Surgical treatment and operation time in human immunodeficiency virus-negative cryptococcal meningitis

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Abstract
There are still no unified guidelines of surgical treatment and timing for human immunodeficiency virus (HIV)-negative patients with cryptococcal meningitis (CM).

The clinical data and follow-up data were collected from HIV-negative CM patients in Xiangya Hospital of Central South University from January 2009 to November 2018, and 42 patients who were treated with surgical intervention were enrolled in the present study. These 42 patients were divided into ventriculostomial (VA) group, ventriculoperitoneal group, external venticle drainage (EVD) group, hydrocephalus (HYC) group, non-HYC group, EVD group, and non-EVD group (VA/ventriculoperitoneal) according to different surgical procedures. Statistical analyses were conducted using SPSS (version 19.0, Chicago, IL).

Signs of headache, fever, and loss of consciousness in the VA group were significantly improved compared with the EVD group at 1 week after operation ($P < .05$). The mortality rate of the VA group was significantly lower than that of the EVD group ($P < .05$). Moreover, male patients were more prone to have HYC ($P < .05$). Younger patients tended to develop HYC ($P < .05$). Cerebrospinal fluid sugar in the non-HYC group was significantly lower compared with the HYC group ($P < .05$). Time of CM-to-operation in the non-HYC group was markedly shorter compared with the HYC group ($P < .01$).

VA procedure could be one of the first choices for the treatment of uncontrollable intracranial hypertension caused by CM. Severe uncontrollable headache, loss of consciousness, and cerebral hernia were indications of emergency surgery. Repeated headache, hearing impairment, and especially progressive loss of vision were indications of early surgery to avoid permanent damage to nerve functions of HIV-negative CM patients.

Abbreviations: CM = cryptococcal meningitis, CSF = cerebrospinal fluid, CT = computed tomography, EVD = external venticle drainage, HIV = human immunodeficiency virus, HYC = hydrocephalus, ICH = intracerebral hypertension, LP = lumbar puncture, LPS = lumbar peritoneal shunt, MRI = magnetic resonance imaging, VA shunt = ventriculostomial shunt, VP shunt = ventriculoperitoneal shunt.

Keywords: cryptococcal meningitis, hydrocephalus, intracranial hypertension, shunt

1. Introduction
As a known opportunistic pathogen, Cryptococcus neoformans is frequently detected in patients with human immunodeficiency virus (HIV) infection or other immunodeficiency diseases. [1,2] Cryptococcal meningitis (CM) can lead to higher rates of mortality and disability if not treated in a timely manner. [3] A recent study has documented that the CD4 expression is correlated with the prognosis of CM patients. [4] HIV is the most important risk factor for CM patients. [5-7] However, infection of Cryptococcus has also been reported in an HIV-negative CM patient recently. [8] It is now certain that uncontrollable intracranial hypertension and hydrocephalus...
(HYC) are the 2 major complications affecting the prognosis of CM patients. The pathogenesis of HYC and uncontrollable intracranial hypertension remains largely unexplored in CM patients. Some reports have proposed the possible pathways as follows:

1. Surface polysaccharides of Cryptococcus block cerebrospinal fluid (CSF) circulation pathway, or
2. Inflammation blocks the CSF circulation pathway.

Early diagnosis and timely treatment can effectively improve the prognosis of CM patients, such as visual and hearing impairment, severe headache, loss of consciousness, and even death. As a surgical intervention, ventriculoperitoneal (VP) operation can effectively relieve the intracerebral hypertension (ICH) in CM patients. However, VP surgery has its unique procedure-related complications, such as CSF overdrainage, shunt infection, or shunt malfunction. If there is a VP procedure-related complication in a CM patient with ICH and HYC, or due to individual reasons, including prior abdominal surgery, other operational procedures should be premeditated. Ventriculoatrial (VA) operation can be used as an alternative at this time. However, very few investigations have documented VA shunt in HIV-negative CM patients. In the treatment of CM, only few reports have studied the criteria, timing, and curative effect of VA operation. In the present study, we recorded clinical symptoms, CSF opening pressure and test results, choice of surgical methods, and imaging findings of 42 HIV-negative CM patients before and after operation, and a comprehensive statistical analysis was conducted. We aimed to assess the effects of different surgical treatment and operation time on HIV-negative CM patients.

2. Methods

2.1. Clinical data collection

Patients in the Xiangya Hospital of Central South University, Changsha, China, were enrolled in this retrospective study from January 2009 to November 2018. The clinical data of 212 HIV-negative CM patients were reviewed, while 170 cases without HYC in HIV-negative CM patients. In the present study, all participants displayed some symptoms of neurological deficit before operation, such as headache, nausea, visual and hearing impairment, and loss of consciousness, among which fever, visual impairment, and loss of consciousness were the most frequently observed clinical symptoms (Table 1). At 1 week after operation, most of the symptoms disappeared, the symptoms of headache, fever, and loss of consciousness were significantly alleviated compared with the EVD group (P < .05). In our observation period, we made phone follow-up and tracked the CT or MRI after the patients were discharged from hospital for at least 4 months. The signs of headache, fever, vomiting, and loss of conscious were markedly improved in the VA group compared with the EVD group (P < .05). VA shunt could significantly alleviate symptoms caused by uncontrollable intracranial hypertension. Moreover, the mortality rate of the VA group was markedly lower than that of the EVD group (P < .05). Regrettably, 10 patients died due to different reasons after operation, such as irreversible visual impairment, respiratory and circulatory failure, loss of consciousness, and inability to afford the high cost of treatment.

2.2. Patients’ definitions

The inclusion criteria for CM patients included comprehensive evaluation of clinical symptoms, laboratory tests (including CSF stress, biochemical routine culture results, and CSF ink staining results), and imaging examinations. CT or MRI was used for the diagnosis of HYC, which was made based on enlargement of the temporal horn of the lateral ventricle if no obvious brain atrophy was observed during the entire therapeutic time window. The demographic data, risk factors, clinical symptoms before and after surgery, CSF characteristics, CT/MR findings, antifungal therapy, and outcomes are listed.

2.3. Laboratory measurement

Repetitive lumbar puncture (LP) was performed in all patients, and CSF opening pressure, differential counts, glucose, protein, chloride, India ink smear, and CSF culture were recorded. The CSF sample was subjected to India ink test.

2.4. Therapeutic methods

All therapeutic methods were performed by SPSS (version 19.0, Chicago, IL). Data were represented as the mean ± standard deviation or median, and categorical variables were expressed as a percentage. P < .05 was considered statistically significant. Variables of normal distribution were analyzed using Student t test, while categorical variables were assessed by Chi-square or Fisher exact test.

3. Results

3.1. Clinical characteristics of all patients

A total of 42 HIV-negative CM patients who underwent the VA or VP shunt or EVD or LPS procedure, were enrolled in this study. Twenty-four VA shunts, 4 VP shunts, 13 EVD, and 1 LPS procedure were performed, including 10 cases with HYC and 32 cases without HYC. All patients received non-programmable shunts, the valves were set to the highest pressure, and the follow-up adjustment of shunt pressure was made according to patient’s symptoms.

3.2. Surgery groups

3.2.1. Clinical characteristics. In the present study, all participants displayed some symptoms of neurological deficit before operation, such as headache, nausea, visual and hearing impairment, and loss of consciousness, among which fever, visual impairment, and loss of consciousness were the most frequently observed clinical symptoms (Table 1). At 1 week after operation, most of the symptoms disappeared, the symptoms of headache, fever, and loss of consciousness were significantly alleviated compared with the EVD group (P < .05). In our observation period, we made phone follow-up and tracked the CT or MRI after the patients were discharged from hospital for at least 4 months. The signs of headache, fever, vomiting, and loss of conscious were markedly improved in the VA group compared with the EVD group (P < .05). VA shunt could significantly alleviate symptoms caused by uncontrollable intracranial hypertension. Moreover, the mortality rate of the VA group was markedly lower than that of the EVD group (P < .05).

3.2.2. Prognostic factors. In our study, all patients were precluded from our current work. Finally, forty-two patients who met the diagnostic criteria were enrolled in our study. Figure 1 presents the details of the enrollment process.

Brain computed tomography (CT) and/or magnetic resonance imaging (MRI) were conducted before and after surgery. The typical brain images of patients with or without HYC are shown in Figure 2. All images were examined by experienced neuroradiologists.

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3.2.2. CSF features. We found VA shunt could significantly decrease ICH ($P < .05$) (Table 2), we did not find significant differences in preoperative and postoperative data of CSF, which could possibly be attributed to the small sample size of enrolled patients in the group.

3.3. HYC group and non-HYC group

3.3.1. Clinical characteristics. Male patients were more prone to have HYC ($P < .05$). Younger patients tended to develop HYC compared with elders ($P < .05$). In addition, no significant difference in clinical symptoms was detected between the HYC group and non-HYC group preoperatively and postoperatively (Table 3).

3.3.2. CSF features. Before the operation, there was no statistical difference in LP's CSF assay between the HYC group and non-HYC group ($P > .05$). At 1-week post-surgery, the non-HYC group exhibited significantly lower CSF sugar level.
Table 1

Clinical characteristics in patients with VA, VP or EVD surgery.

| Characteristic                  | VA (n = 24) | VP (n = 4) | EVD (n = 13) | P1   | P2   | P3   |
|--------------------------------|-------------|------------|--------------|------|------|------|
| Symptoms pre-operation         |             |            |              |      |      |      |
| Sex (M/F)                      | 14/10       | 3/1        | 6/7          | 1.000| .372 | .576 |
| Age [median (range)]           | 39.63 (9-71)| 30.75 (21-46)| 40.08 (21-58)| .171| .467 | .063 |
| Headache                       | 22/24 (91.67%) | 4/4 (100%) | 12/13 (92.31%) | 1.000| 1.000| 1.000 |
| Fever                          | 6/24 (25%)  | 2/4 (50%)  | 8/13 (61.54%) | .555| .039 | 1.000 |
| Vomiting                       | 10/24 (41.67%) | 2/4 (50%)  | 6/13 (46.15%) | 1.000| 1.000| 1.000 |
| Visual loss                    | 10/24 (41.67%) | 2/4 (50%)  | 3/13 (23.08%) | 1.000| .035 | .538 |
| Hearing loss                   | 2/24 (8.33%) | 1/4 (25%)  | 1/13 (7.69%)  | .382| .532 | .235 |
| Loss of conscious              | 7/24 (29.17%) | 0/4        | 3/13 (23.08%) | .545| 1.000| .541 |
| Limbs fatigue                  | 2/24 (8.33%) | 0/4        | 1/13 (7.69%)  | 1.000| .351 | 1.000 |
| Stagger                        | 4/24 (16.67%) | 0/4        | 1/13 (7.69%)  | 1.000| .634 | 1.000 |
| Gaston                         | 0/24        | 0/4        | 0/13         | 1.000| 1.000| 1.000 |
| Psychosis                      | 1/24 (4.17%) | 0/4        | 0/13         | 1.000| 1.000| 1.000 |
| Symptoms improved 1 wk after operation |             |            |              |      |      |      |
| Headache                       | 22/22 (100%) | 3/4 (75%)  | 7/12 (58.33%) | .154| .003 | 1.000 |
| Fever                          | 6/6 (100%)  | 1/2 (50%)  | 3/6 (50%)    | .250| .031 | 1.000 |
| Vomiting                       | 10/10 (100%) | 2/2 (100%) | 5/6 (83.33%) | .375| 1.000| 1.000 |
| Visual loss                    | 8/10 (80%)  | 1/2 (50%)  | 3/3 (100%)   | .455| 1.000| .400 |
| Hearing loss                   | 1/2 (50%)   | 1/1 (100%) | 0/0          | 1.000| /    | /    |
| Loss of conscious              | 7/7 (100%)  | 0/0        | 0/0          | 1.000| /    | /    |
| Stagger                        | 4/4 (100%)  | 0/0        | 0/0          | 1.000| /    | /    |
| Symptoms improved patients discharged from hospital 4 mo at least. |        |            |              |      |      |      |
| Headache                       | 20/22 (90.91%) | 3/4 (75%)  | 5/12 (41.67%) | .408| .004 | .569 |
| Fever                          | 6/6 (100%)  | 1/2 (50%)  | 3/8 (37.50%) | 1.000| .031 | 1.000 |
| Vomiting                       | 9/10 (90%)  | 1/2 (50%)  | 2/6 (33.33%) | .318| .038 | 1.000 |
| Visual loss                    | 7/10 (70%)  | 1/2 (50%)  | 3/3 (100%)   | 1.000| .528 | .400 |
| Loss of conscious              | 6/7 (85.71%) | 0/0        | 0/3          | 1.000| /    | /    |
| Stagger                        | 3/4 (75%)   | 0/0        | 0/1          | 1.000| /    | /    |

P1: VA subgroup with VP subgroup.
P2: VA subgroup with EVD subgroup.
P3: VP subgroup with EVD subgroup.
VA = ventriculoatrial, VP = ventriculoperitoneal, EVD = external ventricle drainage.

Figure 2. Head CT or MR of 2 patients. (A and B) Head CT of a HYC patient before and after operation. (C and D) Head MR of a non-HYC patient before and after operation. CT = computed tomography, HYC = hydrocephalus, MRI = magnetic resonance imaging.
compared with the HYC group ($P < .05$). However, there were no statistical difference in the levels of CSF opening pressure, India ink smear, leukocyte count, protein, and chloride between the 2 groups ($P > .05$) (Table 4).

### 3.4. Operation time and reasons

The time of CM-to-operation in the HYC group was markedly longer compared with the non-HYC group ($P < .01$), and there were no statistical differences in the time of HYC-to-operation and the time of ICH-to-operation ($P > .05$), while both median numbers of the non-HYC group were shorter than those of the HYC group. Emergency ratio of the non-HYC group (19/32, 59.38%) was lower than that of in the HYC group (9/10, 90%), although no statistical difference was found (Table 5).

Retrospective analysis found that the main reasons of emergency surgery included severe headache, impaired consciousness, and the onset of cerebral hernia. Besides, although no emergency surgery was required for uncontrollable headache, progressive loss of hearing and vision, early surgery should be performed to rescue the neurological deficit of the patients (Table 6).

### Table 3

| Clinical characteristics in HYC or non-HYC patients. | HYC (n=10) | Non-HYC (n=32) | $P$ |
|-----------------------------------------------------|------------|----------------|-----|
| Symptoms pre-operation                              |            |                |     |
| Sex (M/F)                                           | 7/3        | 16/16          | .046|
| Age (Y) median (range)                              | 30.5 (9–46) | 40.48 (5.3–71) | .042|
| Headache                                           | 10/10 (100%) | 29/32 (90.63%) | 1.000|
| Fever                                              | 4/10 (40%) | 13/32 (40.63%) | 1.000|
| Vomiting                                           | 3/10 (30%) | 15/32 (46.88%) | .473|
| Visual loss                                         | 5/10 (50%) | 11/32 (34.38%) | .465|
| Hearing loss                                        | 1/10 (10%) | 2/32 (6.25%)   | 1.000|
| Loss of conscious                                   | 2/10 (20%) | 9/32 (28.13%)  | 1.000|
| Limbs fatigue                                       | 1/10 (10%) | 1/32 (3.13%)   | .424|
| Slagger                                             | 0/10       | 5/32 (15.63%)  | .315|
| Gait                                                | 0/10       | 1/32 (3.13%)   | 1.000|
| Posis                                               | 0/10       | 1/32 (3.13%)   | 1.000|
| Psychosis                                           | 1/10 (10%) | 0/32           | .238|
| Symptoms improved 1 wk after operation              |            |                |     |
| headache                                           | 9/1 (90%)  | 22/29 (75.86%) | .653|
| Fever                                              | 3/4 (75%)  | 8/13 (61.54%)  | 1.000|
| Vomiting                                           | 2/3 (66.67%) | 12/15 (80%)   | 1.000|
| Visual loss                                         | 4/5 (80%)  | 9/11 (81.82%)  | 1.000|
| Hearing loss                                        | 0/1        | 2/2 (100%)     | .333|
| Loss of conscious                                   | 2/2 (100%) | 6/9 (66.67%)   | 1.000|
| Headache                                           | 7/10 (70%) | 25/29 (86.21%) | .344|
| Symptoms improved 4 mo at least discharged from hospital |         |                |     |
| Fever                                              | 3/4 (75%)  | 8/13 (61.54%)  | 1.000|
| Vomiting                                           | 1/3 (33.33%) | 14/15 (93.33%) | .056|
| Visual loss                                         | 3/5 (60%)  | 9/11 (81.82%)  | .547|
| Hearing loss                                        | 1/1 (100%) | 1/2 (50%)      | 1.000|
| Loss of conscious                                   | 1/2 (50%)  | 5/9 (55.56%)   | 1.000|

CSF = cerebrospinal fluid, P = HYC subgroup versus Non-HYC subgroup, VA = ventriculoatrial, VP = ventriculoperitoneal, EVD = external ventricle drainage.
3.5. Typical case

Case 17 was a 48-year-old man. He presented headache, nausea, visual impairment and staggering when he came to hospital. After he was diagnosed as CM, he was administered with antifungal agents, amphotericin B, and 5-fluorocytosine. Due to persistent headache, he was given VA shunt, after which most symptoms, except for vision loss, were relieved. The visual acuity of both eyes after operation was only light sense. When he returned home, he fell to death because of irreversible visual impairment.

4. Discussion

Cryptococcosis caused by the encapsulated yeasts, Cryptococcus neoformans, and C. gattii, is acquired from the environment, which is one of the most common opportunistic infections and reasons of morbidity and mortality in HIV-infected or immunosuppressed patients, especially in resource-limited settings, such as sub-Saharan Africa and other developing countries.[12,16,17] In recent years, CM has also been reported in a small number of patients without immunodeficiency disease.[18–23] Therefore, it is essential to further study the clinical characteristics and effective treatment, especially for intracranial hypertension, to reduce the morbidity and mortality rates of CM patients. In the present study, non-HIV CM patients were divided different surgery group, HYC, and non-HYC group. The clinical symptoms, CSF characteristics before and after operation, surgical procedures, operation time of each group were analyzed.

We found that the most common clinical symptoms included headache, nausea, fever, visual impairment, and loss of conscious caused by uncontrollable intracranial hypertension (P < .05). Nevertheless, there was no significant difference in postoperative symptoms between the VA group and VP group (P > .05). The efficacy of VP shunt in the treatment of intracranial hypertension in HIV-positive and HIV-negative CM patients has been widely recognized by neurosurgeons and neurophysicians worldwide.[20,21,24,25] We did not find significant differences in pre-operative and post-operative data between the VP group and EVD group, which could possibly be attributed to the small sample size of enrolled patients in the VP group.

The India ink test, microscopy, and culture methods are widely used for diagnosis of cryptococcal infection in many laboratories in Asian countries.[26–27] With the development of medical test methods, the positive rate of cryptococcal infection in our group was above 96.87%. Except that a few patients received antifungal therapy before positive results were available, most of the cases received standardized antifungal therapy after diagnosis of CM with amphotericin B + 5-fluorocytosine + Fluc. Most patients underwent shunt operation during antifungal therapy. VP shunt is a classical surgery for HYC.[28] In recent years, VA operation is more and more used as an approach to treat HYC and intracranial hypertension. Compared with the VP shunt, VA operation can dramatically diminish complications, such as obstruction of the abdominal end of shunt tube, abdominal infection, ascites formation, and so on. VA shunts have specific complications, such as postoperative neck hematomas, revision in lower end of the tube for growing children, shunt nephritis, and migration of the distal segment.[29] No above-mentioned complications were found in all the patients who underwent VA shunt after operation. In our study, we think it is easier to control Cryptococcus with high concentration of blood drug and avoid the infection of VP in abdominal cavity. Besides, the distance of VA shunt is shorter than that of VP shunt, which

### Table 4

**CSF characteristics in HYC or non-HYC patients.**

| Characteristic | HYC (n=10) | Non-HYC (n=32) | P |
|---------------|------------|---------------|---|
| CSF pre-operation | Indian ink smear (+) | 10/10 (100%) | 31/32 (96.88%) | 1.000 |
| | CSF pressure (mmH2O) median (range) | 333.18 (165–500) | 390 (180–600) | .17 |
| | WBC count (>106/L) median (range) | 80.40 (0–240) | 114.79 (2–640) | .30 |
| | Protein, g/L median (range) | 1.64 (0.19–3.21) | 1.07 (0.26–1.57) | .23 |
| | Glucose (mmol/L) median (range) | 1.32 (0.24–4.20) | 2.53 (0.81–7.5) | .08 |
| | Chloride (mmol/L) median (range) | 121.14 (110–137.2) | 119.23 (112–128) | .26 |
| CSF 1 wk after operation | Indian ink smear (+) | 2/10 (20%) | 9/32 (28.13%) | 1.000 |
| | CSF pressure (mmH2O) median (range) | 163 (40–350) | 211.67 (30–500) | .183 |
| | WBC count (>106/L) median (range) | 24.20 (0–900) | 80 (0–640) | .118 |
| | Protein, g/L median (range) | 2.11 (0.3–1.47) | 2.77 (3.33–3.21) | .105 |
| | Glucose (mmol/L) median (range) | 1.33 (0.9–2.8) | 0.98 (0.57–1.39) | .015 |
| | Chloride (mmol/L) median (range) | 109.81 (108–132.3) | 117 (113–121) | .372 |

CSF = cerebrospinal fluid, P = HYC subgroup versus Non-HYC subgroup.

### Table 5

**Surgery time in HYC or non-HYC patients.**

| | HYC (n=10) | Non-HYC (n=32) | P |
|---------------|------------|---------------|---|
| Time CM to operation (d) | 63.45 (1–289) | 21.73 (1–170) | .099 |
| Time HYC to operation (d) | 29.14 (1–102) | 0 | / |
| Time ICH to operation (d) | 28.27 (1–96) | 25.65 (1–145) | .368 |
| Emergency operation | 9/10 (90%) | 19/32 (59.36%) | .125 |

CM = cryptococcal meningitis, ICH = intracerebral hypertension, P = HYC subgroup versus Non-HYC subgroup.
may reduce the occurrence of fissured ventricular syndrome in ICP patients. Comparison of the VA group and VP group revealed that there were no significant differences in postoperative complications, clinical symptoms, and mortality, while the morbidity and mortality rates of the VA group were remarkably lower compared with the EVD group ($P < .05$) (Table 1). For patients with rapid increase of intracranial pressure in a short period of time, the symptoms worsen rapidly. The effect of shunt operation is more lasting, stable, effective, and safe than that of LP and EVD. The mortality of EVD patients is higher than that of shunt group ($P < .05$, Table 1), so we think VA/VP is more conducive to improve the prognosis of such critical patients. Therefore, our findings suggested that VA procedure was one of the first choices for the treatment of uncontrollable intracranial hypertension caused by CM. But more case studies are still needed to further verify.

In our current investigation, our data indicated that male patients were more prone to have HYC ($P < .05$), and younger patients tended to develop HYC compared with older patients ($P < .05$) (Table 3) This result is different from Liu’s study. Our case number is small, and there may be bias. We need further large samples to verify the correlation between gender, age, and HYC. More importantly, the time of CM-to-operation in the non-HYC group was shorter compared with the HYC group ($P < .01$) (Table 5), indicating that non-HYC HIV-negative CM patients tended to have shorter duration and

### Table 6

| Age/sex | Intracranial pressure first lumbar puncture (mmHg) | Surgery methods | HYC | Emergency operation reason | Not-emergency operation reason |
|---------|-----------------------------------------------|-----------------|-----|-----------------------------|--------------------------------|
| 1       | 32/M                                          | VA Yes 320      |     | Severe headache             |                                |
| 2       | 23/M                                          | VA / No 400     |     | Uncontrollable headache     |                                |
| 3       | 11/M                                          | VA Yes 270      |     | Severe headache             |                                |
| 4       | 51/M                                          | VA / No 500     |     | Uncontrollable headache     |                                |
| 5       | 43/F                                          | VA Yes 370      |     | Loss of consciousness       |                                |
| 6       | 46/M                                          | VA / No 500     |     | Loss of consciousness       |                                |
| 7       | 9/F                                           | VA / No 250     |     | Progressive decline of vision |                                |
| 8       | 32/M                                          | VA / No 360     |     | Progressive loss of vision and hearing |                                |
| 9       | 71/F                                          | VA / No 250     |     | Loss of consciousness       |                                |
| 10      | 46/F                                          | VA / No 500     |     | Uncontrollable headache     |                                |
| 11      | 50/M                                          | EVD + VA / No 500 |     | Progressive decline of vision |                                |
| 12      | 47/M                                          | VA / No 350     |     | Uncontrollable headache     |                                |
| 13      | 40/M                                          | VA / No 500     |     | Progressive decline of vision |                                |
| 14      | 64/F                                          | EVD + VA / No 500 |     | Loss of consciousness       |                                |
| 15      | 22/F                                          | EVD + VA / No 400 |     | Progressive decline of vision |                                |
| 16      | 40/M                                          | VA Yes 165      |     | Loss of consciousness       |                                |
| 17      | 48/M                                          | VA / No 300     |     | Uncontrollable headache     |                                |
| 18      | 10/F                                          | VA / No 350     |     | Uncontrollable headache     |                                |
| 19      | 9/M                                           | EVD + VP + VA / No 480 |     | Uncontrollable headache     |                                |
| 20      | 47/M                                          | VA / No 350     |     | Uncontrollable headache     |                                |
| 21      | 42/F                                          | VA / No 300     |     | Uncontrollable headache     |                                |
| 22      | 52/M                                          | VA / No 300     |     | Uncontrollable headache     |                                |
| 23      | 37/m                                          | EVD / No 360    |     | Severe headache             |                                |
| 24      | 37/f                                          | EVD / No 400    |     | Loss of consciousness       |                                |
| 25      | 5.3/M                                         | LPS / No 580    |     | Loss of consciousness       |                                |
| 26      | 42/f                                          | EVD / No 600    |     | Hernia cerebi               |                                |
| 27      | 48/m                                          | EVD Yes / No 360 |     | Severe headache             |                                |
| 28      | 28/m                                          | EVD Yes / severe headache | No | SEVERE headache             |                                |
| 29      | 27/f                                          | EVD + VP Yes / No 400 |     | Severe headache             |                                |
| 30      | 21/f                                          | EVD / No 400    |     | Severe headache             |                                |
| 31      | 49/f                                          | EVD / No 400    |     | Severe headache             |                                |
| 32      | 42/m                                          | EVD / No 240    |     | Severe headache             |                                |
| 33      | 54/f                                          | EVD / No 180    |     | Loss of consciousness       |                                |
| 34      | 58/m                                          | EVD / No 500    |     | Severe headache             |                                |
| 35      | 50/f                                          | EVD / No 400    |     | Loss of consciousness       |                                |
| 36      | 22/f                                          | EVD / No 300    |     | Severe headache             |                                |
| 37      | 46/f                                          | EVD + VA / No 400 |     | Severe headache             |                                |
| 38      | 43/m                                          | EVD / No 500    |     | Loss of consciousness       |                                |
| 39      | 64/f                                          | VA / No 500     |     | Loss of consciousness       |                                |
| 40      | 29/m                                          | VP / No 500     |     | Severe headache             |                                |
| 41      | 21/m                                          | VP Yes / No 500 |     | Severe headache             |                                |
| 42      | 46/m                                          | VP Yes / No 400 |     | Severe headache             |                                |

HYC = hydrocephalus, VA = ventriculoatrial, EVD = external ventricle drainage.
earlier surgery, which was consistent with Liu’s study.[13] Besides, in our research, there was no difficulty in puncture of ventricles in all non-HYC patients, and there was no fissured ventricular syndrome in these patients. Before further statistical analysis, we assumed that HYC was one of the emergency surgical indications for CM patients with intracranial hypertension. Final results revealed that the emergency ratio in the HYC group (9/10, 90%) was higher than that in non-HYC group (19/32, 59.38%), although there was no statistical significance (Table 5). The results indicated that HYC was not a predictor of rapid deterioration of CM. Moreover, the postoperative morbidity and mortality rates were not significantly different between the HYC group and non-HYC group ($P > .05$) (Table 3), suggesting that HYC was not associated with the prognosis of CM patients. The content of glucose in CSF of the HYC group was dramatically higher compared with the non-HYC group ($P < .05$) (Table 4), which was consistent with Xu’s study.[18]

We found that severe uncontrollable headache, loss of consciousness, and the onset of cerebral hernia were the main reasons of emergency surgery. Besides, although no emergency surgery was required for uncontrollable headache, progressive loss of vision and hearing impairment, early surgery should be performed to rescue the neurological deficit of the patients (Table 6). At present, there is no unified guide to determine the specific operation timing of CM patients. In this study, we reviewed the efficacy of different operation modes and preliminarily explored the selection of operation timing. Besides, the heterogeneity of patients, such as different age and underlying diseases, may indeed lead to different immune responses and outcomes. This needs further study.

It could be an avoidable tragedy that case 17 fell to death because of permanent visual loss. Therefore, we suggested that severe uncontrollable headache, loss of consciousness, and cerebral hernia were indications of emergency surgery. Repeated headache, loss of hearing, and especially progressive visual impairment were indications of early surgery to avoid permanent damage to nerve functions.

5. Conclusions

In the present study, we found that VA procedure could be one of the first choices for the treatment of uncontrollable intracranial hypertension caused by CM. HYC was not associated with the prognosis of HIV-negative CM patients. HIV-negative non-HYC CM patients tended to have shorter duration, earlier surgery. CSF glucose might be related to higher mortality in HIV-negative CM patients, and low CSF glucose was an indication for early surgery. We suggested that severe uncontrollable headache, loss of consciousness and cerebral hernia were indications of emergency surgery. Repeated headache, loss of hearing, and especially progressive visual impairment were indications of early surgery to avoid permanent damage to nerve functions in HIV-negative CM patients.

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Author contributions

Jie Zhao were responsible for the data integrity and the accuracy of the data analysis. Xiang Zhao analyzed the data. Jie Zhao, Ying Liu, and Xiang Zhao prepared the manuscript. Jie Zhao and Ying Liu revised the manuscript and the whole paper, including the figures and legends. All authors read and approved the final manuscript.

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