International Journal of Infectious Diseases 88 (2019) 102–109

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Efficacy of ventriculoperitoneal shunting in patients with cryptococcal meningitis with intracranial hypertension

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ARTICLE INFO

Article history:
Received 20 May 2019
Received in revised form 14 August 2019
Accepted 31 August 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Cryptococcal meningitis
Ventriculoperitoneal shunting
Intracranial pressure
Cryptococcus count
Ventriculomegaly

ABSTRACT

Background: Ventriculoperitoneal (VP) shunting in cryptococcal meningitis (CM) patients with high intracranial pressure (ICP) has been studied extensively.
Methods: A total of 74 CM patients with ICP were identified, including 27 patients with or without ventriculomegaly receiving VP shunting.
Results: Through retrospective analysis, there was an obvious decline in ICP as well as *Cryptococcus* count after VP shunting. Damage to the cranial nerves was improved after the surgery. For those patients receiving VP shunting, there was an obvious decline in ICP as well as *Cryptococcus* count, with less usage of mannitol. Hydrocephalus or ventriculomegaly was improved, and both the clearance time of *Cryptococcus* and the hospitalization time were shortened ($p < 0.05$). The complications of VP shunting were not common.
Conclusions: For patients diagnosed with CM and with apparent ICP, VP shunting can be considered regardless of whether there is damage to the cranial nerves or hydrocephaly.

Introduction

Cryptococcal meningitis (CM) is the most common type of cryptococcosis, accounting for about 77–80% of all cryptococcal infections (Park et al., 2009; Makadzange and McHugh, 2014; Hoang et al., 2011; Sloan and Parris, 2014; Bratton et al., 2012). The main clinical manifestations of CM include fever and high intracranial pressure (ICP), presenting as headache, nausea, and vomiting. Damage to the cranial nerves may lead to vision loss, mental aberrations, consciousness disorders, and hearing loss (Chen et al., 2008; Liu et al., 2018). Among these, persistent high ICP is the most prominent and most harmful feature. Patients with persistent high ICP will suffer from damage to the cranial nerves, which presents as vision loss and hearing loss. Under some severe conditions, cerebral hernia may occur, which is one of the major reasons for death in CM patients.

The 30- and 90-day mortality of incorrectly managed patients has been reported to be 23.9% and 31.8%, respectively (Qu et al., 2017; Rajasingham et al., 2017). In the clinic, ICP is usually reduced with the use of mannitol, although its dehydration effect is low. Moreover, the long-term use of mannitol may lead to side effects such as headache, dizziness, cardiac insufficiency, and renal tubular dysfunction (Day et al., 2013; Lofgren et al., 2017; YP, 2012). Therefore, in surgical practice, shunting is usually used to reduce ICP.

The management of CM consists of initial antifungal therapy, followed by consolidation and maintenance therapy (Sun et al., 2004). The goal of initial therapy is rapid clearance of the pathogens in the cerebrospinal fluid (CSF). Current guidelines recommend 2 weeks of combination intravenous amphotericin B and oral flucytosine as the initial therapy for the treatment of CM (Perfect et al., 2010a). The early fungicidal activity (EFA) is a quantitative measure for evaluating therapeutic efficacy, defined as the rate of fungal clearance per milliliter of CSF per day (Sun et al., 2004). Bicanic et al. reported that a slow rate of clearance of infection is an independent factor associated with increased mortality at 2 and 10 weeks in HIV-associated CM (Bicanic et al., 2009). The guidelines recommend at least 8 weeks of fluconazole (400–800 mg/day) as consolidation therapy (Perfect et al., 2010a). After successful initial and consolidation therapy, culture-negative

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https://doi.org/10.1016/j.ijid.2019.08.034
1201-9712/

patients should be treated with fluconazole (200 mg/day) as maintenance therapy over the long-term (Perfect et al., 2010a).

Ventriculoperitoneal (VP) shunting has been studied extensively with respect to its efficacy in patients with high ICP with hydrocephalus. Its efficacy is definite and has generally been accepted. Meanwhile, some researchers have proposed the use of VP shunting for ICP alone without hydrocephalus (Aschoff et al., 1999; Katchanov et al., 2016). Common complications associated with VP shunting include infection (fungal infection or other secondary infections), shunt obstruction, and excessive shunting, which has restricted the application of this surgery in the clinic. An increasing number of studies have demonstrated the controllability of complications associated with VP shunting (Corti et al., 2014; Sakellaridis et al., 2011; Kim et al., 2014).

The cases recruited in the present study were those receiving VP shunting with or without ventriculomegaly. The purpose was to compare the clinical manifestations, ICP, variation in *Cryptococcus* count, damage to the cranial nerves, duration of hospital stay, and mannitol dose between the VP shunt group and the non-VP shunt group, and also before and after surgery for each group. The efficacy of VP shunting was evaluated for patients with CM combined with high ICP, so as to provide a reference for clinical treatment.

Methods and data

Subjects

The analysis was performed retrospectively. A total of 112 cases diagnosed with CM from December 2008 to December 2018 at the Third Affiliated Hospital of Sun Yat-sen University were recruited. Diagnostic criteria for CM were as follows: clinical manifestations of CM with the growth of *Cryptococcus neoformans* in CSF culture or positive for India ink staining of CSF smear (Chen et al., 2011). The present study strictly conformed to the Declaration of Helsinki (1975). Informed consent was signed by all patients. The protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University.

Inclusion criteria were CM diagnosed during hospital stay and ICP above 250 mmH_2O. Exclusion criteria were combined with other central nervous system infections, AIDS, patients receiving other drainage procedures or already carrying the drainage device before admission (Figure 1).

Methods

Based on the above criteria, 74 cases were finally included. Depending on VP shunting or not, the cases were divided into a VP shunt group ($n = 27$) and a non-VP shunt group ($n = 47$). Clinical features of the two groups were compared. Comparisons were also performed within the same group before and after surgery.

Comparison between VP shunt group and non-VP shunt group

The results showed that the average interval from the onset of symptoms to hospitalization was 4 weeks in all cases. Patients in the VP shunt group underwent surgery at an average of 8 weeks after the onset of symptoms. In order to unify the time points of observation, the week that the patients in the non-VP shunt group were admitted to hospital was defined as week 0. For the VP shunt group, the time of surgery was taken as the reference; i.e. 4 weeks before surgery was considered week 0 in all cases. Changes in clinical indicators were observed for all patients at nine time points: week 0, 1, 2, 4, 8, 12, 16, 20, and 24. The primary observation indicators were (1) the variation tendency of ICP; (2) the variation in *Cryptococcus* count; (3) damage to the vision and hearing nerves and outcomes; and (4) hospital stay. Secondary observation indicators were (1) clinical manifestations: state of consciousness, with or without fever, headache, and vomiting upon admission; (2) CSF test: protein levels and white blood cell count; (3) radiological examination: with or without ventriculomegaly, hydrocephalus, and other conditions; and (4) complications and outcomes.

Comparison before and after VP shunting

First, the reasons for patients in the VP shunt group undergoing surgery were analyzed, and then the indicators were compared before and after VP shunting. Nine observation time points were set up, namely week 4, 2, and 1 before surgery and week 1, 2, 4, 8, and 12 after surgery. The primary observation indicators were (1) variation in ICP; (2) variation in *Cryptococcus* count; (3) excessive shunting, secondary infection, shunt obstruction, and other complications. As a secondary observation indicator, the variation in mannitol dose was assessed.

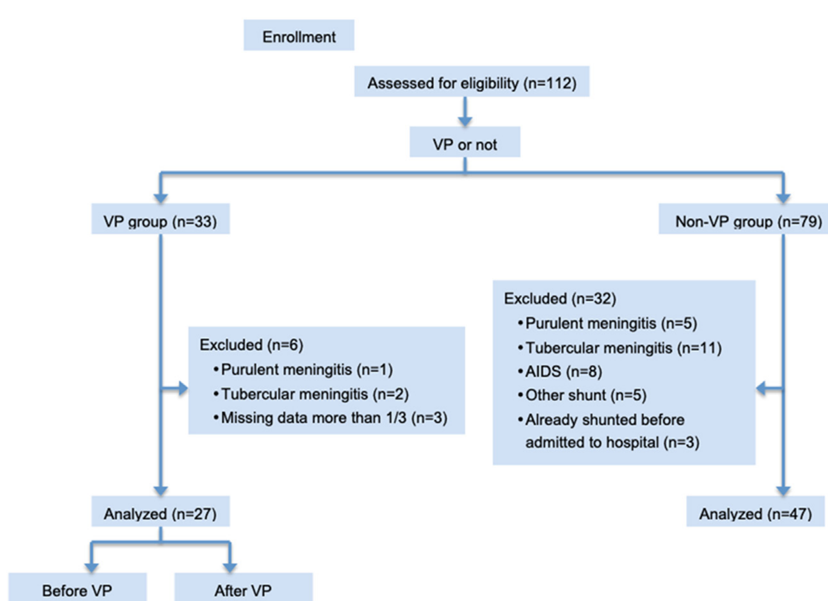

Figure 1. Inclusion and exclusion criteria for cases in the VP shunt group and non-VP shunt group.

Other treatments

All recruited patients were given antifungal therapy. Patients with fever were given physical cooling or antipyretic drugs, and some could also be given hormones for antipyretic treatment. Those with symptoms of high ICP, including headache and vomiting, were given mannitol, hypertonic glucose, or furosemide for dehydration, in addition to anti-emetic treatment.

Efficacy evaluation criteria

Cure was defined as the disappearance of clinical symptoms and signs. Symptom improvement was defined as follows: for restricted eyeball abduction, 'cured' was defined as the symptom of restricted eyeball abduction (unilateral/bilateral) disappearing after VP shunting. For vision loss, 'cured' was defined as the symptom of vision loss disappearing after VP shunting; 'improved' was defined as a decrease in the extent of symptoms (from bilateral to unilateral) or alleviation of the severity of symptoms (from light perception to vision loss). For hearing loss, 'cured' was defined as the symptom of hearing loss disappearing after VP shunting; 'improved' was defined as a decrease in the extent of symptoms (from bilateral to unilateral). for vision and hearing loss, 'cured' was defined as the symptoms of vision loss and hearing loss disappearing after VP shunting; 'improved' was defined as improvements in one or both symptoms of vision loss and hearing loss. For hydrocephalus and ventriculomegaly, 'improved' was defined as the alleviation of the severity of symptoms of hydrocephalus and ventriculomegaly based on imaging findings (from severe to moderate or from moderate to mild).

The patients received CSF smear testing once every 7 days. They were considered 'cured' if the result was negative on three consecutive occasions. 'Improved' was considered an alleviation of clinical symptoms and signs. In the event that *Cryptococcus* was found in every test, this was considered 'deteriorating – the clinical symptoms and signs were aggravated.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA). The clinical and biochemical indicators were expressed as the mean ± standard deviation (SD), or as the median and interquartile range (IQR) regarding the normality assumption. The two groups were compared in terms of age, clinical manifestations, white blood cell counts, neutrophil counts, and protein levels in the CSF by *t*-test. Sex, complications, and prognosis were compared between the two groups by Chi-square test or Fisher's exact test. The *Cryptococcus* count in the CSF ($\log_{10}$ transformed), ICP and *Cryptococcus* count before and after surgery, and hospital stay were compared between the two groups by Mann–Whitney *U*-test. The ICP of the two groups was compared by repeated-measures analysis of variance (ANOVA). The type I error of multiple comparisons was corrected using Sidak's method. A *p*-value of <0.05 (two-tailed) indicated a significant difference.

Results

Baseline patient information

Of the 74 patients, 27 received VP shunting, including 19 male patients and eight female patients; their mean age was 36.150 ± 11.400 years. Forty-seven patients did not receive VP shunting, including 30 male patients and 17 female patients; their mean age was 40.770 ± 12.830 years. The patients had clinical manifestations of fever, headache, vomiting, and disturbance of consciousness. Most of them were positive for signs of meningeal irritation (94.59%, 70/74) and some were positive for pathological signs (21.62%, 16/74). The two groups did not differ significantly in these indicators ($p > 0.05$).

All of the patients had a significant increase in ICP. The maximum ICP in the VP shunt group fluctuated within the range of 300–1020 mmH_2O. For the non-VP shunt group, maximum ICP fluctuated within the range of 300–1070 mmH_2O within the first 1 month after admission. Upon admission, the ICP of the VP shunt group was 348.82 ± 95.23 mmH_2O compared to 324.70 ± 64.00 mmH_2O in the non-VP shunt group, indicating no significant difference between the two groups ($p > 0.05$).

There was vision loss in 27 cases (36.49%), hearing loss in five cases (6.76%), and a combination of vision and hearing loss in 27 cases (36.5%). There was no significant difference between the two groups. There was also no significant difference in concomitant diseases such as diabetes, hypertension, coronary heart disease, cerebrovascular diseases, malignancies, liver fibrosis, and systemic lupus erythematosus (Table 1).

Reasons for receiving surgery in the VP shunt group were as follows: combined hydrocephalus or ventriculomegaly as detected by head computed tomography (CT) or magnetic resonance imaging (MRI) (eight cases); already having apparent damage to the cranial nerves (vision loss, hearing loss, and consciousness disorder) complicated by high ICP upon admission (13 cases), with five cases having hydrocephalus or ventriculomegaly; still having high ICP after antifungal therapy, with ICP above 330 mmH_2O in at least three measurements (eight cases); presenting with cerebral hernia or precursor to hernia or epileptic seizures during the disease (three cases). Patients with persistently high ICP or vision loss, hearing loss, and a consciousness disorder despite internal medicine treatment (their relatives agreed to treatment) would receive VP shunting after excluding surgical contraindications. Those with persistently high ICP but no vision loss, hearing loss, and consciousness disorder and those whose relatives refused surgery would receive internal medicine treatment (Table 2).

Comparison of ICP between patients receiving VP shunting and those not receiving VP shunting

Changes in ICP between patients receiving and those not receiving VP shunting are shown in Figure 2A and in **Supplementary Material** Table S1. It can be seen that ICP decreased significantly in patients receiving VP shunting ($p < 0.01$).

Comparison of Cryptococcus *count between the VP shunt group and the non-VP shunt group*

Changes in *Cryptococcus* count in the VP shunt group and non-VP shunt group are shown in Figure 2A. Regarding the preoperative *Cryptococcus* count, it was higher in the VP shunt group than in the non-VP shunt group ($p < 0.05$). However, the postoperative *Cryptococcus* count did not differ significantly between the two groups ($p > 0.05$).

Changes in ICP, Cryptococcus *count, and mannitol dose before and after surgery for the VP shunt group*

Changes in ICP, *Cryptococcus* count, and mannitol dose before and after surgery in the 27 patients receiving VP shunting are shown in Figure 2B and in **Supplementary Material** Table S2. After surgery, there was a significant decrease in ICP, *Cryptococcus* count, and mannitol dose in the VP shunt group ($p < 0.05$).

Table 1
Baseline characteristics of cases in the VP and non-VP groups.

	VP group	Non-VP group	*p*-Value
Number	27	47	
Male/female	19/8	30/17	0.618
Age, years (mean ± SD)	36.150 ± 11.400	40.770 ± 12.830	0.732
Clinical manifestations			
Disturbance of consciousness, *n* (%)	6 (22)	5 (11)	0.178
Fever, *n* (%)	13 (48)	22 (47)	0.912
Vomiting, *n* (%)	12 (44)	12 (26)	0.094
Headache, *n* (%)	25 (93)	45 (96)	0.965
Meningeal irritation sign, *n* (%)	25 (93)	43 (91)	1.000
Babinski sign, *n* (%)	7 (26)	9 (19)	0.495
Vision loss (*n*)	10	17	0.941
Hearing loss (*n*)	1	4	0.428
Hearing and vision loss (*n*)	8	19	0.353
Cerebrospinal fluid (mean ± SD)			
White blood cells (10^6/l)	174.780 ± 57.090	144.940 ± 21.900	0.417
Neutrophils (10^6/l)	99.410 ± 52.480	43.210 ± 11.940	0.286
Albumin (g/l)	0.560 ± 0.060	0.690 ± 0.060	0.159
Underlying diseases			
Diabetes (*n*)	2	4	0.867
Hypertension (*n*)	3	6	0.791
Coronary heart disease (*n*)	0	1	0.445
Cerebrovascular disease (*n*)	2	2	0.564
Malignant tumors (*n*)	3	2	0.258
Liver cirrhosis (*n*)	1	1	0.687
Systemic lupus erythematosus (*n*)	1	1	0.687

VP, ventriculoperitoneal shunt; SD, standard deviation.

Table 2
Demographic and clinical features of VP patients.

No.	Age/sex	Neurological deficit[a]		Antifungal therapy[b]	Hospital days	Time[c]			Outcome		Sequelae[a]	Surgical complication[d]
		Before VP	After VP			S	O	R	1 month	Final		
1	51/M	H, VL	H, VL	AMB + 5FC, Fluc + 5FC	60	0.5	54	1	Better	Cure	NA	–
2	17/M	LOC, H, V	LOC, H, V	AMB + 5FC + Fluc	120	4	104	1	Better	Cure	NA	–
3	61/F	LOC, H	LOC, H	Fluc, VOR	120	3	36	>6	Better	Cure	NA	–
4	40/M	LOC, H, V, VL	LOC, V, VL	Fluc + 5FC + AMB	180	1	72	2	Better	Better	NA	TRI, IP
5	56/F	H, V	H, V	5FC + Fluc	64	0.5	56	>6	Better	Cure	NA	IP, STS
6	37/M	H, VL, HL	H, VL	AMB + 5FC + Fluc	122	2	109	1	Better	Cure	VL, HL	STS
7	25/M	H, V	H, V	Fluc + 5FC, AMB + 5FC, Fluc + 5FC	32	1	23	>6	Better	Cure	NA	IP
8	38/M	H, V, VL	V, VL	AMB + 5FC + Fluc	79	2	33	1	Better	Cure	NA	SE
9	27/F	V, HL	V	Fluc + 5FC, AMB + 5FC	43	1	34	1	Better	Better	NA	SE
10	28/M	H, V, VL	NA	Fluc + 5FC	113	1	97	>6	Worse	Cure	VL	STS, PAF
11	40/M	H, V, VL, HL	H, V, VL	Fluc + 5FC, AMB + 5FC + Fluc	98	1.5	65	>6	Better	Cure	NA	–
12	22/M	H, LOC	H, LOC	Fluc + 5FC, AMB + 5FC, VOR + 5FC	93	4	80	>6	Better	Cure	NA	IP
13	45/F	H, LOC, VL, HL	NA	Fluc + 5FC, AMB + 5FC	45	1	41	NA	Worse	NA	VL, HL, LOC	STS
14	49/M	H	H	Fluc + 5FC	70	1	57	2	Better	Better	NA	–
15	26/F	H, VL, HL	H, VL, HL	Fluc + 5FC, AMB + 5FC + Fluc	75	1	56	>6	Better	Better	VL	STS
16	47/M	H, V	H, V	AMB + 5FC + Fluc	54	1	40	1	Better	Better	NA	–
17	44/M	H, V, VL	H, V	Fluc + 5FC, AMB + 5FC	111	0.5	106	>6	Better	Cure	NA	STS, SE
18	38/F	H, VL	H	AMB + 5FC, Fluc	33	1	29	>6	Better	Cure	VL	IP, STS, SE
19	23/M	VL, HL	NA	Fluc + 5FC	40	2	37	3	Worse	NA	VL	–
20	41/M	H	H	Fluc + 5FC	10	2	8	>6	Better	Better	VL	–
21	35/M	H, V, VL	H, V	Fluc + 5FC	273	3	199	>6	Better	Cure	VL	STS
22	23/M	H	H	AMB + 5FC + Fluc	313	0.5	34	>6	Better	Better	NA	–
23	27/M	H, VL	H	Fluc + 5FC	204	1	150	>6	Better	Cure	VL	–
24	40/F	H, VL, HL	H	Fluc + 5FC	226	1	140	>6	Better	Worse	VL	STS
25	42/M	H, VL, HL	H, VL	Fluc + 5FC	73	1	59	>6	Better	Better	VL	AFAT, IP, STS
26	21/F	H, V, VL	H, V, VL	Fluc + 5FC	44	1	36	2	Better	Better	NA	–
27	33/M	H, V, VL, HL	H, V	AMB + 5FC + Fluc	25	1.5	7	3	Better	Better	NA	–

VP, ventriculoperitoneal shunt; M, male; F, female; NA, not applicable.
[a] H, headache; V, vomiting; VL, vision loss; HL, hearing loss; LOC, loss of consciousness.
[b] 5FC, flucytosine; Fluc, fluconazole; AMB, amphotericin B; VOR, voriconazole.
[c] Time: S, time from diagnosis to shunt (months); O, time from VP to outpatient (days); R, time to removing drainage tube after VP (months).
[d] TRI, tube-related infection; IP, intracranial pneumatosis; STS, soft tissue swelling; SE, subscalp effusion; PAF, postoperative absorption fever; AFAT, abscess formation around tube.

Postoperative improvement in cranial nerve damage and radiological findings in the VP shunt group

CM patients usually have concomitant cranial nerve damage, resulting in vision loss and hearing loss, as well as restricted eyeball abduction. The mechanism may be related to arachnoid membrane adhesion, hydrocephalus (Mohan et al., 2012; Liliang et al., 2003; Petrou et al., 2012), and papilledema caused by high ICP. For these patients, VP shunting may be effective at achieving a reversible recovery of consciousness, vision, and hearing, as

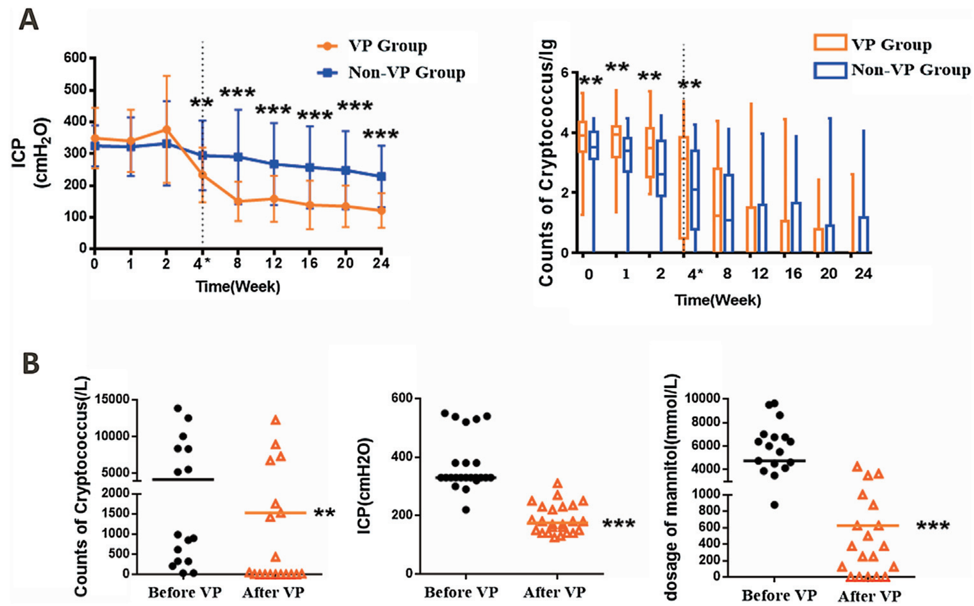

Figure 2. Comparison between the VP shunt group and non-VP shunt group (A), and between before and after surgery in the VP shunt group (B). (A) Comparison of intracranial pressure (ICP) and *Cryptococcus* counts in the VP and non-VP groups. 4* indicates the time of surgery for the VP shunt group; for the VP shunt group, the time of surgery was taken as the reference point, i.e. 4 weeks before surgery was considered week 0 in all cases. The week that the patients in the non-VP shunt group were hospitalized was week 0 for the non-VP shunt group. (B) Comparison of ICP, *Cryptococcus* count, and mannitol dose at 1 week before and after surgery in the VP shunt group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

demonstrated in the present study (Petrou et al., 2012; Chan et al., 1989; Park et al., 1999; Perfect et al., 2010b). After VP shunting, restricted eyeball abduction, vision and hearing loss, hydrocephalus, and ventriculomegaly were significantly improved. This indicates that VP shunting is important for reducing damage to hearing, vision, and the abducens nerves (see Figure 3 and Table 3).

Hospital stay

The overall mean length of hospital stay was 62.79 days in the VP shunt group compared to 73.52 days in the non-VP shunt group (Table 2).

Since the length of hospital stay did not conform to a normal distribution, the rank-sum test was used; $p = 0.016$ (<0.05), indicating a significant difference. The length of hospital stay was shorter in the VP shunt group than in the non-VP shunt group (Table 2).

Associated complications

Of the 27 patients receiving VP shunting, one had a catheter-related infection, one had abscess formation beside the drainage tube, six had intracranial pneumatosis, five had soft tissue swelling, one had postoperative absorption fever, and four had subscalp/subdural effusion. None of the patients had a shunt obstruction or other complications caused by excessive shunting. All of the complications mentioned above improved significantly within 1 week of symptomatic treatment and had disappeared completely within 2 weeks (Table 2).

Discussion

At present, even with effective pathogen-directed therapy, CM is still a refractory disease with a long course and poor prognosis. Persistent and uncorrectable high ICP and associated complications are the primary reasons for failed treatment and a poor prognosis. Therefore, the effective control of high ICP is crucial for a good prognosis (Petrou et al., 2012; Wang et al., 2014).

In this study, focus was placed on CM patients with ICP. It has been shown that elevated ICP can lead to early death (Van der Horst et al., 1997) and vision loss (Denning et al., 1991) in patients with HIV-associated CM. In addition, elevated ICP can result in increased mortality and morbidity in patients with HIV-associated CM (Fessler et al., 1998). Frequent lumbar punctures have been advocated for the management of increased ICP (Graybill et al., 2000). Sun et al. reported that the use of lumbar puncture for the management of elevated ICP can reduce the risk of early mortality and late morbidity (Sun et al., 2004). Conventional dehydration in internal medicine and drainage in surgery are commonly used to control high ICP. Conventional dehydration in internal medicine has the problems of limited efficacy and potential renal damage.

So far, no consensus has been reached as to the surgical indications for VP shunting for CM patients with high ICP (Park et al., 1999). While the opinions are more uniform concerning the use of VP shunting for patients with concomitant hydrocephalus, many CM patients do not have concomitant hydrocephalus or ventriculomegaly in the clinic. For CM patients with high ICP (with or without cranial nerve damage), the recommendation of the Infectious Diseases Society of America is that repeated lumbar puncture should first be attempted and that VP shunting can be considered if the effect is poor (Perfect et al., 2010b). Whether VP shunting should be performed early for such patients is worthy of discussion, and this is also the topic of the present study. Here VP shunting was performed to control high ICP. It was found that ICP decreased significantly after surgery compared to before for the VP shunt group, and the decrease was faster compared with the non-VP shunt group. VP shunting for patients with high ICP (with or without ventriculomegaly and hydrocephalus) can directly lower ICP, reduce postoperative mannitol use, shorten the length of hospital stay, and improve the overall prognosis.

In addition to high ICP, CM patients may also show a significant increase in *Cryptococcus* count in the CSF. Persistent high ICP may be caused by massive proliferation of *Cryptococcus* in the brain; the large amount of capsular polysaccharides produced blocks the normal circulation of the CSF (Wang et al., 2014; Mohan et al., 2006). Pathogen-directed therapy has proven effective and

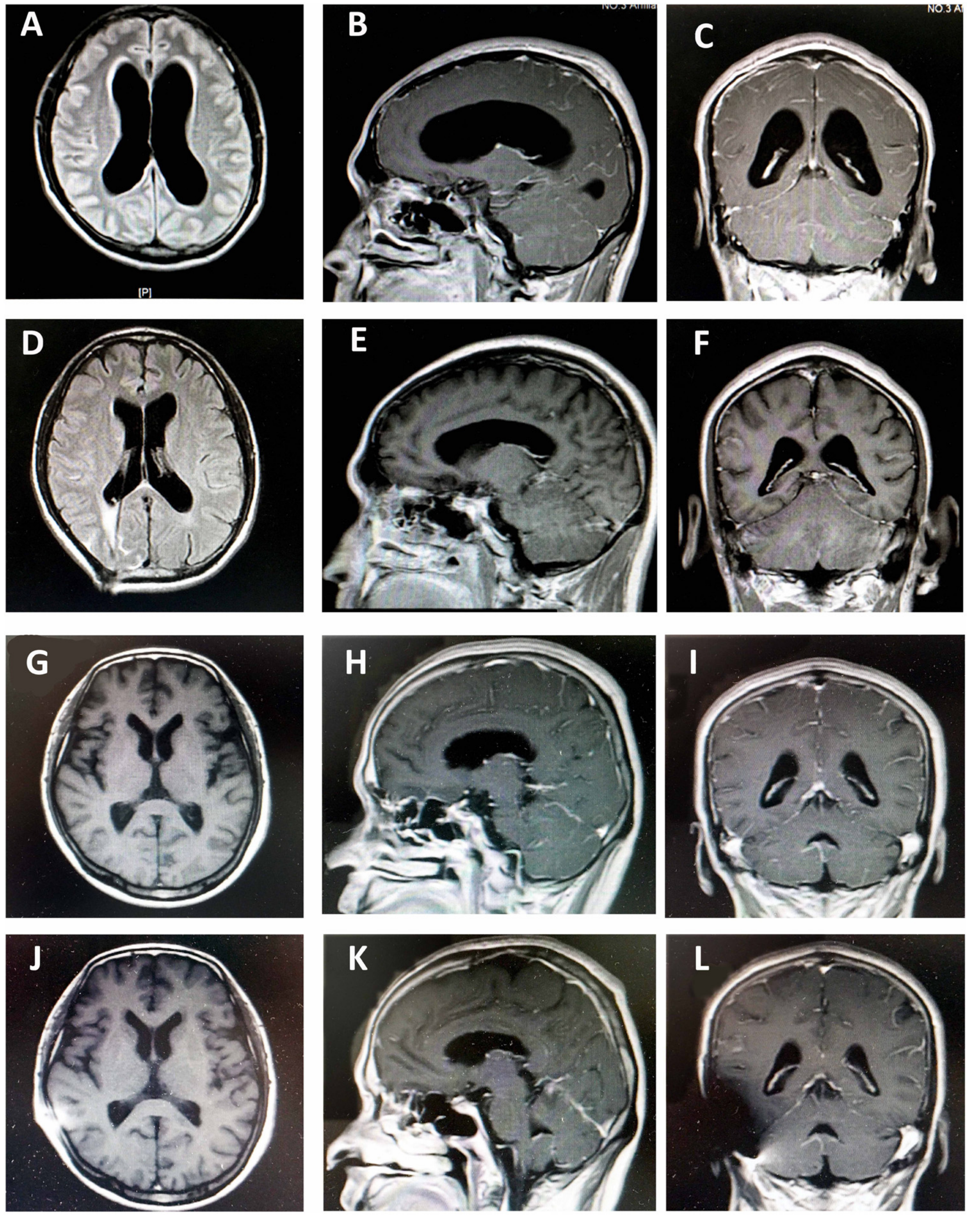

Figure 3. Preoperative and postoperative MRI of the head for a 28-year-old CM patient with ventriculomegaly and a 48-year-old CM patient without ventriculomegaly. The preoperative MRI of the CM patient with high ICP indicated ventriculomegaly (A, horizontal; B, sagittal; C, coronal); the postoperative MRI indicated no ventriculomegaly and ventricular narrowing (D, horizontal; E, sagittal; F, coronal). The preoperative MRI of the CM patient with normal ICP (G, horizontal; H, sagittal; I, coronal); the postoperative CT of the CM patient with normal ICP (J, horizontal; K, sagittal; L, coronal).

Table 3
Outcomes of cranial nerves, hydrocephalus, and ventriculomegaly after the operation in the VP group.

	Cured (n)	Improved (n)	No improvement (n)	Total (n)	Improvement rate (%)
Cranial nerves Abduction dysfunction	2	0	1	3	66.70
Vision loss	6	3	1	10	90.00
Hearing loss	0	1	0	1	100.00
Vision and hearing loss	4	3	1	8	87.50
Total	12	7	3	22	86.36
Hydrocephalus	/	4	2	6	66.7
Ventriculomegaly	/	2	1	3	66.7

VP, ventriculoperitoneal shunt.

necessary, but long-term treatment may bring about many side effects. Moreover, CM patients are usually immunocompromised and may be intolerant to treatment. It was also observed that there was a significant reduction in *Cryptococcus* count after VP shunting ($p < 0.05$). The reason may be that the original CSF was partially drained into the abdominal cavity, resulting in a reduced amount of intracranial CSF and lower ICP. With VP shunting, a large number of *Cryptococcus* are drained into the peritoneal cavity, where conditions are less favorable for the proliferation of *Cryptococcus* (Liu et al., 2013). Meanwhile, the antifungal drugs pass more easily through the blood–peritoneal barrier than through the blood–brain barrier, and thus it is easier to achieve an effective concentration (Huang et al., 2012). There are more powerful phagocytes and immunological function in the peritoneal cavity than in the cranium (Charlier et al., 2009). For this reason, the *Cryptococcus* drained into the peritoneal cavity will find it more difficult to survive. VP shunting can significantly reduce the *Cryptococcus* count in the intracranial CSF within a short time, thereby improving the efficiency of pathogen-directed therapy. Furthermore, as the burden of *Cryptococcus* lowers, the overall condition of the patient will also improve, thus making the patient more tolerant to the antifungal therapy.

CM patients usually present cranial nerve damage, resulting in vision loss and hearing loss, as well as restricted eyeball abduction. The mechanism may be related to arachnoid membrane adhesion, hydrocephalus, and papilledema caused by high ICP. For these patients, VP shunting may be effective for achieving a reversible recovery of consciousness, vision, and hearing, as demonstrated in the present study (Portelinha et al., 2014; Liu et al., 2014; Govender et al., 2013; McGirt et al., 2003).

Common complications associated with VP shunting include infection (fungal infection or other secondary infections), shunt obstruction, and excessive shunting. Proper placement and immobilization of the shunt may reduce the risk of shunt obstruction. However, once obstruction occurs, it may be necessary to adjust the shunt position or replace it with a new one. Postoperative monitoring of protein levels in the CSF is highly important, and shunt obstruction may occur if the protein levels are too high. CM patients usually have low anti-infective ability. Intraoperative procedures performed under less strict sterile conditions and placement of the shunt as a foreign body may be the causes of postoperative infection. In order to reduce the risk of postoperative infection, antibiotics can be used preoperatively as a prophylactic measure and all intraoperative procedures should be performed under strict sterile conditions. In addition, the surgeons should improve their operative skills and reduce surgical trauma. Once postoperative infection occurs, the drainage tube should be removed early, and other anti-infective measures should be taken (McGirt et al., 2003). After the infection is completely controlled, secondary surgery can be performed, with placement of the shunt in a new position. Excessive shunting may cause headache due to low ICP. Lumbar puncture should be performed regularly to monitor ICP and adjustments should be made accordingly to achieve the appropriate ICP (Liu et al., 2014; McGovern et al., 2014; Liliang et al., 2002). In the present study, the procedure-associated complications basically disappeared within 2 weeks after symptomatic treatment.

Based on the research findings, we recommend VP shunting for CM patients with high ICP, a high *Cryptococcus* count in the CSF, and cranial nerve damage. This procedure has proven to be safe and effective.

However, the present study had a small sample size, and more cases will be included in future studies.

Author contributions

Y.L. carried out the statistical analyses. X.P. collected the tissue specimens and patient information. W.W. participated in collecting patient information. J.Z. drafted the manuscript. H.C. edited the manuscript. S.X. supervised the project, conceived the study, and wrote and guided the editing of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

All data and materials are well documented.

Ethical approval and consent to participate

There is no issue about ethics approval and consent to participate in the study. Informed consent was signed by all patients. The protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University.

Consent for publication

All authors have read and approved the article and declare no potential conflicts of interest in the paper.

Funding

This work was funded by the Natural Science Foundation of Guangdong Province (No. 2017A030313620), the National Natural Science Foundation of China (No. 81802536) and Sun yat-sen Youth Training Teacher Project (F320193161004).

Conflict of interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.08.034.

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