier studies reported the variable prognosticators of unfavorable outcome. This is caused by the variation in the definition of unfavorable outcomes, the time of final assessment, and the baseline clinical as well as the immunity status of the enrolled patients. The reported predictors of unfavorable outcome among HIV-infected patients with CM included advanced age, low Glasgow Coma Scale score at presentation, papilledema, high CSF opening pressure (> 250 mmH_2O), low CSF white blood cell count, low body weight, and high CSF CrAg titer (> 1:1024) [4,5,7–9]. To our knowledge now, there have been few studies investigating the final outcome of the patients with other immune-compromised backgrounds. According to the current study, the positivity of anti-HIV serology had no significant impact on the outcomes. The lower number of enrolled cases and the shorter time before the final evaluation possibly contributed to this result. A CSF protein above 270 mg/dL was a significant independent predictor of unfavorable outcome when it was adjusted for the all other results of the CSF analysis. We propose that the chronic interruption of CSF absorption from subarachnoid space into systemic blood circulation by CM leads to the accumulation

Table 2
Univariate analysis of the predictors of unfavorable outcome from the presenting clinical characteristics and the initial CSF analysis results in the patients with cryptococcal meningitis.

Parameter (Yes *vs.* No)	Crude OR (95% CI)	P (LR-test)
Age (years)[#], median (IQR)	1.07 (1.01 to 1.13)	> 0.999
Underlying diseases[a]	13.00 (2.55 to 66.40)	> 0.999
Systemic malignancies	12.57 (1.00 to 157.73)	> 0.999
Concurrent immunosuppressive agents use	2.69 (0.22 to 33.28)	> 0.999
Fever	0.17 (0.04 to 0.79)	> 0.999
Nausea and/or vomiting	0.12 (0.02 to 0.65)	> 0.999
Seizure[b]	0.68 (0.07 to 6.31)	> 0.999
Alteration of consciousness	2.71 (0.55 to 13.49)	> 0.999
Cranial nerve palsy[c]	5.12 (0.91 to 28.76)	< 0.001*
Anti-HIV serology: positive	0.17 (0.04 to 0.79)	> 0.999
Serum cryptococcal antigen: positive	0.50 (0.10 to 2.40)	> 0.999
CSF India ink stain: positive for encapsulated yeast cells	0.76 (0.18 to 3.22)	> 0.999
CSF culture: positivity for *Cryptococcus* spp.	3.25 (0.37 to 28.65)	> 0.999
CSF cryptococcal antigen	1.00 (1.00 to 1.00)	0.264
Elevated CSF open pressure (cmH_2O)[#]	1.00 (0.94 to 1.05)	0.864
Elevated CSF glucose (mg/dL)[#]	0.94 (0.81 to 0.99)	0.006*
Elevated CSF protein (mg/dL)[#]	1.01 (1.00 to 1.02)	0.002*
Elevated CSF WBC count (cells/ mm^3)[#]	1.00 (0.99 to 1.01)	0.941
Modes of onset; ref. Acute (0-7 days)		0.288
Sub-acute (8-14 days)	0.21 (0.02, 2.02)	
Chronic (≥ 15 days)	0.42 (0.07, 2.51)	
Repeated lumbar punctures for reduction of CSF pressure	0.73 (0.19, 2.86)	0.654

Abbreviation: CSF: cerebrospinal fluid. WBC: white blood cell
* $p < 0.05$.
[a] Diseases that caused low host immunity (diabetes mellitus, end stage renal disease, and liver cirrhosis).
[b] Disorders of all cranial nerves (CN) including CN II (5 cases), and other CNs (2 cases).
[c] All seizure types.
[#] continuous variables.

Table 3
Multivariate regression analysis of predictors of unfavorable outcome from the results of the initial cerebrospinal fluid (CSF) analysis.

	Crude OR (95% CI)	adj. OR (95% CI)[#]	P (LR-test)
Opening pressure (cmH_2O) > 24 vs. ≤24	2.3 (0.2 to 22.4)	3.2 (0.1 to 95.6)	0.472
WBC count (cells/ mm^3) > 45 vs. ≤45	1.1 (0.2 to 7.1)	1.8 (0.2 to 21.3)	0.656
Glucose (mg/dL) ≤36 vs. > 36	7.1 (0.7 to 70.2)	4.8 (0.3 to 69.7)	0.219
Protein (mg/dL) > 270 vs. ≤270	23.3 (1.6 to 338.4)	27.1 (1.1 to 678.5)	0.034*
Cryptococcal antigen > 1:640 vs. ≤1:640	7.1 (0.7 to 70.2)	5.4 (0.3 to 90.2)	0.203

Abbreviations: OR, odds ratio; CI, confidence interval; adj. OR, adjusted odds ratio, LR, likelihood ratio, WBC, white blood cell.
* $p < 0.05$.
[#] Adjusted for all other CSF analysis results.

of CSF protein content eventually. Therefore, our findings suggest that the level of CSF protein from the first CSF analysis may reflect the long-standing course and severity of CM, and may be used as a predictor of unfavorable outcome at the time of hospital discharge.

The retrospective nature of this study is a major limitation for the strength of this study. The application of individual evaluation score may not be suitable to assess the global outcome on hospital discharge, because the final outcome of CM can be affected or complicated by several concurrent medical comorbidity. Moreover, the correlation of the outcome on hospital discharge with the long term outcome is unable to be determined in this study, due to a short period of clinical observation during hospitalization and no data of long term clinical outcome were recruited. However, the authors considered that the first CSF analysis, particularly the level of CSF protein can predict the outcome at hospital discharge.

5. Conclusion

CM is a devastating meningeal infection, notably among the individuals with various causes of impaired immunity. Based on this study, the outcomes at the hospital discharge may be useful for short-term prognosis among the hospitalized CM patients. Additionally, some baseline clinical presentations and the results of the initial CSF analysis may be practically useful for prognostication of the outcome at hospital discharge.

Funding and support

There is no funding or support related to this study

Data availability statement

The data generated from this research and its relevant materials (i.e. statistical analysis plan and results) are made available as soon as the research is published. The shared data can be obtained upon a request to the corresponding author from any qualified investigators or their official representatives by contacting through the corresponding author's email address provided.

Author contribution

Pornchai Sathirapanya: Conceptualization of the study idea; methodology design; research supervision and review and editing the final draft for submission.

Nichanan Ekpitakdamrong: Data investigation, collection and curation; formal data analysis; and writing the original draft of manuscript.

Sarunyou Chusri: Conceptualization of the study idea and methodology design.

Nannapat Pruphetkaew: Formal analysis of the data.

Pensri Chongphattararot: Formal analysis of the data.

Paveena Nanphan: Formal analysis of the data.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgement

The authors appreciate the help from Glenn K. Shingledecker of International Affairs Unit, Faculty of Medicine, Prince of Songkla University in editing English grammar and writing of this manuscript.

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