JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Ventriculoperitoneal shunt in the treatment of cryptococcal meningitis with intracranial hypertension

Cheng'an Cao[1 #], Lun Luo[1 #], Tengchao Huang[1], Wenhan Zheng[1], Cong Ling[1], Ying Guo[1]

[1] Department of Neurosurgery, The third affiliated hospital, Sun Yat-Sen University, Guangzhou, China

# Authors contributed equally to this work.

Abstract

Introduction: Cryptococcal meningitis (CM) combined with intracranial hypertension is associated with a poor prognosis. This study aimed to investigate the therapeutic efficacy and prognostic factors of ventriculoperitoneal (VP) shunt in non-human immunodeficiency virus (HIV) CM patients with intracranial hypertension.

Methodology: A total of 136 non-HIV CM patients with intracranial hypertension treated in our hospital from July 2010 to December 2019 were retrospectively included. 57 patients underwent VP shunt placement (shunt group) and 79 patients received conservative therapy (conservative group). The clinical symptoms after treatment, cerebrospinal fluid (CSF) test results, and therapeutic outcomes were compared between the groups.

Results: VP shunt significantly reduced the incidences of headache, vomiting, cranial nerve injury, intracranial pressure, and CSF leukocyte level in CM patients (all $p < 0.05$). The shunt group had a significantly higher curative rate, shorter seroconversion time, hospitalization time, and disease duration (all $p < 0.001$). However, no significant difference in the survival outcome was observed between the groups ($p = 0.163$). Cox proportional-hazard regression analysis showed that seroconversion time was the only independent factor associated with the survival outcome.

Conclusions: Our results suggested that the VP shunt is an effective and safe treatment for non-HIV CM patients combined with intracranial hypertension. Seroconversion time was the only independent factor associated with the survival outcome.

Key words: cryptococcal meningitis; intracranial hypertension; ventriculoperitoneal shunt.

J Infect Dev Ctries 2024; 18(12):1949-1956. doi:10.3855/jidc.19341

(Received 04 October 2023 – Accepted 28 February 2024)

Introduction

Cryptococcal meningitis (CM) is a severe fungal infection of the brain and surrounding membranes caused by *Cryptococcus neoformans* or *Cryptococcus gattii* [1], which is associated with significant morbidity and mortality in both immunocompetent and immune-compromised patients [2]. CM is characterized by insidious onset, long incubation period, rapid progress, and long disease course [3]. The annual incidence of human immunodeficiency virus (HIV)-related CM has been estimated to be approximately 1 million cases, resulting in more than 600,000 associated deaths worldwide [4]. It has been shown that approximately 80% of CM cases occur along with HIV in the USA [5]. Nevertheless, in China, CM occurs more commonly in non-HIV patients than in HIV patients [6]. Autoimmune diseases, diabetes, immunosuppressant utilization, malignancy, and organ transplantation are reported to be crucial predisposing factors for cryptococcosis in non-HIV patients [7].

A significant proportion of CM patients present severe intracranial hypertension or hydrocephalus and may develop severe neurological dysfunction with disease progression. In the case of CM patients with intracranial hypertension, a large amount of *Cryptococcus* in the cerebrospinal fluid (CSF) would cause intracranial inflammatory response, causing excessive secretion of CSF. The pathogen and the secretions cover the surface of the brain, affecting the absorption of CSF. The fungal detritus and inflammatory substances increase the osmotic pressure of the CSF and stiffen the brain parenchyma [8], resulting in reduced efficacy of conventional medical treatment of intracranial pressure, such as mannitol [9]. Intracranial hypertension has been identified as a crucial risk factor for neurological deficits and early death in CM patients [10–12]. In addition, reducing the intracranial pressure to normal levels is associated with improved prognosis in CM patients [13].

Ventriculoperitoneal (VP) shunting is an effective method for the treatment of hydrocephalus and

intracranial hypertension caused by various factors. Studies on employing VP shunt in the treatment of CM have been documented. Most of the reported cases have good therapeutic efficacy, and uncontrollable intracranial hypertension could be relieved by VP shunt [14]. However, many studies focus on HIV-related CM [15–18], whereas studies on non-HIV CM are relatively limited. In recent years, some case studies have reported the effectiveness of VP shunt in non-HIV CM patients [17,19]. However, these reports are limited by their small sample size.

This study aimed to investigate the therapeutic efficacy and prognostic factors of VP shunt in non-HIV CM patients with intracranial hypertension.

Methodology

Patients

A total of 136 CM cases that met the inclusion criteria were treated in the Infectious Diseases Department, Neurology Department, or Neurosurgery Department of our hospital from July 2010 to December 2019, and their medical records were retrospectively reviewed. 57 patients underwent VP shunt placement (designated as the shunt group), and 79 patients received conservative therapy (designated as the conservative group).

The inclusion criteria were: 1) India ink test was positive for *Cryptococcus* in the CSF, or positive CSF culture for *Cryptococcus neoformans*; 2) clinical manifestations of meningitis; 3) lumbar puncture examination showed a lumbar puncture pressure ≥ 250 mm H_2O (according to the 2010 Clinical Practice Guidelines for the Management of Cryptococcal Disease by the Infectious Diseases Society of America [20]); 4) had clinical manifestations of increased intracranial pressure such as a headache, nausea, vomiting, and decreased consciousness. The exclusion criteria were: 1) combined with tuberculous meningoencephalitis or bacterial encephalitis; 2) history of immunocompromised diseases, such as acquired immunodeficiency syndrome (AIDS), lymphoma, leukemia, organ transplantation; 3) with peritonitis or ascites; 4) combined with another organ failure.

This was a retrospective study and was approved by the Ethics Committee of the Third Affiliated Hospital, Sun Yat-Sen University. This study complied with the Declaration of Helsinki.

The indications for VP shunt included: 1) persistent and increased intracranial pressure (≥ 250 mm H_2O); 2) hydrocephalus.; and 3) symptoms of cranial nerve damage. The contraindications for VP shunt were abnormal blood coagulation and patients not tolerant to surgery.

Examinations and treatment

All patients received the standard antifungal treatment recommended by the Infectious Diseases Society of America (IDSA) [20]. The antifungal treatment plan during hospitalization was as follows: amphotericin B deoxycholate (AmBd; 0.7–1.0 mg/kg per day; intravenous, IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 4 weeks for induction therapy. The 4-week induction therapy was reserved for persons with meningoencephalitis without neurological complications and CSF yeast culture results that were negative after 2 weeks of treatment. The antifungal treatment plan during the follow-up period was as follows: after induction and consolidation therapy, maintenance therapy with fluconazole (200 mg [3 mg/kg] per day orally) was administered for 6–12 months.

All patients underwent lumbar puncture for CSF analysis, including pressure, biochemical tests, routine tests, and *Cryptococcus* count. All the included patients had a baseline cerebrospinal fluid pressure ≥ 250 mm H_2O, and the laboratory examination was abnormal.

All patients underwent head computed tomography (CT) or magnetic resonance imaging (MRI) scan. There was no manifestation of hydrocephalus in any of the patients. Only 11 patients showed ventricular dilatation in the head CT or MRI.

Ventriculoperitoneal shunt placement

After treatment with regular internal antifungal drugs, 56 patients underwent VP shunt using the Strata Adjustable Pressure Shunt (model: 42866, Medtronic Ps Medical, Minneapolis, Minnesota, USA) or the Delta Shunt (model: 25132-5, Medtronic Ps Medical, Minneapolis, Minnesota, USA). The patient was placed in a supine position for general anesthesia. A 2 cm straight incision was made 2 cm from the midline of the right coronal suture. The skull was drilled and the dura was cut. The right ventricle was punctured with a ventricular catheter. A 2 cm incision was made behind the right ear, and a 1 cm incision was made under the xiphoid process, through which a shunt catheter was inserted. The ventricle shunt catheter was guided and exported from the incision behind the ear. The ventricle end of the shunt catheter was connected to the inflow end of the shunt pump, and the abdominal end of the shunt catheter was connected to the outflow end of the shunt pump. A 1.5 cm incision was made inferior to the umbilicus, and a regular laparoscope setting was

performed with a pneumoperitoneum pressure of 13 mmHg. Under the laparoscopic guidance, a 16F separable sheath was used to puncture into the abdomen via the incision under the xiphoid process, and the stylet was removed. The abdominal end of the shunt catheter was inserted into the abdominal cavity. The incisions were then sutured.

Therapy efficacy evaluation

The efficacy of the therapy was categorized as short-term and long-term outcomes. Short-term evaluation occurred at the time of patient discharge, and long-term evaluation was conducted during the patient's follow-up period. During these evaluations, we primarily assessed symptoms and examined the CSF.

Seroconversion was defined as CSF smear-negative for *Cryptococcus neoformans*. "Cured" was defined as the condition where clinical symptoms and signs (such as fever, coma, headache, or cranial nerve injury) disappeared, intracranial pressure decreased to normal, and three consecutive cerebrospinal fluid cryptococcal smears were negative (with an interval of more than 3 days). "Improved" was defined as clinical symptoms and signs alleviated, including no fever, relief of consciousness, headache, and vomiting; reduction of cranial nerve damage (including improvement of vision and hearing); and intracranial pressure < 200 mm H_2O for two consecutive lumbar punctures. "Deterioration" was defined as the condition where clinical symptoms and signs were aggravated, and intracranial pressure did not decrease, or increase; or when the patient died of cryptococcal meningitis and its complications during hospitalization.

The therapeutic outcome: "better" was defined as "cured" or "improved"; "worse" was defined as "deterioration".

Statistical analysis

Continuous data were indicated as the mean ± standard deviation (SD) and compared by Student's paired t-test. Wilcoxon signed-rank test was used if normality was not assumed. Student's paired t-test was also used to compare the results before and after surgery in the shunt group. Categorical data were presented with numbers and percentages (%) and tested by the Chi-square test or Fisher's exact test (if an expected value < 5 was found). Cox proportional-hazard regression models were used to investigate the factors that were possibly associated with independent variables and patient survival outcomes. Patient's group, gender, and age were adjusted as covariates in the multivariate model. Only the independent variables which were significant in both univariate and multivariate models were recognized as associated factors. The significance level of all analyses was set at a $p < 0.05$, two-tailed. All analyses were performed using IBM SPSS version 20 (IBM Corporation, Somers, New York, USA).

Results

Patient's demographic and clinical characteristics

A total of 136 non-HIV CM patients (90 males, 46 females; median age = 41 years, range: 17–71 years) were included in this study. Of them, 57 patients underwent VP shunt placement (shunt group) while the other 79 patients received conservative therapy (conservative group) (detailed information in Table 1).

The baseline (before treatment) symptoms (such as, consciousness status, headache, vomiting), other clinical characteristics (such as, cranial nerve injury, body temperature, intracranial pressure, *Cryptococcus* count), and CSF analysis results (leukocyte, protein, and glucose levels) were summarized in Table 2. Most patients had an intracranial pressure of > 330 mm H_2O and had a poor response to mannitol and hormone treatment for reducing intracranial pressure. There were no significant differences in the demographic baseline and clinical characteristics between the shunt group and the conservative group (all $p > 0.05$, Tables 1 and 2), indicating good comparability between the two groups.

Comparison of clinical characteristics before and after VP shunt in the shunt group

The clinical characteristics before and after the VP shunt and the post-surgery results in the shunt group are presented in Table 2. It was found that after VP shunt surgery, the incidences of headache, vomiting, cranial nerve injury, intracranial pressure, and CSF leukocyte level were significantly reduced as compared with those before treatment (all $p < 0.05$, Table 2), whereas the CSF protein level, was significantly elevated ($p < 0.05$, Table 2).

Table 1. Patient's demographic and clinical characteristics.

Parameters	Shunt (n = 57)	Conservative (n = 79)	Total (n = 136)	*p*
Gender				0.918
Male	38 (66.67)	52 (65.82)	90 (66.18)	
Female	19 (33.33)	27 (34.18)	46 (33.82)	
Age (years)	41.63 ± 12.96	40.42 ± 14.05	40.93 ± 13.57	0.512

Table 2. Symptoms in shunt and conservative groups.

Parameters	Shunt (n = 57)	Conservative (n = 79)	Total (n = 136)	*p*
Consciousness - before treatment				0.986
Conscious	52 (91.23)	72 (91.14)	124 (91.18)	
Coma	5 (8.77)	7 (8.86)	12 (8.82)	
Consciousness - after VP shunt				-
Conscious	54 (94.74)	-	54 (94.74)	
Coma	3 (5.26)	-	3 (5.26)	
Headache - before treatment				0.874
No	4 (7.69)	5 (6.94)	9 (7.26)	
Yes	48 (92.31)	67 (93.06)	115 (92.74)	
Headache - after VP shunt *				-
No	51 (94.44)	-	51 (94.44)	
Yes	3 (5.56)	-	3 (5.56)	
Vomit - before treatment				0.873
No	4 (7.02)	5 (6.33)	9 (6.62)	
Yes	53 (92.98)	74 (93.67)	127 (93.38)	
Vomit - after VP shunt *				-
No	51 (89.47)	-	51 (89.47)	
Yes	6 (10.53)	-	6 (10.53)	
Cranial nerve injury - before treatment				0.826
No	27 (47.37)	36 (49.32)	63 (48.46)	
Yes	30 (52.63)	37 (50.68)	67 (51.54)	
Cranial nerve injury - after VP shunt *				-
No	51 (89.47)	-	51 (89.47)	
Yes	6 (10.53)	-	6 (10.53)	
Body temperature (continuous) - before treatment (℃)	1.35 ± 0.64	1.46 ± 0.78	1.41 ± 0.72	0.510
Body temperature - before treatment (℃)				0.709
Normal	41 (71.93)	53 (67.09)	94 (69.12)	
Mild/low grade fever	13 (22.81)	20 (25.32)	33 (24.26)	
Moderate grade fever	2 (3.51)	2 (2.53)	4 (2.94)	
High grade fever	1 (1.75)	4 (5.06)	5 (3.68)	
Body temperature (continuous) – after VP shunt (℃)	1.40 ± 0.65	-	1.40 ± 0.65	-
Body temperature - after VP shunt (℃)				-
Normal	38 (66.67)	-	38 (66.67)	
Mild/low grade fever	16 (28.07)	-	16 (28.07)	
Moderate grade fever	2 (3.51)	-	2 (3.51)	
High grade fever	1 (1.75)	-	1 (1.75)	
Intracranial pressure - before treatment (mmH_2O)	350.18 ± 52.22	356.46 ± 56.34	353.82 ± 54.54	0.675
Intracranial pressure - after VP shunt * (mmH_2O)	105.44 ± 22.92	-	105.44 ± 22.92	-
Cryptococcus count - before treatment(/ml)	13210.09 ± 20362.05	16690.24 ± 36308.47	15231.65 ± 30604.67	0.675
Cryptococcus count - after VP shunt(/ml)	64.67 ± 195.86	-	64.67 ± 195.86	-
CSF leukocyte - before treatment (10^6/L)	35.84 ± 35.98	32.24 ± 29.15	33.75 ± 32.11	0.384
CSF leukocyte - after VP shunt * (10^6/L)	31.95 ± 36.88	-	31.95 ± 36.88	-
CSF Protein - before treatment (g/L)	1.09 ± 0.93	0.95 ± 0.88	1.01 ± 0.90	0.233
CSF Protein - after VP shunt * (g/L)	1.15 ± 0.58	-	1.15 ± 0.58	-
CSF glucose - before treatment (mmol/L)	2.86 ± 0.84	2.88 ± 0.99	2.87 ± 0.92	0.982
CSF glucose - after VP shunt (mmol/L)	3.15 ± 0.72	-	3.15 ± 0.72	-

* $p < 0.05$, compared to before-treatment results in the shunt group. CSF: cerebrospinal fluid; VP: ventriculoperitoneal. Reference values: mild/low grade fever: 37.3–38.0 ℃; moderate grade fever: 38.1–39.0 ℃; high grade fever: > 39.0 ℃; CSF protein: 0.15–0.40 g/L; CSF glucose: 2.50–3.90 mmol/L; CSF leukocyte: (0–10)10^6/L; *Cryptococcus* count: 0/mL. Missing values management: the median or mean complement was used for continuous variables; the value with the largest category mode was used for classified variables.

Therapeutic outcomes

A comparison of the therapeutic outcomes between groups is presented in Table 3. The shunt group had a significantly better outcome rate (80.70% vs. 54.43%, $p = 0.001$), shorter seroconversion time (38.37 ± 29.86 days vs. 102.09 ± 56.44 days, $p < 0.001$), shorter hospitalization time (52.68 ± 37.15 days vs. 96.27 ± 59.75 days, $p < 0.001$), and shorter disease duration (63.02 ± 41.25 days vs. 148.51 ± 70.03 days, $p < 0.001$). However, there was no significant difference in the survival outcome between groups ($p = 0.163$).

Follow-up

Routine follow-up treatment was conducted for a period of 12 to 24 months after discharge. The first follow-up visit was scheduled within 3 months for successfully discharged patients. However, only approximately half of the patients completed follow-up for more than 24 months, with all of them experiencing recovery and discontinuing antifungal treatment.

During the follow-up period, the most commonly reported residual symptom was mild headaches, while other symptoms encompassed seizures, impaired vision, hearing difficulties, limb fatigue, and psychiatric symptoms.

Table 3. Follow-up and clinical outcomes in shunt and conservative group patients.

Parameters	Shunt (n = 57)	Conservative (n = 79)	Total (n = 136)	*p*
Therapeutic outcome				0.001
Worse	11 (19.30)	36 (45.57)	47 (34.56)	
Better	46 (80.70)	43 (54.43)	89 (65.44)	
Time of seroconversion, days	38.37 ± 29.86	102.09 ± 56.44	69.16 ± 54.79	< 0.001
Hospitalization time, days	52.68 ± 37.15	96.27 ± 59.75	78.00 ± 55.68	< 0.001
Length of follow-up, day	786.77 ± 658.53	2160.94 ± 839.19	1585.00 ± 1024.65	< 0.001
Disease duration (from onset to cure), day	63.02 ± 41.25	148.51 ± 70.03	104.33 ± 71.11	< 0.001
Period from onset to surgery, day	27.91 ± 20.14	-	27.91 ± 20.14	-
Survival outcomes				0.163
Survival	50 (87.72)	62 (78.48)	112 (82.35)	
Dead	7 (12.28)	17 (21.52)	24 (17.65)	

Surgical complications after the VP shunt

Two patients with seroconversion to negative for *Cryptococcus* in CSF could not tolerate the shunt catheter and had repeated low-grade fever. No evidence of bacterial or fungal infection was found in the CSF. The symptoms were relieved after removal of the shunt.

Three patients developed a shunt-related bacterial intracranial infection at 1month post-surgery. After the shunt was removed, the infection was controlled by anti-infective treatment.

Independent factors associated with the survival outcome

To identify independent factors associated with survival outcomes, Cox proportional-hazard regression was performed. As shown in Table 4, the time of seroconversion was the only variable that was significant both in the univariate and multivariate analyses (HR = 0.93, 95% CI: 0.86–1.00, $p = 0.039$).

Table 4. Cox proportional-hazard regression model results.

Parameters	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Group				
VP shunt	ref.	-		
Conservative	0.52 (0.20–1.35)	0.182	1.76 (0.31–9.93)	0.523
Gender				
Male	ref.	-		
Female	1.52 (0.66–3.51)	0.331	3.36 (0.94–11.97)	0.061
Age, year	1.01 (0.98–1.04)	0.491	1.05 (1.01–1.09)	0.021
Hospitalization, days	0.98 (0.97–0.99)	0.006	1.03 (0.98–1.09)	0.265
Therapeutic outcome				
Worse	ref.	-		
Better	0.92 (0.40–2.11)	0.847		
Time of seroconversion, days	0.97 (0.95–0.99)	0.008	0.93 (0.86–1.00)	0.039
Consciousness - before treatment				
Conscious	ref.	-		
Coma	2.16 (0.78–5.97)	0.138		
Headache - before treatment				
No	ref.	-		
Yes	0.50 (0.11–2.17)	0.353		
Vomit - before treatment				
No	ref.	-		
Yes	1.47 (0.20–10.94)	0.705		
Cranial nerve injury - before treatment				
No	ref.	-		
Yes	0.96 (0.40–2.32)	0.930		
Body temperature - before treatment		0.786		
Normal	ref.	-		
Mild/low grade fever	0.87 (0.32–2.38)	0.790		
Moderate grade fever	0.00 (0.00–0.00)	0.982		
High grade fever	2.03 (0.46–8.85)	0.348		
Intracranial pressure - before treatment	1.00 (1.00–1.01)	0.433		
***Cryptococcus* count - before treatment, log10**	1.55 (0.91–2.66)	0.107		
CSF leukocyte - before treatment	1.00 (1.00–1.01)	0.328		
Protein - before treatment	1.23 (0.85–1.78)	0.275		
Glucose - before treatment	0.86 (0.57–1.31)	0.478		

Patient's group, gender, and age were adjusted as covariates in the multivariate model. Cryptococcus count: To avoid missing values of zero during logarithmic conversion, a unit is added to all observations. CSF: cerebrospinal fluid; VP: ventriculoperitoneal.

Discussion

In this study, we investigated the therapeutic efficacy of VP shunt in non-HIV CM patients with intracranial hypertension. The results showed that VP shunt significantly reduced the incidences of headache, vomiting, cranial nerve injury, intracranial pressure, and CSF leukocyte level in CM patients. The shunt group had significantly better outcome rates, shorter seroconversion time, hospitalization time, and disease duration. However, no significant difference in the survival outcome was observed between the groups. Cox proportional-hazard regression analysis showed that seroconversion time was a factor associated with the survival outcome. Taken together, our results suggested that the VP shunt is an effective and safe treatment for non-HIV CM patients with intracranial hypertension.

Wang *et al*. demonstrated the therapeutic efficacy of VP shunt in 12 non-HIV CM patients [19]. They found that the VP shunt significantly decreases CSF pressure and *Cryptococcus* count, but not the leukocyte count, CSF protein, and CSF glucose [19]. Liu *et al.* reported that VP shunt can effectively reduce CSF pressure and *Cryptococcus* count in 23 non-HIV CM patients with or without ventriculomegaly, and they suggested that VP shunt should be performed before CM patients present with symptoms of severe neurological deficit [17]. Baddley *et al.* also reported early identification of patients with increased and persistent ICP in CM, and that taking measures such as shunting, could influence management decisions and mortality [21]. Consistent with these observations, our study found that the VP shunt effectively reduced CSF pressure and relieved the symptoms of headache, vomiting, and cranial nerve injury. The majority of CM patients have increased intracranial pressure, leading to clinical manifestations, such as a headache, vomiting, and even cranial nerve injury such as loss of vision or hearing [22]. Even with regular antifungal and symptomatic treatments, patients still suffer from these pains for a long time. After the decrease of intracranial pressure following the VP shunt (from 350.18 ± 52.22 to 105.44 ± 22.92 mmH_2O), these clinical symptoms of patients can be significantly alleviated. The therapeutic outcomes better rate, seroconversion time, hospitalization time, and disease duration may be regarded as indicators of therapeutic efficacy. Our results showed that there were significant differences in all four parameters between the shunt group and the conservation group, strongly suggesting that VP shunt possessed good therapeutic efficacy on non-HIV CM patients combined with intracranial hypertension, which is also aligned with several previous studies [17,19].

It was shown that in CM patients with intracranial hypertension, the imaging finding does not show a ventricle enlargement in the majority of cases [23]. Of the 136 CM patients in this group, only 11 patients (8.08%) had ventricular enlargement in the imaging scan. As for postoperative complications, shunt obstruction and infection were the most common complications of VP shunt [24]. In this study, 3 patients (5.26%) developed shunt infection at one-month post-surgery, but the infection was controlled by anti-infective treatment after the shunt was removed. Regarding the cause of shunt obstruction, one hypothesis suggests that high CSF protein levels may contribute to shunt obstruction [24] and some surgeons are concerned about the high CSF protein level in CM patients that may lead to early shunt obstruction. Nevertheless, a study by Rammos *et al.*, on hydrocephalus patients following subarachnoid hemorrhage has demonstrated that there is no association between shunt failure and high CSF protein level [25]. Liliang *et al.* have reported a shunt obstruction rate of 11.11% in CM patients undergoing VP shunt [11], which is similar to that in other diseases [26]. Among the 57 cases receiving VP shunt placement, only 2 cases (3.5%) had shunt obstruction, which is lower than Liliang *et al*.'s study [11]. Another concern of the VP shunt is that the *Cryptococcus* would be drained to the abdominal cavity, which may result in cryptococcal infection in the abdominal organs. However, based on our clinical experience, there is no abdominal cryptococcosis after the VP shunt. Under regular antifungal treatment, the serum concentration of antifungal drugs is 50 times higher than that in CSF. In addition, the peritoneum possesses a strong anti-infective capacity. Although it has high pathogenicity, the *Cryptococcus* within the CSF drained to the abdominal cavity, can be easily killed, so peritonitis is not common after the VP shunt [27,28]. In this study, all the CM patients did not develop abdominal cryptococcosis following the VP shunt. Therefore, we believe that the VP shunt is an effective and safe treatment for non-HIV patients with intracranial hypertension, and high CSF protein level should not be a contraindication for the VP shunt in CM patients.

There were some limitations of this study. First, this study was limited by its retrospective nature. Furthermore, the coronavirus disease 2019 (COVID-19) pandemic has had a significant impact on the enrollment of patients with cryptococcal meningitis and increased intracranial pressure. As a result, hospital

admissions were reduced, and follow-up efforts were hindered. Consequently, the data collection for this study could not extend beyond 2019, thus limiting the sample size. In the future, a well-designed prospective clinical trial with a larger sample size should be conducted to further validate the findings of this study.

Conclusions

Our findings demonstrated that VP shunt can effectively reduce intracranial pressure; improve therapeutic outcomes rate; and shorten seroconversion time, hospitalization time, and disease duration; making it an effective and safe treatment for non-HIV CM patients combined with intracranial hypertension. Our study also highlighted that seroconversion time was the only independent factor associated with the survival outcome, suggesting that the target of treatment, including antifungal treatment or VP shunt, was to reduce the time of seroconversion. Thus, VP shunt can improve the survival outcome of patients and may be used in clinical treatment.

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki, and was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. Requirement for informed consent was waived by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University, because of the retrospective nature of the study.

Availability of data and material

The datasets used and/or analyzed in the study are available from the corresponding author upon reasonable request.

Funding

This study was supported by Project for Guangdong Medical Research Fund(A2021027).

Authors' contributions

CC, LL: conception, design, and execution of experiments; data analysis; table preparation; manuscript writing–drafts, review, and approval of final draft. TH, WZ, CL: data analysis; table preparation; manuscript writing, review, and approval of final draft. YG: conception and design of experiments; manuscript writing–drafts, review, and approval of final draft. All authors read and approved the final manuscript.

References

1. Sloan DJ, Parris V (2014) Cryptococcal meningitis: epidemiology and therapeutic options. Clin Epidemiol 6: 169–182. doi: 10.2147/CLEP.S38850.
2. Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS (2016) Cryptococcal meningitis: epidemiology, immunology, diagnosis, and therapy. Nat Rev Neurol 13: 13–24. doi: 10.1038/nrneurol.2016.167.
3. Warkentien T, Crum-Cianflone NF (2010) An update on cryptococcosis among HIV-infected persons. Int J STD AIDS 21: 679–684. doi: 10.1258/ijsa.2010.010182.
4. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM (2009) Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS 23: 525–530. doi: 10.1097/QAD.0b013e328322ffac.
5. Pyrgos V, Seitz AE, Steiner CA, Prevots DR, Williamson PR (2013) Epidemiology of cryptococcal meningitis in the US: 1997–2009. PLoS One 8: e56269. doi: 10.1371/journal.pone.0056269.
6. Liu Y, Kang M, Wu SY, Ma Y, Chen ZX, Xie Y, Tang JT (2017) Different characteristics of cryptococcal meningitis between HIV-infected and HIV-uninfected patients in the Southwest of China. Med Mycol 55: 255–261. doi: 10.1093/mmy/myw075.
7. Fang W, Fa Z, Liao W (2015) Epidemiology of *Cryptococcus* and cryptococcosis in China. Fungal Genet Biol 78: 7–15. doi: 10.1016/j.fgb.2014.10.017.
8. Brouwer AE, Siddiqui AA, Kester MI, Sigaloff KCE, Rajanuwong A, Wannapasni S, Chierakul W, Harrison TS (2007) Immune dysfunction in HIV-seronegative, *Cryptococcus gattii* meningitis. J Infect 54: e165–168. doi: 10.1016/j.jinf.2006.10.002.
9. Bicanic T, Harrison TS (2004) Cryptococcal meningitis. Br Med Bull 72: 99–118. doi: 10.1093/bmb/ldh043.
10. Vidal JE, Gerhardt J, Peixoto de Miranda ÉJ, Dauar RF, Oliveira Filho GS, Penalva de Oliveira AC, Boulware DR (2012) Role of quantitative CSF microscopy to predict culture status and outcome in HIV-associated cryptococcal meningitis in a Brazilian cohort. Diagn Microbiol Infect Dis 73: 68–73. doi: 10.1016/j.diagmicrobio.2012.01.014.
11. Liliang P-C, Liang C-L, Chang W-N, Chen H-J, Su T-M, Lu K, Lu C-H (2003) Shunt surgery for hydrocephalus complicating cryptococcal meningitis in human immunodeficiency virus-negative patients. Clin Infect Dis 37: 673–678. doi: 10.1086/377208.
12. Fessler RD, Sobel J, Guyot L, Crane L, Vazquez J, Szuba MJ, Diaz FG (1998) Management of elevated intracranial pressure in patients with cryptococcal meningitis. J Acquir Immune Defic Syndr Hum Retrovirol 17: 137–142. doi: 10.1097/00042560-199802010-00006.
13. De Vedia L, Arechavala A, Calderón MI, Maiolo E, Rodríguez A, Lista N, Di Virgilio E, Cisneros JC, Prieto R (2013) Relevance of intracranial hypertension control in the management of *Cryptococcus neoformans* meningitis related to AIDS. Infection 41: 1073–1077. doi: 10.1007/s15010-013-0538-4.
14. Corti M, Priarone M, Negroni R, Gilardi L, Castrelo J, Arechayala AI, Messina F, Franze O (2014) Ventriculoperitoneal shunts for treating increased intracranial pressure in cryptococcal meningitis with or without ventriculomegaly. Rev Soc Bra Med Trop 47: 524–527. doi: 10.1590/0037-8682-0176-2013.

15. Cherian J, Atmar RL & Gopinath SP (2016) Shunting in cryptococcal meningitis. J Neurosurg 125: 177–186. doi: 10.3171/2015.4.JNS15255.
16. Genebat M, Mayorga-Buiza MJ, Castillo-Ojeda E, Rivero-Garvía M, Márquez-Rivas FJ, Jiménez-Mejías ME (2017) Cryptococcal infection of the ventriculoperitoneal shunt in an HIV-infected patient with an excellent immunovirologic status. World Neurosurg 99: 810.e11–810.e13. doi: 10.1016/j.wneu.2016.12.100.
17. Liu L, Zhang R, Tang Y, Lu H (2014) The use of ventriculoperitoneal shunts for uncontrollable intracranial hypertension in patients with HIV-associated cryptococcal meningitis with or without hydrocephalus. Biosci Trends 8: 327–332. doi: 10.5582/bst.2014.01070.
18. Woodworth GF, McGirt MJ, Williams MA, Rigamonti D (2005) The use of ventriculoperitoneal shunts for uncontrollable intracranial hypertension without ventriculomegally secondary to HIV-associated cryptococcal meningitis. Surg Neurol 63: 529–531. Discussion: 531–532. doi: 10.1016/j.surneu.2004.08.069.
19. Wang H, Ling C, Chen C, He H, Luo L, Ning X (2014) Evaluation of ventriculoperitoneal shunt in the treatment of intracranial hypertension in the patients with cryptococcal meningitis: a report of 12 cases. Clin Neurol Neurosurg 124: 156–160. doi: 10.1016/j.clineuro.2014.07.001.
20. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen M, Pappas PG, Powderly WG, Singh N, Sobel JD, Sorrell TC (2010) Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 50: 291–322. doi: 10.1086/649858.
21. Baddley JW, Thompson GR3rd, Riley KO, Moore MK, Moser SA, Pappas PG (2019) Factors associated with ventriculoperitoneal shunt placement in patients with cryptococcal meningitis. Open Forum Infect Dis 6: z241. doi: 10.1093/ofid/ofz241.
22. Qu J, Zhou T, Zhong C, Deng R, Lü X (2017) Comparison of clinical features and prognostic factors in HIV-negative adults with cryptococcal meningitis and tuberculous meningitis: a retrospective study. BMC Infect. Dis 17: 51. doi: 10.1186/s12879-016-2126-6.
23. Tien RD, Chu PK, Hesselink JR, Duberg A, Wiley C (1991) Intracranial cryptococcosis in immunocompromised patients: CT and MR findings in 29 cases. Am J Neuroradiol 12: 283–289.
24. Paff M, Alexandru-Abrams D, Muhonen M, Loudon W (2018) Ventriculoperitoneal shunt complications: a review. Interdiscip Neurosurg 13: 66–70. doi: 10.1016/j.inat.2018.04.004.
25. Rammos S, Klopfenstein J, Augspurger L, Augsburger L, Wang H, Wagenbach A, Poston J, Lanzino G (2008) Conversion of external ventricular drains to ventriculoperitoneal shunts after aneurysmal subarachnoid hemorrhage: effects of site and protein/red blood cell counts on shunt infection and malfunction. J Neurosurg 109: 1001–1004. doi: 10.3171/JNS.2008.109.12.1001.
26. Singh A, Vajpeyi I (2013) Comparative study of lumboperitoneal shunt versus ventriculoperitoneal shunt in post meningitis communicating hydrocephalus in children. Neurol India 61: 513–516. doi: 10.4103/0028-3886.121932.
27. Lindvall P, Ahlm C, Ericsson M, Gothefors L, Naredi S, Koskinen LD (2004) Reducing intracranial pressure may increase survival among patients with bacterial meningitis. Clin Infect Dis 38: 384–390. doi: 10.1086/380970.
28. Yao ZR, Liao W, Chen R (2005) Management of cryptococcosis in non-HIV-related patients. Med Mycol 43: 245–251. doi: 10.1080/13693780410001731628.

Corresponding author

Ying Guo, PhD
Department of Neurosurgery, The Third Affiliated Hospital,
Sun Yat-Sen University, 600 Tianhe Road, Tianhe District, Guangzhou, China.
Tel: 8615918679290
Fax: 020-85253336
Email: guoy@mail.sysu.edu.cn;

Conflict of interests: No conflict of interests is declared.