Predictive Model for Permanent Shunting in Cryptococcal meningitis

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Abstract. Cryptococcal meningitis may have long-term morbidity and requires a permanent cerebrospinal fluid shunt. This study aimed to evaluate the risk factors and create a predictive model for permanent shunt treatment in cryptococcal meningitis patients. This was a retrospective analytical study conducted at Khon Kaen University. The study period was from January 2005 to December 2015. We enrolled all adult patients diagnosed with cryptococcal meningitis. Risk factors predictive for permanent shunting treatment were analyzed by multivariate logistic regression analysis. There were 341 patients diagnosed with cryptococcal meningitis. Of those, 64 patients (18.7%) were treated with permanent shunts. There were three independent factors associated with permanent shunt treatment. The presence of hydrocephalus had the highest adjusted odds ratio at 56.77. The resulting predictive model for permanent shunt treatment (y) is $(-3.85) + (4.04 \times \text{hydrocephalus}) + (2.13 \times \text{initial cerebrospinal fluid (CSF) opening pressure (OP)} > 25 \text{ cm H}_2\text{O}) + (1.87 \times \text{non-human immune deficiency virus (HIV)})$. In conclusion, non-HIV status, initial CSF OP greater than or equal to 25 cm H₂O, and the presence of hydrocephalus are indicators of the future necessity for permanent shunt therapy.

INTRODUCTION

Cryptococcal meningitis, caused by *Cryptococcus neoformans*, is associated with high rates of morbidity and mortality. In developed countries, 95% of HIV-associated cryptococcal meningitis cases resulted in severe morbidity. The overall mortality rate is approximately 500,000 patients/year worldwide.^{1,2} The most common complication of cryptococcal meningitis is intracranial hypertension leading to impaired mental status, neurological deterioration, and severe disability.^{1,2}

There are several strategies to treat increased intracranial pressure in cases of cryptococcal meningitis. Antifungal drugs, without steroid therapy, are currently recommended for those with intracranial hypertension associated with cryptococcal meningitis.² Serial lumbar puncture (LP), or shunt treatment, is reported to control headaches and improve neurological outcomes.^{3,4} However, shunt treatment should be performed as early as possible.

If patients have a Glasgow Coma Scale score of less than eight or have been comatose for more than 48 hours, the outcomes are poor even with shunt treatment.⁵ A recent study recommended that female patients with elevated cerebrospinal fluid (CSF) cryptococcal antigen undergo continuous CSF drainage.⁶ However, the study included only 50 patients, 98% of whom were HIV-positive and the outcome was CSF drainage and not specific to permanent shunting. This research aimed to study the risk factors for permanent shunt treatment becoming necessary in cryptococcal meningitis patients using a larger sample size.

METHODS

This was a retrospective analytical study conducted at Khon Kaen University, Khon Kaen, Thailand. The study period was from January 2005 to December 2015. The inclusion criteria

were adult patients aged > 18 years who had been diagnosed as having cryptococcal meningitis based on positive CSF india ink staining results, positive CSF cultures, or positive CSF cryptococcal capsular antigen as determined by the latex agglutination method. We excluded patients with cryptococcoma, subdural empyema, or abscesses. We collected clinical data at baseline and clinical outcomes of all eligible patients.

Hydrocephalus was diagnosed according to matching any of the following criteria^{7,8}: dilated lateral ventricles, effaced sulci, both temporal horns > 2 mm, Sylvian and interhemispheric fissures effaced, ratio of the largest width of frontal horns: internal diameter from inner table to inner table > 0.5, ratio of the largest width of frontal horns to maximum biparietal diameter > 30%, periventricular low density due to transependymal absorption, “Mickey Mouse” ventricles—aqueductal obstruction, bicornuate ratio > 0.25, or the ratio of maximal frontal horn ventricular width to the transverse inner diameter of the skull (Evans’ index) > 0.3. However, the most frequently used criterion in this research was the Evans’ index.^{7,8}

For this study, patients were categorized into two groups based on the type of treatment they received (either serial LP or permanent shunt treatment). Permanent shunts included ventriculoperitoneal (VP) shunts and lumboperitoneal shunts (LP shunt). Temporary external lumbar drainage procedures were defined as a serial LP.

Clinical practice guidelines recommend shunt therapy if there is persistent CSF pressure greater than 25 cm H₂O, in the presence of concurrent antifungal therapy, and repeated daily LP has failed to stabilize symptoms (B-III).² Patients in this study underwent the following process: 1) Cryptococcal meningitis patients who present with a headache or other signs of increased intracranial pressure undergo serial LP to measure the initial opening pressure (OP) and CSF profile. 2) If persistent OP is greater than 25 cm H₂O for 7–10 days with no clinical improvement, permanent shunt therapy is considered unless unstable clinical and vital signs (e.g., severe sepsis or septic shock, coagulopathy, or other medical conditions resulting in a high risk for general anesthesia) are present. 3a) In such cases, a temporary shunt is considered (continuous lumbar drainage if computed tomography (CT) of the brain shows no ventricular dilation or ventriculostomy if

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TABLE 1
Clinical features of patients with cryptococcal meningitis who received serial lumbar puncture or CSF permanent shunt

Factors	Serial LP N = 277	Permanent shunt N = 64	P value
Age, years	35.35 (10.23)	37.38 (11.40)	0.103
Male sex, n (%)	167 (60.29)	41 (64.06)	0.575
Presenting symptoms: headache, n (%)	269 (97.11)	54 (85.71)	0.001
Initial Glasgow Coma Scale: severe, n (%)	10 (3.61)	2 (3.13)	0.798
Hydrocephalus, n (%)	3 (1.08)	29 (45.31)	< 0.001
Open CSF pressure, cm H ₂ O	25.90 (11.11)	43.91 (14.15)	< 0.001
CSF white blood cell, $\times 10^3$ cells/mm ³	13.41 (18.60)	10.75 (12.32)	0.913
CSF protein, mg/dL	89.43 (52.05)	85.42 (37.91)	0.395
CSF glucose, mg/dL	44.87 (15.35)	47.00 (30.51)	0.393
Plasma glucose, mg/dL	116.31 (20.02)	116.20 (11.45)	0.566
CSF india ink: positive, n (%)	267 (96.39)	63 (98.44)	0.364
CSF cryptococcal antigen: positive, n (%)	268 (96.75)	64 (100.00)	0.218
CSF cryptococcal antigen titer (1:10,000), n (%)	7 (9.59)	0 (0.00)	0.802
Anti-HIV: positive, n (%)	265 (95.67)	48 (75.00)	< 0.001
CD4, cells/mm ³	37.09 (69.37)	6.46 (95.71)	0.045

Data presented as mean (standard deviation) unless indicated otherwise; CSF = cerebrospinal fluid; the total numbers of patients in serial lumbar puncture (LP shunt) and ventriculoperitoneal (VP) shunt group may not equal to 277 and 64, respectively due to missing data.

CT of the brain shows ventricular dilation). 3b) For patients meeting the criteria for permanent shunt placement, a VP shunt is placed if ventricular dilation is present or a LP shunt if there is no ventricular dilation.

The study was approved by the Khon Kean University Ethics Committee for Human Research (HE581130) Statistical analysis. Clinical factors were compared between the two groups using descriptive statistics. Factors associated with permanent shunts were determined using logistic regression analysis. Univariate logistic regression analysis was used to identify possible predictors of permanent shunting. Those factors with *P* values of less than 0.20 were consecutively subjected to multivariate logistic regression analysis. The predictive model for permanent shunt treatment in cryptococcal meningitis was determined using the final multivariate logistic regression model. All analysis was performed using the STATA software version 14.0 (College Station, TX).

RESULTS

During the study period, there were 341 patients diagnosed with cryptococcal meningitis. Of those, 64 patients (18.7%) were treated with permanent shunts. Age and sex were comparable between the two study groups (Table 1). There were four significant factors that differed between patients who received serial LP and those who received permanent shunts. These included headaches, hydrocephalus, HIV status, and CD4 count (Table 1). The proportions of patients presenting with headaches and who were HIV-positive were significantly higher in the serial LP group than in the permanent shunt group (97.11% versus 85.71% of patients experienced headaches and 95.67% versus 75.00% were HIV-positive). However, a higher percentage of patients who received permanent shunts developed hydrocephalus than did those who underwent serial LP (45.31% versus 1.08%; *P* value < 0.001). In addition, the average CD4 level was also higher in the permanent shunt group than in the serial LP group (6.46/64, 95.71% versus 37.09/277, 69.37%; *P* value = 0.045).

There were three independent factors associated with permanent shunt treatment (Table 2). The presence of hydrocephalus had the highest adjusted OR at 56.77. The predictive model for permanent shunt treatment (*y*) is $(-3.85) + (4.04 \times \text{hydrocephalus}) + (2.13 \times \text{initial CSF OP} > 25 \text{ cm H}_2\text{O})$

+ $(1.87 \times \text{Non-HIV})$. The value is one if there is presence of hydrocephalus, initial CSF OP > 25 cm H₂O, and negative non-HIV. Otherwise, the value is 0. The probability of permanent shunt treatment is $1/1 + e^{(-y)}$. If all three risk factors were present, the probability of patients undergoing permanent shunt treatment was 98.5%, while the probability in the presence of any two risk factors was between 53.7% and 91.1% (Table 3).

DISCUSSION

As previously mentioned, shunt treatment should be performed within an appropriate timeframe to prevent long-term morbidity from cryptococcal meningitis. This study found three independent factors that were predictive of shunt treatment in cryptococcal meningitis: presence of hydrocephalus, high initial CSF OP, and non-HIV status (Table 2).

Contrary to the results of the previous study mentioned previously,⁶ sex and cryptococcal antigen levels were not significant factors in predicting the use of shunt treatment (Table 1). These findings may be explained by differences in study populations including ethnicity, total size, and percentage of HIV patients. The previous study was performed on 50 Americans, almost 100% of whom were HIV-infected patients, while the present study was conducted in 150 Thai patients, 92% of whom were HIV-infected.

Hydrocephalus, secondary to cryptococcal meningitis, varies widely across studies and has been reported in 9–63% of patients.⁹ Hydrocephalus may represent blockage of CSF flow resulting in high intracranial pressure. Shunt treatment is, therefore, required for this permanent consequence of cryptococcal meningitis. If HIV-infected patients present with

TABLE 2
Factors associated with permanent shunt management in patients with cryptococcal meningitis by logistic regression analyses

Factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Initial CSF OP ≥ 25 cm H ₂ O	11.81 (4.17, 33.39)	8.44 (2.66, 26.72)
Hydrocephalus	70.98 (20.54, 245.29)	56.77 (15.06, 214.07)
Anti-HIV: negative	7.36 (3.28, 16.53)	6.48 (2.28, 18.4)

CSF = cerebrospinal fluid; OP = opening pressure.

TABLE 3
Predictive model

Case scenario	CT brain	Initial OP	Non-HIV	Pr (Y-1)	Probability
Case 1	1	1	1	4.19	0.985
Case 2	1	1	0	2.32	0.911
Case 3	1	0	1	2.06	0.887
Case 4	1	0	0	0.91	0.547
Case 5	0	1	1	0.51	0.537
Case 6	0	1	0	-1.72	0.152
Case 7	0	0	1	-1.98	0.121
Case 8	0	0	0	-3.85	0.021

Probability = probability to permanent shunting.

hydrocephalus at the time of cryptococcal meningitis diagnosis, the probability of that patient undergoing shunt treatment is 54.7% (Table 3). That number is even higher than non-HIV patients with initial CSF OP greater than or equal to 25 cm H₂O.

An elevated intracranial pressure in cryptococcal meningitis is defined by CSF OP of more than 20 cm H₂O. A previous study found that 25% of patients with elevated intracranial pressure had OP greater than 35 cm H₂O,¹⁰ however, it could not be determined from the study whether the authors referenced initial, highest, persistent, or some other form of OP. High CSF OP has not been shown to be related to fungal burden,¹¹ but may indicate severe disease resulting in high morbidity.¹¹ Previous studies have shown shunt treatment to have beneficial effects in cases of cryptococcal meningitis with high intracranial pressure, regardless of hydrocephalus.^{4,12}

Non-HIV status is another predictor of the necessity of shunt therapy (Table 3). Unlike the HIV-associated cryptococcal meningitis, non-HIV cryptococcal meningitis patients seem to have subtle clinical manifestations (also found in children) with higher immune response.^{13,14} In this study, the time from the appearance of initial symptoms to diagnosis was significantly longer in the immunocompetent group than in the immunocompromised group (81 versus 34 days; *P* value < 0.001). Pulmonary cryptococcosis was also higher in the non-HIV than in the HIV-group (40% versus 10%). Patients in the non-HIV group tended to have stronger immune responses than those in the HIV group, as evidenced by them having more CSF pleocytosis (CSF white blood cells > 100 cells/mm³: 58% versus 14%), more CSF protein (CSF protein > 40 mg/dL: 92% versus 75%), and higher CSF OP (> 40 cm H₂O: 36% versus 15%).¹⁵

This study had a large study population, almost 10% of which consisted of non-HIV-infected patients. The probability of shunt therapy in cases with various risk factors is also provided (Table 3) and may be useful as a user-friendly tool to help neurosurgeons decide at a glance whether shunt therapy is necessary. However, there are some limitations. First, because of the retrospective study design, some factors are missing, such as CD4 levels, particularly in non-HIV-infected patients. Second, all patients were Thai. The results of this study may not be applicable to other populations.

CONCLUSIONS

Non-HIV status, initial CSF OP greater than or equal to 25 cm H₂O, and the presence of hydrocephalus are indicators

of the future necessity for shunt therapy. Neurosurgeons may consider shunt therapy in these patients to prevent long-term complications from cryptococcal meningitis.

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