Ventriculoperitoneal shunt is associated with increased cerebrospinal fluid protein level in HIV-infected cryptococcal meningitis patients

Ran Tao1,2†, Lijun Xu1,2†, Yongzheng Guo1,2, Xiaoke Xu1,2, Jiesheng Zheng3 and Biao Zhu1,2*†

Abstract

Background: The impact of ventriculoperitoneal shunt on cerebrospinal fluid (CSF) biochemical profiles in HIV-associated cryptococcal meningitis (HCM) patients remains unclear.

Methods: Twenty-nine HCM patients who underwent ventriculoperitoneal shunt (the VPS group) and 57 HCM patients who did not undergo ventriculoperitoneal shunt (the non-VPS group) were enrolled in this propensity score matching analysis. Demographic characteristics, symptoms, CSF biochemical profiles, and adverse events were compared between the two groups. The Kaplan–Meier method was used to analyze the survival rate. Univariate and multivariate logistic regression analyses were performed to identify the risk factors for increased CSF protein levels.

Results: After 24 weeks of treatment, the intracranial pressure was significantly lower in the VPS group than in the non-VPS group (mmH2O; 155.0 [120.0–190.0] vs. 200.0 [142.5–290.0]; P = 0.025), and the rate of neuroimaging improvement was significantly higher in the VPS group (16/17 [94.1%] vs. 2/10 [20%]; P < 0.001). Furthermore, the 24-week cumulative survival rates were also significantly higher in the VPS group (96.6% vs. 83.5%, P = 0.025). Notably, the CSF protein levels were higher in the VPS group than in the non-VPS group at each examination time, and the CSF glucose was lower in the VPS group than in the non-VPS group even at the 12-week follow-up. In the multivariate analysis, we found that VPS placement was an independent risk factor for increased CSF protein (odds ratio [OR]: 27.8, 95% confidence interval [95% CI] 2.2–348.7; P = 0.010).

Conclusions: VPS decreased the intracranial pressure, improved neuroimaging radiology and reduced the 24-week mortality in HCM patients. However, VPS significantly altered the CSF profiles, which could lead to misdiagnosis of tuberculous meningitis and some of them were diagnosed with immune reconstitution inflammatory syndrome. Physicians should be aware of these changes in the CSF profiles of patients with HCM undergoing VPS.

Keywords: Ventriculoperitoneal shunt, Human immunodeficiency virus, Cryptococcal meningitis, Survival, Cerebrospinal fluid

Background

HIV-infected patients are susceptible to Cryptococcus, and cryptococcal meningitis is a life-threatening central nervous system infectious disease caused by Cryptococcus. Importantly, high intracranial pressure (HICP) can occur in approximately 50% of patients, leading to increased mortality in patients with HCM.
Thus, HICP control is a critical determinant of HCM patient mortality [5].

Daily lumbar puncture and the placement of ventriculoperitoneal shunts (VPSs) are important management strategies for HICP patients. However, the placement of VPSs in HIV-infected patients is debatable. Some studies have indicated that VPS placement in immunosuppressed patients may lead to shunt infection, blockage of the shunt device owing to the high fungal load, and peritoneal Cryptococcus seeding by draining Cryptococcus into the abdominal cavity [6–8]. Meanwhile, other studies have demonstrated that VPS placement can rapidly relieve symptoms and improve the prognosis of HICP patients with rare postoperative infections. In addition, VPS placement could decrease the excess volume of cerebrospinal fluid (CSF) and the fungal polysaccharide load in the ventricles [9–12]. VPS is more reliable and stable than lumbar puncture and can maintain long-term shunt effects [6].

To further study the safety and efficacy of VPS placement in HCM patients and evaluate the effects of VPS placement on the CSF biochemical profiles of HCM patients, we conducted this study. In this study, we compared the demographic characteristics, symptoms, and CSF chemical profiles between HCM patients who underwent VPS placement and HCM patients who did not undergo VPS placement.

**Methods**

**Study cohort and patient enrollment**

Between January 2011 and December 2019, 151 HCM patients from the First Affiliated Hospital of Zhejiang University were eligible for this retrospective cohort study. Of these patients, 36 (23.8%) underwent VPS placement (the VPS group), and 115 (76.2%) did not undergo VPS placement (the non-VPS group). Propensity score matching for age, sex, body mass index (BMI), positive India ink staining of the CSF, positive Cryptococcus cultures, initial CSF profiles (intracranial pressure [ICP], CSF glucose levels, CSF protein levels, and CSF white blood cell [WBC] counts), and routine blood test results (C-reactive protein levels, WBC counts, hemoglobin levels, platelet counts, and albumin levels) at admission was used to match the patients at a ratio of 1:2. Thirty-five patients in the VPS group and 62 in the non-VPS group were initially selected for the study. Finally, 29 patients who accepted VPS placement and 57 who did not accept VPS placement were enrolled in this study after 11 repeated cases were excluded. The patient selection process is illustrated in Fig. 1.

**Diagnostic criteria**

Cryptococcal meningitis (CM) was diagnosed if at least one of the following criteria was present in our previous study [13]: (i) a positive CSF culture for Cryptococcus neoformans; (ii) positive India ink staining of cryptococci in centrifuged CSF sediment; (iii) encapsulated yeast cells in brain tissue, as observed using Gomori-methenamine silver and/or periodic acid–Schiff staining; and (iv) a positive CSF sample cryptococcal antigen test.

**Therapeutic approaches**

All patients were treated with antifungal therapy immediately after diagnosis with cryptococcal meningitis. The induction regimens for HCM patients included amphotericin B (AmB) (0.7–1.0 mg/kg/day) plus 5-flurouracil (5FC) (100 mg/kg/day) and fluconazole (1200 mg/day) ± 5FC (100 mg/kg/day) according to previous recommendations [14]. Routine lumbar puncture was performed weekly to monitor CSF profiles and ICP or in response to HICP symptoms (such as headache, vomiting, and dizziness). Mannitol and furosemide were administered to patients with an ICP of 200–300 mmH2O [15], whereas VPS placement was performed in patients with an ICP of ≥300 mmH2O who were willing to undergo operation to control the opening pressure, while daily lumbar puncture was performed in those not willing to undergo operation. Highly active antiretroviral therapy (HAART) was initiated after 4 weeks of antifungal therapy. The patients were followed up for 24 weeks and then discharged.

**Laboratory tests**

Routine blood tests, biochemical tests, and CSF assays (opening pressure, WBC counts, glucose levels, protein
levels, India ink staining, and cultures) were performed upon the first admission and at subsequent follow-up visits. Neuroimaging findings were independently assessed by two experienced neuroradiologists in a blinded manner.

**Follow-up and data collection**

Patient data (BMI, blood test results, imaging examination results, treatments received, and follow-ups) were obtained from the hospital’s electronic medical record system (HEMRS). Week 0 was defined as the time of patient admission, and Week 1 was the first week after VPS placement for the VPS group and the first week of antifungal treatment for the non-VPS group. Patients were followed up for 24 weeks. Data from weeks 0 (W0), 1 (W1), 2 (W2), 4 (W4), 12 (W12), and 24 (W24) were analyzed.

**Statistical analyses**

Continuous normally distributed variables are presented as the means ± standard deviations. Continuous nonnormally distributed variables are presented as the medians (interquartile ranges). Categorical variables are presented as the numbers of cases (percentages). Continuous variables were compared using Student’s t test or the Mann–Whitney U test, whereas categori cal variables were compared using the χ² test or Fisher’s exact test. CSF profile data from W24 and W0 in the VPS and non-VPS groups were compared using a paired t test or Wilcoxon test. Survival was analyzed using the Kaplan–Meier method. Risk factors for increased CSF were analyzed using logistic regression, and a univariate analysis of covariates was performed. Continuous normally distributed variables are presented as the means ± standard deviations. Continuous nonnormally distributed variables are presented as the medians (interquartile ranges). Categorical variables are presented as the numbers of cases (percentages).

**Results**

**Baseline characteristics**

There were 86 patients (including 29 in the VPS group and 57 in the non-VPS group) enrolled in the present study. Of these patients, 78/86 (90.7%) were male, and 8/86 (9.3%) were female. The mean age was 34.5 ± 8.4 years old, and the BMI was 20.5 ± 2.8 kg/m². Positive cryptococcus blood cultures totalled 9/29 (31.0%) in the VPS group and 19/57 (33.3%) in the non-VPS group (P = 0.830). No significant difference in the initial ICP was observed between the VPS and non-VPS groups (mmH2O; 335.0 [252.5–416.3] vs. 300.00 [195.0–400.0]; P = 0.446). The initial CSF protein level and initial CD4 count were similar between the two groups (CSF protein [g/L]: 0.6 [0.4–1.0] vs. 0.6 [0.4–0.9], P = 0.980; CD4 count [/mL]: 11.0 [6.0–24.8] vs. 27.5 [13.0–41.8]; P = 0.386). The most common symptoms were headache (59/86, 68.6%), fever (51/86, 59.3%), vomiting (28/86, 32.6%), and dizziness (13/86, 15.1%). There was no difference in the occurrence of fever (P = 0.578), headache (P = 0.587), vomiting (P = 0.083), or dizziness (P = 0.096) between the two groups (Table 1). However, patients in the VPS group had a significantly higher incidence of seizures than those in the non-VPS group (6/29 [20.7%] vs. 2/57 [3.5%]; P = 0.010). The demographic characteristics and laboratory test results are shown in Table 1.

**Changes in clinical symptoms and CSF profiles after 24 weeks of follow-up**

The most common symptoms included headache (13/73, 17.8%) and fever (6/73, 8.2%) in all patients after 24 weeks of treatment. Patients in both groups reported no dizziness, hearing loss, or loss of consciousness after 24 weeks of treatment. Fever, headache, dizziness, and vomiting improved significantly in both groups after 24 weeks of treatment (Table 2).

In the VPS group, the ICP decreased rapidly 1 week after VPS placement (mmH2O; VPS group: 155.0 [120.0–190.0] mmH2O) was significantly lower than that in the non-VPS group (6/29 [20.7%] vs. 2/57 [3.5%]; P = 0.010). The demographic characteristics and laboratory test results are shown in Table 1.

**Ethics approval**

This study protocol was conducted in accordance with the 1975 Helsinki Declaration and was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (Hangzhou, China) (No. 2017-688). All data analyzed were anonymous. The ethics committee waived the requirement of written informed consent for participation.
The CSF protein was 0.6 (0.4–1.0) g/L at W0, 1.3 (0.9–1.7) g/L at W1, and 1.1 (0.6–1.6) g/L at W24 in the VPS group, whereas the CSF protein was 0.6 (0.4–0.9) g/L at W0, 0.5 (0.4–0.7) g/L at W1, and 0.4 (0.3–0.7) g/L at W24 in the non-VPS group (P = 0.98; P < 0.001; P = 0.002, respectively) (Fig. 2C). At W24, 17/19 (89.5%) patients in the VPS group and 7/16 (43.8%) in the non-VPS group had CSF protein levels ≥ 0.5 g/L (P = 0.004).

There was no significant difference in CSF chlorine, CSF WBC count and CSF cryptococcus count during the 24 week follow up between the two groups (Fig. 2D–F).

Risk factors for increased CSF protein levels ≥ 0.5 g/L at W24 were analyzed. In the unadjusted model, we found that VPS placement (odds ratio [OR]: 10.9, 95% confidence interval [95% CI] [1.9–64.0], P = 0.008), an increase in the CD4 count of >100 cells/mL after 24 weeks (OR: 8.5, 95% CI [0.9–76.9], P = 0.058), a positive CSF culture (OR: 2.9, 95% CI [0.7–11.7], P = 0.127), and an initial CD4 count of > 20 cells/mL (OR: 0.3, 95% CI [0.1–1.4], P = 0.112) were risk factors for increased CSF protein levels. However, in the multivariable model, VPS placement (OR: 27.8, 95% CI [2.2–348.7], P = 0.010) and an increase in the CD4 count of > 100 cells/mL (OR: 21.9, 95% CI [1.2–408.5], P = 0.039) were independent risk factors for increased CSF protein levels (Table 3).

### Complications of VPS placement

Of the 29 patients in the VPS group, one (3.5%) patient died from postoperative infection, nine (31.0%) had

---

**Table 1** Differences in the clinical features of patients with HCM between the VPS and Non-VPS groups

| Factors                        | Non-VPS group (n = 57) | VPS group (n = 29) | P-value |
|-------------------------------|------------------------|--------------------|---------|
| Sex (male), n (%)             | 52 (91.2%)             | 26 (89.7%)         | 0.812   |
| Age (years)                   | 34.3 ± 5.0             | 34.5 ± 9.0         | 0.438   |
| BMI                           | 19.95 ± 2.9            | 20.58 ± 2.9        | 0.309   |
| Interval from symptom onset to the initiation of anticryptococcal therapy (days) | 10.0 (1.5–27.0) | 10.0 (5.5–22.5) | 0.985 |
| Blood cryptococcus culture positivity, n (%) | 19 (33.3%) | 9 (31.0%) | 0.830 |
| Clinical manifestations, n (%) |                        |                    |         |
| Fever                         | 35 (61.4%)             | 16 (55.2%)         | 0.578   |
| Headache                      | 38 (66.7%)             | 21 (72.4%)         | 0.587   |
| Dizziness                     | 6 (10.5%)              | 7 (24.1%)          | 0.096   |
| Seizures                      | 2 (3.5%)               | 6 (20.7%)          | 0.010   |
| Vomiting                      | 15 (26.3%)             | 13 (44.8%)         | 0.083   |
| Vision loss                   | 3 (5.3%)               | 2 (6.9%)           | 0.76    |
| Hearing loss                  | 2 (3.5%)               | 2 (6.9%)           | 0.481   |
| Disturbance of consciousness  | 7 (12.3%)              | 2 (6.9%)           | 0.441   |
| First CSF assay               |                        |                    |         |
| ICP (mmH2O)                   | 300.0 (195.0–400.0)    | 335.0 (252.5–416.3)| 0.446   |
| Glucose (mmol/L)              | 2.5 (1.9–2.9)          | 2.4 (1.7–3.3)      | 0.866   |
| Total protein (g/L)           | 0.6 (0.4–0.9)          | 0.6 (0.4–1.0)      | 0.98    |
| WBC count (x 10^9/L)          | 10.0 (2.8–34.0)        | 3.0 (0–20.0)       | 0.084   |
| Chlorine (mmol/L)             | 116.4 ± 6.3            | 119.7 ± 5.6        | 0.192   |
| Cryptococcus neoformans count (HPF) | 3.0 (0.8–28.5)     | 3.0 (0.0–27.0)     | 0.213   |
| Positive India ink staining, n (%) | 47 (82.5%) | 25 (86.2%) | 0.656 |
| Positive Cryptococcus culture, n (%) | 48 (84.2%) | 27 (93.1%) | 0.243 |
| Blood test results            |                        |                    |         |
| C-reactive protein (mg/L)     | 605 (3.2–24.0)         | 78 (3.4–18.8)      | 0.82    |
| WBC (x 10^9/L)                | 5.0 (3.3–6.7)          | 5.8 (4.4–7.8)      | 0.084   |
| Hemoglobin (g/L)              | 124.4 ± 27.5           | 123.3 ± 21.8       | 0.853   |
| Platelet (x 10^9/L)           | 204. 9 ± 77.1          | 218.2 ± 116.1      | 0.526   |
| Albumin (g/L)                 | 38.4 (33.4–42.9)       | 39.1 (37.2–40.4)   | 0.594   |
| CD4 (mL)                      | 27.5 (13.0–41.8)       | 11.0 (6.0–24.8)    | 0.386   |

CM = cryptococcal meningitis, CSF = cerebrospinal fluid, HCM = HIV-associated cryptococcal meningitis, HIV = human immunodeficiency virus, HPF = high-power field, ICP = intracranial pressure, VPS = ventriculoperitoneal shunt, WBC = white blood cell
transient fever after VPS placement, and one (3.5%) had intestinal perforation.

**Treatment and outcomes**

A total of 62.1% (18/29) of the patients in the VPS group and 61.4% (35/57) in the non-VPS group ($P = 0.952$) were administered an AmB-based regimen. Of the total patients, an integrase strand transfer inhibitor (INSTI)-based regimen was used in 53.8% (14/26) of patients in the VPS group and 21.2% (7/33) of patients in the non-VPS group among patients with accepted available antiviral therapy data ($P = 0.009$). The initial time of antiviral therapy was 24.0 [11.0–31.0] days in the VPS group and 28.0 [19.0–37.0] days in the non-VPS group after antifungal treatment ($P = 0.261$).

The rate of neuroimaging abnormalities was 14/28 [45.2%] in the VPS group and 20/27 [74.1%] in the non-VPS group before antifungal therapy initiation ($P = 0.026$). However, the rate of neuroimaging improvement was 16/17 [94.1%] in the VPS group and 2/10 [20.0%] in the non-VPS group ($P < 0.001$).

During the 24-week follow-up, 1 patient in the VPS group died, and 12 patients in the non-VPS group died. The 24-week cumulative survival rate was 83.5% in the non-VPS group and 96.6% in the VPS group (log-rank, $P = 0.025$; Fig. 3).

Of note, 24.1% (7/29) of patients in the VPS group and 3.5% (2/57) of patients in the non-VPS group were misdiagnosed with tuberculous meningitis and underwent antituberculosis treatment ($P = 0.003$). In addition, 55.2% (16/29) of the patients in the VPS group and 14% (8/57) of the patients in the non-VPS group used corticosteroids at W24 for the treatment of immune reconstitution inflammatory syndrome (IRIS; $P < 0.001$).

**Discussion**

Although VPS placement is one of the most effective treatments for HCM patients with HICP, its effects on the long-term outcomes of these patients remain unclear. In our present study, we found the following: (1) VPS placement effectively decreased the HICP and mortality of HCM patients; (2) the CSF profiles of HCM patients in the VPS group were profoundly changed (especially increased CSF protein levels and decreased glucose levels); and (3) the frequencies of misdiagnosis with tuberculosis and immune reconstitution inflammatory syndrome were significantly higher in the VPS group than in the non-VPS group.

We observed that the CSF profiles in the VPS group in our study were significantly changed. This is consistent with the findings of previous studies [6, 7, 12]. To date, the underlying mechanisms of the increase in CSF protein content in patients with VPS are unclear. First, a predisposition for “paradoxical” IRIS may have existed. “Paradoxical” IRIS is characterized by initial improvement in clinical manifestations after antifungal therapy

| Table 2 | Changes in clinical symptoms and CSF profiles after 24 weeks in the groups |
|---------|--------------------------------------------------------------------------|
|         | VPS group | Non-VPS group |
|         | Baseline-W0 (n = 29) | 24 weeks of follow-up (n = 28) | P-value | Baseline-W0 (n = 57) | 24 weeks of follow-up (n = 45) | P-value |
| Cerebrospinal fluid | | | | | | |
| ICP (mmH2O) | 335.0 (252.5–407.5) | 155.0 (120.0–190.0) | 0.001 | 300.0 (195.0–400.0) | 200.0 (142.5–290.0) | 0.394 |
| Glucose (mmol/L) | 2.4 (1.7–3.3) | 2.4 (2.2–3.1) | 0.868 | 2.5 (1.9–2.9) | 2.8 (2.6–3.4) | 0.072 |
| Chlorine (mmol/L) | 119.7 ± 5.6 | 120.2 ± 5.0 | 0.496 | 116.4 ± 6.3 | 121.0 ± 5.8 | 0.066 |
| Total protein (g/L) | 0.6 (0.4–1.0) | 1.1 (0.6–1.6) | 0.045 | 0.6 (0.4–0.9) | 0.4 (0.3–0.7) | 0.14 |
| WBC count (× 10^9/L) | 3.0 (0–20.0) | 10 (1.0–30.0) | 0.641 | 10.0 (2.5–34.0) | 15.0 (3.0–36.5) | 0.433 |
| Cryptococcus neoformans count (/ HPF) | 3.0 (0.0–27.0) | 0 (0–1.0) | 0.002 | 3.0 (0.8–28.5) | 0 (0–1.0) | 0.003 |
| Clinical manifestations, n (%) | | | | | | |
| Fever | 16 (55.2%) | 1 (3.6%) | < 0.001 | 35 (61.4%) | 5 (11.1%) | < 0.001 |
| Headache | 21 (72.4%) | 7 (25.0%) | < 0.001 | 39 (67.6%) | 6 (13.3%) | < 0.001 |
| Dizziness | 7 (24.1%) | 0 (0) | 0.006 | 6 (10.5%) | 0 (0) | 0.025 |
| Seizures | 23 (79.3%) | 7 (25.0%) | 0.141 | 2 (3.5%) | 0 (0) | 0.24 |
| Vomiting | 13 (44.8%) | 2 (7.1%) | 0.001 | 15 (26.3%) | 0 (0) | < 0.001 |
| Vision loss | 2 (6.9%) | 0 (0) | 0.157 | 3 (5.3%) | 1 (2.2%) | 0.432 |
| Hearing loss | 2 (6.9%) | 0 (0) | 0.157 | 2 (3.5%) | 0 (0) | 0.2 |
| Disturbance of consciousness | 2 (6.9%) | 0 (0) | 0.157 | 7 (12.3%) | 0 (0) | 0.014 |

HCM HIV-associated cryptococcal meningitis, HPF high-power field, ICP intracranial pressure, VPS ventriculoperitoneal shunt, WBC white blood cell
Fig. 2 Comparison of CSF profiles and ICP values between the VPS and non-VPS groups (*P < 0.050, **P < 0.010, ***P < 0.001). CSF cerebrospinal fluid, HPF high-power field, ICP intracranial hypertension, VPS ventriculoperitoneal shunt, WBC white blood cell
Table 3  Risk factors for raised CSF protein levels in patients with cryptococcal meningitis identified in a logisitic regression analysis

| Factor                          | Number | Univariate |      |      | Multivariate |      |      |
|--------------------------------|--------|------------|------|------|--------------|------|------|
|                                |        | OR     | 95%CI| P value | OR     | 95%CI| P value |
| Age (years)                    |        |         |      |      |              |      |      |
| > 50                           | 9      | 0.6    | 0.1–4.5 | 0.657 |          |      |      |
| ≤ 50                           | 77     |         |      |      |              |      |      |
| Anticryptococcal therapy       |        |         |      |      |              |      |      |
| Contained AmB                  | 53     | 0.4    | 0.0–3.7 | 0.405 |          |      |      |
| Did not contain AmB            | 34     |         |      |      |              |      |      |
| HAART regimens                 |        |         |      |      |              |      |      |
| Missing data                   | 29     | 1.8    | 0.4–7.9 | 0.454 |          |      |      |
| INSTI                          | 21     |         |      |      |              |      |      |
| Non-INSTITI                    | 37     |         |      |      |              |      |      |
| VPS placement                  |        |         |      |      |              |      |      |
| Yes                            | 29     | 10.9   | 1.9–64.0 | 0.008 | 27.8   | 2.2–348.7 | 0.010 |
| No                             | 57     |         |      |      |              |      |      |
| CSF culture                    |        |         |      |      |              |      |      |
| Missing data                   | 7      |         |      |      |              |      |      |
| Positive                       | 54     | 2.9    | 0.7–11.7 | 0.127 |          |      |      |
| Negative                       | 26     |         |      |      |              |      |      |
| Blood culture                  |        |         |      |      |              |      |      |
| Missing data                   | 1      |         |      |      |              |      |      |
| Positive                       | 28     | 1.6    | 0.3–7.6 | 0.556 |          |      |      |
| Negative                       | 58     |         |      |      |              |      |      |
| Increase of CD4 count after 24 weeks/mL | | | | | | | |
| Missing data                   | 45     |         |      |      |              |      |      |
| > 100                          | 14     | 8.5    | 0.9–76.9 | 0.058 | 21.9   | 1.2–408.5 | 0.039 |
| ≤ 100                          | 28     |         |      |      |              |      |      |
| Initial CD4 count/mL          |        |         |      |      |              |      |      |
| Missing data                   | 28     |         |      |      |              |      |      |
| > 20                           | 26     | 0.3    | 0.1–1.4 | 0.112 |          |      |      |
| ≤ 20                           | 33     |         |      |      |              |      |      |
| Initial CSF ICH (mmH₂O)        |        |         |      |      |              |      |      |
| Missing data                   | 5      |         |      |      |              |      |      |
| > 300                          | 52     | 1.4    | 0.3–5.9 | 0.633 |          |      |      |
| ≤ 300                          | 30     |         |      |      |              |      |      |
| Initial CD4 count /mL          |        |         |      |      |              |      |      |
| Missing data                   | 28     |         |      |      |              |      |      |
| > 20                           | 26     | 0.3    | 0.1–1.4 | 0.112 |          |      |      |
| ≤ 20                           | 33     |         |      |      |              |      |      |
| Initial CSF protein level (g/L)|        |         |      |      |              |      |      |
| Missing data                   | 7      |         |      |      |              |      |      |
| > 0.5                          | 45     | 0.8    | 0.2–3.7 | 0.801 |          |      |      |
| ≤ 0.5                          | 35     |         |      |      |              |      |      |
| Initial CSF WBC (× 10⁹/L)      |        |         |      |      |              |      |      |
| Missing data                   | 10     |         |      |      |              |      |      |
| > 55                           | 64     | 1.5    | 0.3–8.4 | 0.644 |          |      |      |
| ≤ 55                           | 13     |         |      |      |              |      |      |
| Time of HAART initiation       |        |         |      |      |              |      |      |
| Missing data                   | 35     |         |      |      |              |      |      |
| Before 4 weeks                 | 27     | 3.6    | 0.3–38.2 | 0.282 |          |      |      |
| After 4 weeks                  | 25     |         |      |      |              |      |      |
followed by deterioration because of HAART-mediated immune restoration in patients with HCM [16], which is similar to our patients’ clinical manifestations. Our study also found that VPS placement and increased CD4 counts were independent risk factors for increased CSF protein levels. Therefore, “paradoxical” IRIS may have triggered changes in clinical presentations and CSF profiles. Second, the placement of a shunting device may have caused increased CSF protein levels. Previous studies [17, 18] have suggested that CSF protein levels are increased by the placement of external drainage devices in patients with Alzheimer’s disease and are associated with trauma resulting from ventricular drain insertion. Therefore, we speculated that the placement of an external drainage device may increase CSF protein levels. Third, the placement of an external drainage device may have stimulated the production of cytokines/chemokines, such as vascular endothelial growth factor, transferrin, and brain-derived protein, in CSF, leading to higher CSF protein levels [17, 19, 20].

Notably, some patients in the VPS group were misdiagnosed with tuberculous meningitis, and some patients were diagnosed with IRIS based on CSF profile changes. A CSF profile similar to that observed in tuberculous meningitis may also be a manifestation of IRIS, and this aspect should be investigated in further studies.

Although one study found that the 10-week survival rate of patients after 1 week of AmB therapy was higher than that after 2 weeks of AmB therapy in an African population [21], our previous study found that the 90-day survival rate of patients treated with AmB for >14 days was significantly higher than that of patients treated for <14 days [13]. Wu et al. also found that the duration of AmB-containing treatment during the induction period was a protective factor for better prognoses [22]. Some additional factors, such as CSF WBC, intracranial pressure and CSF glucose, were associated with patient outcomes. Overall, AmB + 5FC was associated with an increased survival rate but was not the sole favorable factor.

This study had some limitations. First, the sample size was small. However, compared with previous studies on VPS, this study included the largest sample size of patients with HCM. Second, the specific mechanisms underlying increased CSF protein levels were not fully investigated. Larger studies focusing on the pathogenesis of increased CSF protein levels after VPS placement are needed. We believe that a comprehensive understanding of the pathogenesis of increased CSF protein levels after VPS placement will improve clinicians’ decisions regarding the management of these patients. Third, our study only included Chinese patients, which may affect the generalizability of our results.

Conclusions
In conclusion, although VPS placement is effective in controlling intracranial hypertension in HCM patients, it can result in extremely high CSF protein levels and low CSF glucose levels after VPS placement. This could lead to misdiagnosis of tuberculous meningitis and some of them were diagnosed with immune reconstitution inflammatory syndrome. Physicians should be aware of this change in the CSF profiles of HCM patients with VPSs to reduce misdiagnoses and improve long-term prognoses.

Abbreviations
HIV: Human immunodeficiency virus; CM: Cryptococcal meningitis; HCM: Human immunodeficiency virus-associated cryptococcal meningitis; HICP: High intracranial pressure; VPS: Ventriculoperitoneal shunt; OR: Odds ratio; CI: Confidence interval; ICH: Intracranial hypertension

Acknowledgements
We thank the staff of the HIV/AIDS ward in the First Affiliated Hospital, School of Medicine, Zhejiang University.
Authors’ contributions
RT and BZ designed the study. RT, YZG, and XKX collected the data. JSZ performed the operation. RT analyzed the data. RT and LJX wrote the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by the National Special Research Program for Important Infectious Diseases (Grant number 2017ZX10202102). The funding organization had no involvement in the study or in the decision to submit the article for publication.

Availability of data and materials
The datasets used and/or analyzed during the current study are included within the article and are available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All data analyzed were anonymous. The ethics committee waived the requirement of written informed consent for participation.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1. National Clinical Research Center for Infectious Diseases, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China. 2. The State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China. 3. Department of Neurosurgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.

Received: 16 August 2021 Accepted: 16 March 2022
Published online: 26 March 2022

References
1. Graybill JR, Sobel J, Saag M, van Der Horst C, Powderly W, Cloud G, Riser L, Hamill R, Dismukes W. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAD Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis. 2000;30(1):47–54.
2. York J, Bodt J, Reeves I, Riordan-Eva P, Easterbrook PJ. Raised intracranial pressure complicating cryptococcal meningitis: immune reconstitution inflammatory syndrome or recurrent cryptococcal disease? J Infect. 2005;51(2):163–71.
3. Sun HY, Hung CC, Chang SC. Management of cryptococcal meningitis with extremely high intracranial pressure in HIV-infected patients. Clin Infect Dis. 2004;38(12):1790–2. [discussion 1282–1283].
4. Bach MC, Tally PW, Godofsky EW. Use of cerebrospinal fluid shunts in patients having acquired immunodeficiency syndrome with cryptococcal meningitis and uncontrollable intracranial hypertension. Neurosurg. 1997;41(6):1280–2. [discussion 1282–1283].
5. Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, Sobel JD, Dismukes WE. Practice guidelines for the management of cryptococcal meningitis: Infectious Diseases Society of America. Clin Infect Dis. 2000;30(6):710–8.
6. Woodworth GF, McGirt MJ, Williams MA, Rigamonti D. The use of ventriculoperitoneal shunts for uncontrollable intracranial hypertension without ventriculomegaly secondary to HIV-associated cryptococcal meningitis. Surg Neurol. 2005;63(6):529–31. [discussion 531–522].
7. Corti M, Prionone M, Negroni R, Gilardi L, Castrello J, Arechayala AJ, Messina F, Franzce O. Ventriculoperitoneal shunts for treating increased intracranial pressure in cryptococcal meningitis with or without ventriculomegaly. Rev Soc Bras Med Trop. 2014;47(4):524–7.
8. Genebat M, Mayorga-Buiza MJ, Castillo-Ojeda E, Rivero-Garvia M, Marquez-Rivas FJ, Jimenez-Mejias ME. Cryptococcal infection of the ventriculoperitoneal shunt in an HIV-infected patient with an excellent immunovirologic status. World Neurosurg. 2017;99:810.e811–810.e813.
9. Liu Y, Peng X, Weng W, Zhu J, Cao H, Xie S. Efficacy of ventriculoperitoneal shunting in patients with cryptococcal meningitis with intracranial hypertension. Int J Infect Dis. 2019;88:102–9.
10. Liu J, Chen ZL, Li M, Chen C, Yi H, Xu L, Tan F, Peng FH. Ventriculoperitoneal shunts in non-HIV cryptococcal meningitis. BMC Neurol. 2018;18(1):58.
11. Wang H, Ling C, Chen C, He HY, Luo L, Ning XJ. Evaluation of ventriculoperitoneal shunt in the treatment of intracranial hypertension in the patients with cryptococcal meningitis: a report of 12 cases. Clin Neurol Neurosurg. 2014;124:156–60.
12. Liu L, Zhang R, Tang Y, Lu H. The use of ventriculoperitoneal shunts for uncontrollable intracranial hypertension in patients with HIV-associated cryptococcal meningitis with or without hydrocephalus. Biosci Trends. 2014;8(6):327–32.
13. Xu L, Tao R, Wu J, Dai X, Hu C, Huang Y, Chen Y, Zhu B, He J. Short-course rather than low-dose amphotericin B may exert potential influence on mortality in cryptococcal meningitis patients treated with amphotericin B plus flucytosine alone or in combination with fluconazole. Front Microbiol. 2019;10:2082.
14. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen MH, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. Clin Infect Dis. 2010;50(3):291–322.
15. Hu Z, Yang Y, Cheng J, Cheng C, Chi Y, Wei H. The use of mannitol in HIV-infected patients with symptomatic cryptococcal meningitis. Drug Discov Ther. 2017;10(6):329–33.
16. Longley N, Harrison TS, Jarvit JN. Cryptococcal immune reconstitution inflammatory syndrome. Curr Opin Infect Dis. 2013;26(1):26–34.
17. Brandner S, Thaler C, Buchfelder M, Kleindienst A. Brain-derived protein concentrations in the cerebrospinal fluid: contribution of trauma resulting from ventricular drain insertion. J Neurotrauma. 2013;30(13):1205–10.
18. Saul T, McGuire D, Mayo M, Fellmann J, Carvalho J, Silverberg GD, et al. Shunting in AD increases ventricular CSF protein levels. Cerebrospinal Fluid Res. 2007;4:1.
19. Yang J, Dombrowski SM, Krishnan C, Krajcir N, Deshpande A, El-Khoury S, Guruprakash DK, Luciano MG. Vascular endothelial growth factor in the CSF of elderly patients with ventriculomegaly: variability, periodicity and levels in drainage responders and non-responders. Clin Neurol Neurosurg. 2013;115(9):1729–34.
20. Murakami Y, Matsumoto Y, Hoshi K, Ito H, Fuwa TJ, Yamaguchi Y, Nakajima M, Miyajima A, Ari H, Nollet K, et al. Rapid increase of “brain-type” transferrin in cerebrospinal fluid after shunt surgery for idiopathic normal pressure hydrocephalus: a prognosis marker for cognitive recovery. J Biochem. 2018;164(3):205–13.
21. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda O, Nfirianga S, Temfack E, Lakh S, Lesikari S, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. N Engl J Med. 2018;378(11):1004–17.
22. Wu L, Xiao J, Song Y, Gao G, Zhao H. The clinical characteristics and outcome of cryptococcal meningitis with AIDS in a tertiary hospital in China: an observational cohort study. BMC Infect Dis. 2020;20(1):912.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.