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Original Article

# Risk factors and outcomes of cerebrospinal fluid overdrainage in HIV-negative patients with cryptococcal meningitis after the ventriculoperitoneal shunting procedure

Chih-Wei Hung [a], Wei-Che Lin [b], Wen-Neng Chang [c], Tsung-Ming Su [d], Chia-Te Kung [a], Nai-Wen Tsai [c], Hung-Chen Wang [d], Chih-Cheng Huang [c], Ben-Chung Cheng [e,f], Yu-Jih Su [e], Ya-Ting Chang [c,f], Chih-Min Su [a,f], Sheng-Yuan Hsiao [a,f], Cheng-Hsien Lu [b,f,g,*]

[a] *Department of Emergency Medicine, Taiwan*
[b] *Department of Radiology, Taiwan*
[c] *Department of Neurology, Taiwan*
[d] *Department of Neurosurgery, Taiwan*
[e] *Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[f] *Department of Biological Science, National Sun Yat-Sen University, Kaohsiung, Taiwan*
[g] *Department of Neurology, Xiamen Chang Gung Memorial Hospital, Xiamen, China*

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**Abstract** *Purpose:* Shunt procedures used to treat cryptococcal meningitis complicated with hydrocephalus and/or increased intracranial pressure (IICP) could result in cerebrospinal fluid (CSF) overdrainage, thereby presenting therapeutic challenges.
*Methods:* We analyzed the clinical features and neuroimaging findings after the ventriculoperitoneal (VP) shunt procedure in 51 HIV (Human Immunodeficiency Virus)-negative patients with cryptococcal meningitis, to assess the risk factors associated with post-shunt CSF overdrainage.
*Results:* Symptomatic CSF overdrainage occurred in 12% (6/51) of patients with cryptococcal meningitis who underwent the shunt procedure. Rapid deterioration of neurological conditions was found in 6 patients after the shunt procedure was performed, including disturbed consciousness, quadriparesis, and dysphasia in 5 patients and severe ataxia in 1. The mean

* Corresponding author. Department of Neurology, Chang Gung Memorial Hospital 123, Ta Pei Road, Niao Sung Hsiang, Kaohsiung, Taiwan. Fax: +886 7 7318762.
*E-mail addresses:* chlu99@adm.cgmh.org.tw, chlu99@ms44.url.com.tw (C.-H. Lu).

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duration of CSF overdrainage after the shunting procedure was 2—7 days (mean 4 days). The mean interval between meningitis onset to shunting procedure remained independently associated with CSF overdrainage, and the cut-off value for predicting CSF overdrainage in interval between meningitis onset to shunting procedure was 67.5 days.
*Conclusions:* CSF overdrainage after the VP shunt procedure is not rare, especially in patients with a high-risk of cryptococcal meningitis who also have a prolonged duration of hydrocephalus and/or IICP.


## Introduction

Cryptococcal meningitis remains a potentially fatal central nervous system infection despite the advances in neurosurgical techniques, anti-fungal agents, and imaging technologies[1—3] In clinical practice, uncontrollable increased intracranial pressure (IICP) and hydrocephalus are two complications of cryptococcal meningitis. Delays in diagnosis and treatment are directly related to poor outcomes including various degrees of residual neurological sequelae.[1—4] Since the early 1980s, ventriculoperitoneal (VP) shunt has been used to relieve hydrocephalus or uncontrollable IICP resulting from cryptococcal meningitis.[4—7] However, shunt procedures do not result in good outcomes for all patients.[5,6] These procedures can result in shunt infection, CSF overdrainage, or shunt malfunction.[1—6] Furthermore, the criteria used to determine patients who require shunt procedures remains unclear.

Previous studies have focused on either children or adult patients with normal-pressure hydrocephalus.[8—13] To our knowledge, no study has examined the clinical features of CSF overdrainage in HIV-negative patients with cryptococcal meningitis after the ventriculoperitoneal shunting procedure. This hospital-based study may provide accurate information on the degree of hydrocephalus and IICP in patients with cryptococcal meningitis, the effects of the VP shunt procedure on neurological and functional outcomes, and post-shunt complications. Owing to the possible benefits of VP shunts in reducing functional morbidity, there is a need for better delineation of potential complications and outcomes in hospitalized patients who receive VP shunt treatment. This study presents the clinical experiences and analyzes the clinical features, neuroimaging findings, and clinical scores after the VP shunt procedure in 51 HIV-negative patients with cryptococcal meningitis who had hydrocephalus or uncontrollable IICP.

## Patients and methods

### Study population

The medical records of HIV-negative patients with cryptococcal meningitis admitted to Kaohsiung Chang Gung Memorial Hospital were reviewed for blood cultures, microbiological records, and neuroimaging findings by using pre-existing standardized evaluation forms.

### Diagnostic criteria for cryptococcal meningitis

HIV-negative patients with cryptococcal meningitis were included if they matched any of the following criteria: (1) *Cryptococcus neoformans* detected in one or more CSF samples, (2) positive titer for CSF cryptococcal antigen, (3) clinical features of meningitis detected using CSF India ink staining, or (4) *C. neoformans* detected in blood cultures with clinical presentations of meningitis and typical CSF features.[1] In this study, 51 of the 180 patients who underwent the VP shunt procedure were enrolled. The hospital's Institutional Review Committee on Human Research approved the study protocol (IRB 97-0467B).

### Definitions of hydrocephalus and uncontrollable intracranial hypertension

All patients underwent brain computed tomography (CT) in the emergency room. Follow-up brain CT and/or magnetic resonance imaging (MRI) was performed post-surgery if clinical deterioration was observed, such as acute onset focal neurological deficits, seizures, status epilepticus, or progressively disturbed consciousness. Hydrocephalus was judged retrospectively on the basis of dilation of the temporal horn of the lateral ventricle and/or an Evans' index of $> 0.3$ as measured by an initial CT scan. Evans' index is the ratio of the ventricular width of the bilateral frontal horn to the maximum biparietal diameter.[7] Uncontrollable IICP is defined as an extremely high opening pressure ($>$ 350 mm $H_2O$) and failure to control IICP symptoms through frequent lumbar punctures and other medical approaches such as the use of corticosteroids, mannitol, or acetazolamide.[14] Typically, programmable VP shunts or anti-siphon VP shunts are used to prevent CSF overdrainage, but it could cause shunt obstruction in patients with meningitis. Our standard protocol was to choose non-programmable VP shunts for patients with meningitis to decrease the possibility of obstruction after the VP shunt procedure was completed. CSF overdrainage is defined as an excessive removal of a patient's CSF using a shunt in a patient. This condition can present relatively early after shunt insertion, along with subdural effusion or hematoma.[11]

### Statistical analysis

Two separate statistical analyses were performed. First, the risk factors including interval between meningitis onset

to shunting procedure, interval between hospitalization to shunting procedure, age, gender, mean GCS at emergency room and after shunt procedures, peripheral blood test measurements; CSF analysis at emergency room and before VP shunt implantation, positive CSF culture or not and different shunt devices on CSF overdraining were analyzed by univariate logistic regression. Second, stepwise logistic regression was used to evaluate the relationships between significant variables and CSF overdraining, with adjustments made for other potential confounding factors. Variables with a score of 0 in a $2 \times 2$ table were eliminated from logistic analysis, while those that had a strong association with fatality rate ($p < 0.05$) were included in the final model. Receiver operating characteristic (ROC) curves were generated for significant variables and the areas under the ROC curves were also calculated. All statistical tests were two-tailed. All statistical analyses were conducted using the SPSS software package, version 13.0.

## Results

### Baseline data of the study patients

Fifty-one of the 180 HIV-negative patients with cryptococcal meningitis experienced hydrocephalus or uncontrolled IICP and underwent the VP shunt procedure. These included 35 men and 16 women (mean ages, 48.8 and 59.0 years, respectively; range, 18–81 years). Hydrocephalus was observed in 32 patients, uncontrollable IICP was observed in 12, and both conditions were observed in the remaining 7. Among the 51 patients who underwent the shunt procedure, 6 had CSF overdrainage and 1 had shunt infection. The characteristics of the patients are listed in Tables 1–3. All patients received non-programmable VP shunts, and the valves were set to medium pressure. Two Codman-Hakim shunts and 49 Medtronic shunts were used (Table 1).

### Neuroimaging findings

The neuroimaging findings of patients with and of those without CSF overdrainage are listed in Table 1. Findings included cerebral infarction, gyral enhancement, basal cistern effacement, pseudo-cyst, dilated Virchow-Robin space, and mass lesions. Follow-up neuroimaging studies in the 6 patients who had overdrainage after the shunt procedure showed thin-layer subdural effusion in both hemispheres (Fig 1).

### Clinical features and outcomes

Neurological conditions deteriorated rapidly (within 1 week) in the 6 patients who had CSF overdrainage after having undergone the shunting procedure. The symptoms

**Table 1** Comparison of baseline clinical features, neuroimaging findings and outcome between cryptococcal meningitis patients received ventriculoperitoneal shunt with or without overdrainage.

| | Overdrainage n = 6 | No overdrainage n = 45 | p-value |
|---|---|---|---|
| Clinical features during hospitalization | | | |
| Fever/chills | 4 | 25 | 0.69 |
| Headache | 5 | 24 | 0.22 |
| Disturbed consciousness at emergency room | 4 | 20 | 0.40 |
| Visual disturbance | 0 | 7 | 0.58 |
| Hearing impairment | 0 | 5 | 1 |
| New clinical manifestations after shunt procedures | | | |
| Ataxia | 1 | 0 | 0.118 |
| Quadriparesis | 3 | 0 | 0.001 |
| Progressive disturbed consciousness | 4 | 0 | <0.0001 |
| Underlying disease | | | |
| Diabetes mellitus | 1 | 7 | 1 |
| Liver cirrhosis | 0 | 4 | 1 |
| Systemic lupus erythematosus | 0 | 1 | 1 |
| Malignancy | 0 | 2 | 1 |
| Cushing syndrome | 0 | 1 | 1 |
| Neuroimaging findings during hospitalization | | | |
| Hydrocephalus | 6 | 39 | 1.0 |
| Cerebral infarction | 1 | 7 | 1 |
| Gyral enhancement | 1 | 7 | 1 |
| Basal cistern effacement | 1 | 3 | 0.40 |
| Pseudocyst | 1 | 3 | 0.40 |
| Dilated Virchow-Robin space | 2 | 3 | 0.1 |
| Mass lesions | 0 | 4 | 1 |
| Outcome | | | |
| In-hospital Mortality | 1 | 15 | 0.65 |
| Mean hospitalization days | 74.7 ± 32.0 | 70.6 ± 54.1 | 0.80 |

**Table 2** Risk factors associated with overdrainage after VP shunting procedures.

| | overdrainage n = 6 | No overdrainage n = 45 | Crude OR (95% CI) | p-value | Adjusted OR (95%CI) | p-value |
|---|---|---|---|---|---|---|
| Interval between meningitis onset to shunting procedure (days) | 68.7 ± 27.1 | 38.7 ± 23.1 | 1.05 (1.0–1.09) | 0.025 | 1.05 (1.0–1.11) | 0.041 |
| Interval between hospitalization to shunting procedure (days) | 42.2 ± 21.1 | 21.6 ± 16.6 | 1.06 (1.0–1.11) | 0.036 | | |
| Age | 57.7 ± 15.6 | 51.2 ± 18.9 | 1.02 (0.97–1.07) | 0.43 | | |
| Sex (Male/Female) | 6/0 | 29/16 | 1.21 (1.04–1.40) | 0.16 | | |
| Mean GCS at emergency room | 14.0 ± 1.5 | 12.6 ± 3.5 | 1.2 (0.81–1.79) | 0.37 | | |
| Mean GCS after VP shunting procedure | 11.8 ± 1.7 | 12.6 ± 3.1 | 0.93 (0.72–1.20) | 0.56 | | |
| Peripheral blood test measurements | | | | | | |
| Glucose (mg/dL) | 198.3 ± 113.0 | 145.6 ± 63.1 | 1.0 (1.0–1.02) | 0.23 | | |
| Hyponatremia | 0 | 8 | 0.86 (0.76–0.97) | 0.57 | | |
| Thrombocytopenia | 0 | 6 | 0.87 (0.77–0.97) | 1 | | |
| Leukocytosis | 1 | 18 | 3.3 (0.36–30.95) | 0.29 | | |
| CSF analysis at Emergency room | | | | | | |
| Opening pressure ($mmH_2O$) | 305 ± 80.9 | 387.3 ± 154.1 | 1.0 (0.99–1.0) | 0.22 | | |
| Sugar (mg/dL) | 38 ± 20.7 | 38.68 ± 41.885 | 1.0 (0.98–1.02) | 0.97 | | |
| Total Protein (mg/dL) | 131.0 ± 82.5 | 303.2 ± 284.0 | 1.02 (1.0–1.10) | 0.04 | | |
| Lactate (mg/dL) | 67.5 ± 43.5 | 62.4 ± 40.6 | 1.0 (0.98–1.02) | 0.79 | | |
| CSF analysis before VP shunt implantation | | | | | | |
| Opening pressure ($mmH_2O$) | 320 ± 67.2 | 359 ± 149.2 | 0.99 (0.99–1.0) | 0.52 | | |
| Sugar (mg/dL) | 34 ± 9.4 | 36.7 ± 38.84 | 1.0 (0.97–1.03) | 0.88 | | |
| Total Protein (mg/dL) | 148.3 ± 56.65 | 237.8 ± 357.97 | 1.0 (0.99–1.01) | 0.60 | | |
| Lactate (mg/dL) | 43.2 ± 9.06 | 61.0 ± 41.7 | 0.98 (0.93–1.02) | 0.29 | | |
| CSF Culture | 3 | 17 | 1.65 (0.30–9.1) | 0.57 | | |
| Shunt devices | | | | | | |
| Metronic | 6 | 43 | 0.88 (0.79–0.97) | 1.0 | | |
| Codman-Hakim | 0 | 2 | | | | |

Abbreviation: GCS: Glasgow Coma Scale, CSF: cerebrospinal fluid; VP = ventriculoperitoneal.

observed in these 6 patients were disturbed consciousness and acute quadriparesis with dysphasia in 5 patients, and severe ataxia in 1. The time duration between the completion of shunt procedure and when the new symptoms first appeared was 2–7 days (mean, 4 days). To treat CSF overdrainage, the VP shunts were ligated in 4 patients, and the shunts were revised in 2 patients.

## Risk factors associated with CSF overdrainage after the ventriculoperitoneal procedure

The risk factors associated with CSF overdrainage after the ventriculoperitoneal procedure was completed are listed in Table 1. The interval between meningitis onset to shunting procedure was 68.7 ± 27.1 days and 38.7 ± 23.1 days for

**Table 3** Clinical data of patients with overshunting.

| No. | Age (years) /sex | Reasons for ventricular relief | Effect of ventricular relief | Outcomes |
|---|---|---|---|---|
| 1 | 58/M | Hydrocephalus | Fluctuation in consciousness | Good recovery |
| 2 | 71/M | Hydrocephalus | Unsteady gait, bilateral subdural effusion | Good recovery |
| 3 | 29/M | Hydrocephalus, IICP | No improvement in consciousness, bilateral subdural effusion | Death |
| 4 | 55/M | Hydrocephalus, IICP | Drowsiness, bilateral subdural effusion | Good recovery |
| 5 | 61/M | Hydrocephalus, IICP | Fluctuation in consciousness, bilateral subdural effusion | Good recovery |
| 6 | 72/M | Hydrocephalus | Ataxia, frontoparietal subdural hemorrhage | Good recovery |

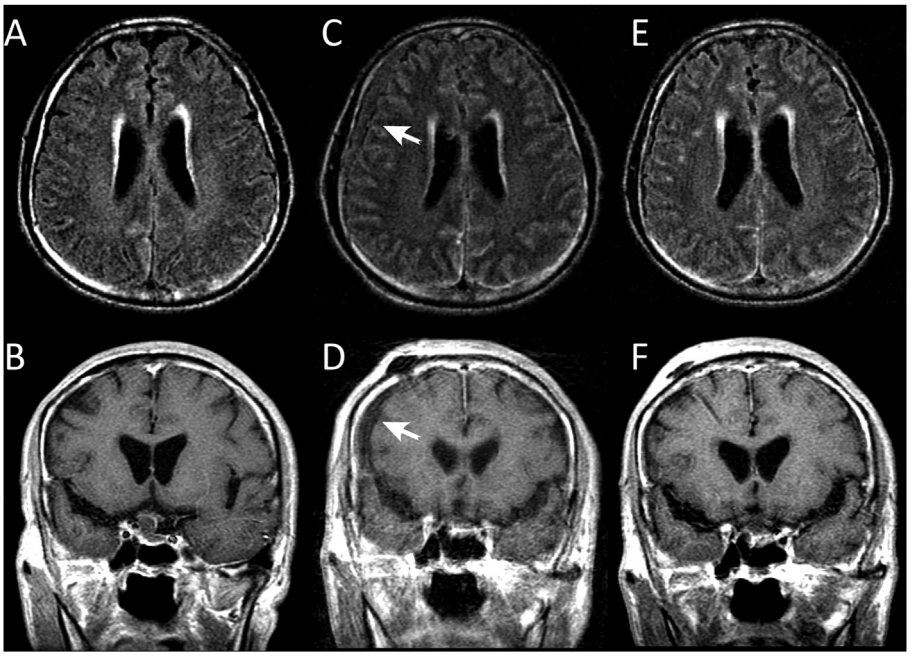


**Figure 1.** Axial fluid-attenuated inversion-recovery (A, C, E) and T1-weighted (B, D, F) magnetic resonance imaging (MRI) scans of a 55-year-old man with cryptococcal meningitis (Patient 4) at admission (A, B), on treatment with a ventriculoperitoneal shunt (C, D), and after clipping the shunt (E, F). MRI scans on readmission revealed marked ventricular enlargement (A, B). A ventriculoperitoneal (VP) shunt was placed (C, D). However, shunting procedure led to a rapid deterioration of mental status without an obvious decrease in the ventricular size, as measured by repeat MRI 4 days postoperatively. Brain imaging also revealed a thin layer of subdural effusion in the right cerebrum (arrow), indicating CSF overdrainage. After clipping the VP shunt, the patient immediately showed symptom improvement, with regression of the right cerebral subdural effusion (E, F).

patients with and for those without CSF overdrainage, respectively (P = 0.008). The interval between hospitalization to shunting procedure was 42.2 ± 21.1 days and 21.6 ± 16.6 days for patients with and for those without CSF overdrainage, respectively (P = 0.019). The mean Glasgow Coma Scale (GCS) score at emergency room was 14.0 ± 1.5 and 12.6 ± 3.5 for patients with and for those without CSF overdrainage, respectively (P = 0.12). The mean CSF opening pressure at emergency room was 305 ± 80.9 mm$H_2O$ and 387.3 ± 154.1 mm$H_2O$ in patients with and in those without CSF overdrainage, respectively (P = 0.09). The mean hospitalization duration was 74.7 ± 32.0 days and 70.6 ± 54.1 days for patients with and for those without CSF overdrainage, respectively (P = 0.80). Fever, headache, and conscious disturbance were the three most common clinical manifestations in both groups. The other clinical features associated with post-shunt CSF overdrainage are listed in Tables 1–3. The in-hospital fatality rate was 16.7% (1/6) and 33.3% (15/45) among patients with and those without CSF overdrainage, respectively (P = 0.65). Statistical analysis of the baseline clinical manifestations, neuroimaging findings at emergency room, and peripheral blood and CSF findings at admission between the overdrainage and non-overdrainage groups revealed that interval between meningitis onset to shunting procedure ($p$ = 0.025), interval between hospitalization to shunting procedure ($p$ = 0.036), and the CSF protein level ($p$ = 0.04) were significant variables. These variables were then used in the stepwise logistic-regression model analysis. After analysis, only the mean interval between onset to shunting procedure ($p$ = 0.04, odds ratio = 1.05, 95% confidence interval [CI] = 1.0–1.11) remained independently associated with CSF overdrainage. An increase of 1 day in the mean interval between meningitis onset to shunting procedure increased the CSF overdrainage rate by 5.3%. The area under the receiver operating characteristic curve for interval between meningitis onset to shunting procedure was 0.790 (95% CI = 0.581–1.0; $p$ = 0.027), and the cut-off value for predicting CSF overdrainage was 67.5 days (67% sensitivity and 93% specificity).

## Discussion

Most clinical studies on overdrainage were performed in pediatric populations with and in those without shunt infection.[15–18] To our knowledge, this is the first study to assess the risk factors and outcomes of overdrainage in adult patients with cryptococcal meningitis after a VP shunt procedure. This study demonstrated that overshunting occurred in 12% (6/51) of HIV-negative patients with cryptococcal meningitis who received the VP shunt procedure to relieve hydrocephalus and/or IICP.

The pathogenesis of CSF overdrainage in HIV-negative patients with cryptococcal meningitis after the VP shunting procedure seems complex and multifactorial.[8–13] The prevailing hypothesis regarding the pathophysiology of this phenomenon is that siphoning is spurred by postural alterations of the patients,[8–13] especially when those patients had a prolonged duration of hydrocephalus and/or IICP.

In the present study, we examined the risk factors of CSF overdrainage in HIV-negative patients with cryptococcal meningitis after the shunt procedure and found that a higher mean interval between meningitis onset to shunting procedure remained independently associated with CSF overdrainage. An increase of 1 day in the mean duration between completion of the shunting procedure and the onset of symptoms increased the CSF overdrainage rate by 5.3%, and the cut-off value for predicting overshunting was 67.5 days.

IICP and hydrocephalus are common complications occurring in both HIV-negative and HIV-positive patients[19–21]; they are also the major causes of morbidity and mortality in patients with cryptococcal meningitis.[19–21] Fungal polysaccharides can aggregate and accumulate in arachnoid villi and subarachnoid spaces, causing blockage of channels for CSF drainage, impaired absorption owing to high protein levels, and obstruction of mechanical CSF outflow, all of which are implicated in the development of IICP with communicating hydrocephalus in patients with cryptococcal meningitis.[21–24]

Several neurological manifestations associated with the development of hydrocephalus and/or IICP include headaches, papilledema, visual and hearing impairment, changes in mental state, and cerebral infarctions.[1,25,26] Therapeutic regimens for hydrocephalus and/or IICP involve a diversion of ventricular CSF through a VP shunt or external ventricular drainage.[20,21] Although most experts recommend early shunt surgery for hydrocephalus and/or IICP to prevent irreversible neurological complications,[27] the diversion of CSF through a VP shunt does not result in any significant improvement in several patients.[22]

Although our study demonstrated that a higher mean duration between completion of the shunt procedure and meningitis onset indicated a high risk for overdrainage in patients, this study has several limitations. First, this is a retrospective study; therefore, it is subject to bias of unmeasured factors. Usually, a diagnosis of chronic meningitis precedes hydrocephalus by weeks or months, and the clinical course may be indolent. Therefore, the duration between diagnosis of cryptococcal meningitis and the development of hydrocephalus cannot be precisely evaluated in patients. Second, not all patients underwent neuroimaging (e.g. MRI or CT) that followed a standard protocol before and after the shunt procedure. Therefore, the findings may underestimate the true frequency of CSF overdrainage in this study. Third, the symptoms of CSF overdrainage may be indolent or may spontaneously resolve after conservative treatment, which can also result in underestimation of the true frequency of CSF overdrainage in this study.

In summary, early shunt surgery is mandatory for the treatment of cryptococcal meningitis complicated by hydrocephalus and/or IICP to avoid irreversible neurological complications. Our study demonstrated that post-shunt CSF overdrainage is common among patients with cryptococcal meningitis who additionally have a prolonged duration of hydrocephalus and/or IICP. Emergency neuroimaging studies should be undertaken for early detection of CSF overdrainage if neurological conditions rapidly deteriorate after shunting procedures.

## Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

## Ethical approval

The study was approved by Chang Gung Memorial Ss Institutional Review Committee on Human Research (97-0467B).

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