Original Article

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The use of ventriculoperitoneal shunts for uncontrollable intracranial hypertension in patients with HIV-associated cryptococcal meningitis with or without hydrocephalus

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Summary **Extremely elevated intracranial pressure (ICP) in patients with HIV and cryptococcal meningitis is a poor prognostic predictor of death during initial therapy. The risks associated with implanting a cerebrospinal fluid (CSF) shunt into immunocompromised patients with ongoing CSF infection have historically discouraged surgeons from implanting CSF shunts in patients with HIV and cryptococcal meningitis. An unanswered question is whether ventriculoperitoneal (VP) shunts can effectively provide long-term treatment for patients with intracranial hypertension and HIV-associated cryptococcal meningitis in China. Outcomes for 9 patients with HIV-associated cryptococcal meningitis who were given VP shunts for increased ICP were retrospectively analyzed. Each patient's age, sex, clinical manifestations, CD4+ lymphocyte count, HIV viral load, neurological status, CSF features, image findings, anad other opportunistic infections were recorded for analysis. All patients had signs and symptoms of increased ICP, including headaches, nausea, and vomiting. Seven patients (77.78%) had visual loss due to persistent papilledema. The median time from diagnosis of cryptococcal meningitis to VP shunting in the 9 patients was 5 months (range 0.5-12.5 months). Seven patients (77.78%) had good outcomes, with recovery from 1 month to 48 months. Two patients had poor outcomes; one died six months after shunting due to severe adverse reactions to antiretroviral drugs, and the other died two weeks after surgery. Patients with intracranial hypertension and HIV-associated cryptococcal meningitis who cannot tolerate cessation of external lumbar CSF drainage or frequent lumbar punctures may be eligible for VP shunt placement, despite severe immunosuppression and persistent CSF cryptococcal infection.**

Keywords: Intracranial pressure, ventriculoperitoneal shunts, HIV, cryptococcal meningitis

1. Introduction

Cryptococcal meningitis is the most common life threatening fungal infection and the most common neurological complication in patients with HIV (*1,2*). After *Pneumocystis jirovecii* pneumonia (PCP) and tuberculosis, cryptococcal meningitis is the third leading cause of death in patients with HIV in Shanghai. Despite the advent of new antifungal drugs and modern imaging techniques, the mortality and morbidity of HIV-associated cryptococcal meningitis remain high. Persistently increased intracranial pressure (ICP) is the most accurate predictor of poor prognosis in patients with HIV-associated cryptococcal meningitis (*3-5*), which can cause deterioration of neurological status and mental acuity and impairment of vision (*6*). Although serial high-volume lumbar puncture remains the standard of care for *Cryptococcus*-associated intracranial hypertension, some patients cannot tolerate intermittent cerebrospinal fluid (CSF) drainage. Additionally, the risk

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of brain herniation caused by frequent lumbar punctures for elevated ICP has been a major concern among clinicians (*7*). Cerebrospinal fluid shunts may allow patients with HIV who have intracranial hypertension to leave the hospital with sustained alleviation of symptoms. The risk of shunt infection in the context of severe immune-suppression, shunt obstruction by elevated CSF protein, and peritoneal *Cryptococcus* seeding from direct transport of infected fluid has historically discouraged surgeons from implanting CSF shunts in patients with HIV and cryptococcal meningitis. However, several cases of ventriculoperitoneal (VP) shunt placement in HIV-infected patients with elevated ICP and cryptococcal meningitis have been reported (*8*), and most of these cases succeeded in long-term symptomatic improvement (*9*). However, no such cases have been reported in China. The question remains whether VP shunts can effectively provide long-term treatment for patients with intracranial hypertension and HIV-associated cryptococcal meningitis in China.

Reported here are 9 HIV-infected patients with extremely elevated ICP and active cryptococcal meningitis who were successfully treated with VP shunts. One patient has been treated for almost 4 years without complications. In contrast, two patients died after surgery. Nonetheless, the key task is to determine the effectiveness and safety of VP shunts in HIV-infected patients with cryptococcal meningitis.

2. Patients and Methods

2.1. *Patients*

During a period of 5 years (2009-2013), 90 HIV-infected patients with cryptococcal meningitis were identified at Shanghai Public Health Clinical Center. Of these patients, 9 were treated with VP shunts.

HIV infection was defined as a positive result on a screening test and confirmation of the presence of antibodies to HIV. Cryptococcal meningitis was defined as isolation of *Cryptococcus neoformans* from ≥ 1 CSF culture, a positive CSF cryptococcal antigen titer, or positive results of CSF India ink studies. Hydrocephalus was diagnosed based on the presence of a dilated temporal horn of the lateral ventricle, without obvious brain atrophy on the initial and/or follow-up CT or MRI. To avoid interference in statistical results, the exclusion criteria for this study were as follows: (*i*) evidence of concomitant acute meningitis not due to *C. neoformans*, (*ii*) lack of follow-up data on antifungal treatment, (*iii*) presence of recurrence of cryptococcal meningitis, and (*iv*) neurological deficits due to previous head injury, cerebral infarction, or intracranial hemorrhage.

2.2. *Data collection*

This retrospective study was approved by the ethics committee of Shanghai Public Health Clinical Center. All patient records were anonymous and a de-identified ID number was used prior to analysis.

For each patient, the age, sex, clinical manifestations, CD4+ lymphocyte count, HIV viral load, neurological status, CSF features, image findings, and presence of other opportunistic infections were all recorded for analysis.

2.3. *CSF opening pressure*

The CSF opening pressure measured *via* a lumbar puncture was recorded.

2.4. *CSF analysis*

Samples of CSF obtained *via* a lumbar puncture were sent to the laboratory for cell analysis and determination of glucose and protein levels before and after VP shunting.

2.5. *Treatment*

Antifungal regimens including amphotericin B plus flucytosine and voriconazole were added in the first 2 weeks of treatment. Patients with increased ICP were given intravenous mannitol or underwent repeated lumbar punctures. If there was further deterioration of neurological status, decreased mental acuity, or impaired vision due to increased pressure, the patient was transferred to Neurosurgery for surgery. Eight patients were treated with a VP shunt (Medtronic system). All patients underwent antiretroviral therapy (ART) after 2 to 4 weeks of antifungal treatment. Only one patient was ART- naïve when undergoing VP shunting.

2.6. *Therapeutic outcome*

Therapeutic outcomes 1, 3, 6, and 12 months after placement of the VP shunt were determined based on the results of CSF analysis and relief of clinical symptoms. Asymptomatic status, mild disability, and moderate disability were considered to be favorable outcomes. Major disability, vegetative status, and death were considered to be poor outcomes. Some patients were followed-up in the Outpatient department after discharge from hospital, and others were interviewed by telephone to determine their neurological outcomes.

3. Results

The general characteristics of the 9 patients after admittance to the hospital are shown in Table 1. All patients were in the late stage of AIDS with very low CD4+ T lymphocyte levels and a very high plasma HIV viral load. When cryptococcal meningitis was

Table 1. Clinical characteristics of patients upon admission

Patient	Age/sex	CD4 count (cells/μL)	HIV viral load (copies/mL)	CSF pressure (cm H_2O)	CSF protein (mg/L)	CSF glucose (mmol/L)	Symptom	CT/MRI scan findings	Anti-fung. therapy
1	31/M	2	ND	> 400	171	3.5	FE, HA, N/V	No	Amph B,5-FC,Fluc
2	38/M	1	581000	> 400	228	3.64	FE, HA, N/V	No	Amph B,5-FC,Fluc
3	23/M	11	110000	> 400	85	2.33	HA, N/V, CO	No	Amph B,5-FC,Fluc
4	30/M	9	62700	> 400	57	3.36	HA	No	Amph B,5-FC,Fluc
5	35/M	15	30800	> 400	342	2.6	HA, N/V, LOC	No	Amph B,5-FC,Fluc
6	28/M	4	251000	> 400	86	2.89	HA, VL, CO, DEM	No	Amph B,5-FC,Fluc
7	34/M	32	98300	> 400	257	2.09	HA, VL	No	Amph B,5-FC,Fluc
8	43/M	12	969000	> 400	114	2.47	HA, N/V, LOC	No	Amph B,5-FC,Fluc
9	28/M	7	1310000	> 400	257	3	HA, N/V	No	Amph B,5-FC,Fluc

LOC indicates loss of consciousness; FE, fever; HA, headaches; N/V, nausea and vomiting; VL, visual loss; CO, convulsions; DEM, impaired eye movement; Amph B, amphotericin B; 5FC, 5-flucytosine; Fluc, fluconazole; ND, not done.

diagnosed, patients received antifungal treatment. All patients had headaches and vomiting, and some presented with other neurological symptoms including visual loss, convulsions, and impaired eye movement (Table 1).

The general characteristics of these patients who underwent shunting and various outcomes are shown in Table 2. After effective treatment, the CSF cultures of 7 patients (7 of 9, 77.78%) tested negative for *Cryptococcus neoformans* when they underwent shunting (Table 2). The other two patients tested positive for *Cryptococcus neoformans* at the time of surgery. Eight patients had received ART before VP shunting, and the median time from ART to surgery was 4.5 months (range 0.5-12.5 months). Notably, 6 of these patients had complete viral suppression (HIV viral load below the test limit, Table 2) when they underwent surgery. The CD4+ lymphocyte count in these patients increased after ART but remained below 100 cells/μL. Two patients had a high HIV viral load at the time of surgery - one was ART-naïve and the other had undergone 0.5 months of ART.

All patients underwent VP shunting because of deteriorating neurological status or loss of consciousness, decreased mental acuity, or vision loss associated with persistently increased ICP. All patients had signs and symptoms of increased ICP including headaches, nausea, and vomiting. Seven patients (77.78%) had visual loss due to persistent papilledema. One of these 7 patients presented with deafness, another with ptosis, and another with impaired eye movement. Five patients (55.56%) had convulsions or a loss of consciousness due to greatly increased ICP. Only 3 patients (33.33%) had hydrocephalus with ventricular dilatation according to brain CT or MRI scans. The median time from diagnosis of cryptococcal meningitis to VP shunting in these 9 patients was 5 months (range 0.5-12.5months).

Two patients underwent anti-tuberculosis therapy at the time of surgery. One patient had been on anti-TB therapy for 5 months and the other for 2 months. Sputum TB cultures for both patients were negative before surgery. One of these two patients died two weeks after surgery.

All patients (100%) had an increased CSF opening pressure (> 400 mm H_2O) over a prolonged period. The cell count, protein levels, and glucose levels of the CSF were all within the normal ranges. The CSF opening pressure returned to normal after shunting in all patients. CSF protein levels were elevated in 5 patients (55.56%), with levels in 4 between 1,000 and 2,000 mg/L. Only one patient had a CSF protein level over 3,000 mg/L, and this patient died two weeks after shunt placement.

Of the 9 patients, 7 (77.78%) had good outcomes with recovery from 1 month to 48 months. The first patient has been treated with VP shunting for almost 4 years without complication. Only two patients had poor outcomes. One died half a year after shunt placement due to severe adverse reactions to antiretroviral drugs, and the other died two weeks after surgery. The CSF protein levels in this patient increased to 3,770 mg/L after surgery. These levels increased again to 13,000 mg/L 2 days later and the cell count was 260 cell/L. The patient experienced a loss of consciousness 7 days after shunt placement and a CT scan revealed hypodense lesions in the basal ganglia and periventricular areas on the left. Infection was clinically diagnosed, so the patient was treated with both antibiotics and anti-TB drugs because the pathogen could not be identified. The shunt became obstructed, and eventually the patient died.

4. Discussion

CSF shunts have been used to manage increased ICP after cryptococcal meningitis in patients with and without HIV (*6,10*). The presumed increase in risk of shunt infection resulting from immunosuppression, shunt obstruction from elevated CSF protein, and peritoneal *Cryptococcus* seeding from direct transport of infected fluid has traditionally discouraged the placement of CSF shunts in patients with HIV and cryptococcal meningitis (*9*). In addition, the historically

Table 2. Clinical characteristics of and outcomes for patients receiving VP shunts for elevated ICP and HIV-associated cryptococcal meningitis with long-term follow-up over 12 months

Patient	Duration of ART before VP shunt (mo)	CD4 count (cells/μL)	HIV viral load (copies/mL)	CSF pressure (cm H_2O)	CSF culture of *Cryptococcus neoformans*	Neuro-deficit	CT/MRI scan findings	Medication for other OI	Time (mo) from diagnosis/ treatment to shunt	Outcome, 1 mo	Outcome, 3 mos	Outcome, 6 mos	Outcome, 12 mos
1	12	90	< 40	> 400	Neg	HA, N/V, LOC, VL, CO	Ventriculomegaly	No	12.5	Recover	Recover	Recover	Recover
2	9	40	< 40	> 400	Neg	HA, N/V, LOC, CO	Ventriculomegaly	No	9.5	Recover	Recover	Recover	*
3	4	27	ND	> 400	Neg	HA, N/V, LOC, VL, CO	Ventriculomegaly	No	5	Recover	Recover	Recover	Recover
4	3	26	< 40	> 400	Neg	HA, N/V, ptosis, CO	NO	No	3.5	Recover	Recover	Recover	Recover
5	3	29	< 40	> 400	Neg	HA, N/V, LOC, VL, deafness	NO	No	3.5	Recover	Recover	Recover	Recover
6	0	4	251000	> 400	Pos	HA, VL, CO, DEM	NO	No	0.5	Recover	Recover	--	--
7	12	76	< 40	> 400	Neg	HA, VL	NO	No	12.5	Recover	Recover	--	--
8	0.5	12	969000	> 400	Pos	HA, N/V, LOC, VL	NO	No	2	**	--	--	--
9	5	27	< 40	> 400	Neg	HA, N/V, VL	NO	No	6.5	Recover	Recover	--	--

LOC indicates loss of consciousness; HC, hydrocephalus; CC, cryptococcoma; HA, headaches; N/V, nausea and vomiting; VL, visual loss; CO, convulsions; DEM, impaired eye movement; Neg, negative; Pos, positive; TB, tuberculosis. * died half a year after shunt placement due to severe adverse reactions to antiretroviral drugs. ** died two weeks after surgery.

poor life expectancy of patients with end-stage HIV/AIDS has caused further questioning of the long-term benefits of VP shunting. Reported here are outcomes for 9 patients with elevated ICP secondary to HIV-associated cryptococcal meningitis. Eight patients were successfully treated with VP shunts for several months without complication, and only one patient died two weeks after surgery. Although 4 patients had CSF protein levels between 1,000 and 2,000 mg/L, and shunt obstruction did not occur. Shunt infection did not occur as a complication despite severely compromised immune function (median CD4 count: 27 cells/μL). Two patients died. One died half a year after shunt placement; death was due to severe adverse reactions to antiretroviral drugs and unrelated to VP shunting. The other patient died two weeks after the surgery because of a severe central nervous system infection. The patient had significantly increased CSF protein levels and an elevated cell count, suggesting infection. The pathogen of infection was unclear. Eventually, the patients died despite receiving antibiotics and anti-TB medications. The cause of death could not be verified because the patient's relatives refused an autopsy. Because the patient was also infected with tuberculosis, tuberculosis was assumed to have disseminated to the central nervous system after surgery because of poor control. The use of VP shunts in patients co-infected with other uncontrolled opportunistic infections should be carefully evaluated.

Among the 7 patients who had good outcomes, 6 had complete HIV viral suppression. One ART-naïve patient who underwent VP shunting only 0.5 month after diagnosis with a very high HIV viral load but also had a very good outcome. No studies have examined whether a high HIV viral load is a factor related to the prognosis for VP shunting in such patients. The suppression of HIV could promote immune reconstitution, protecting patients from other infections after surgery and providing surgeons with protection from HIV infection after possible exposure. The limited sample in the current study precluded determination of whether a high viral load affects prognosis.

VP shunting resolved symptoms for a number of months after surgery. The first patient has been treated with VP shunting for almost 4 years without complication. The median time from diagnosis of cryptococcal meningitis to VP shunting in these 9 patients was 5 months (range: 0.5-12.5 months). The symptoms of decreased mental acuity and impaired vision due to persistently increased ICP resolved soon after VP shunting. Ptosis eventually disappeared, and vision was gradually restored. Woodworth *et a*l. (*9*) reported two patients with intracranial hypertension and HIV-associated cryptococcal meningitis who underwent VP shunting but who were unable to tolerate cessation of external lumbar CSF drainage or frequent lumbar punctures. In these two patients, the time from

when cryptococcal meningitis was diagnosed to when VP shunting was performed was 5 and 0.5 months, respectively. These patients remained asymptomatic for 12 and 16 months after surgery without evidence of shunt infection or malfunction. Two of the current patients underwent surgery with no control of *Cryptococcus neoformans* infection. One had a good outcome, and the other died of infection after surgery. The duration of anti-cryptococcal treatment is not a key factor when choosing VP shunting.

Several factors contributed to the decision to place a VP shunt. Patients had a typical presentation of HIV-associated cryptococcal meningitis with substantially increased opening pressures along with severe headaches, nausea and vomiting, loss of consciousness, marked visual changes, ptosis, or ataxia. Patients responded favorably to removal of a large volume of CSF *via* a lumbar puncture but required continuous lumbar CSF drainage to remain neurologically asymptomatic. However, continuous papilledema can cause vision loss in some patients, severely impacting their daily lives. Of the 9 current patients, 7 (77.78%) had visual loss due to persistent papilledema. In addition, the inability to tolerate cessation of continuous CSF drainage, due to acute symptom recurrence despite maximal antifungal therapy, suggested the need for VP shunting. VP shunting should be given priority when vision loss appears despite continuous lumbar punctures. Only three patients (33.33%) had hydrocephalus with ventricular dilatation according to brain CT or MRI scans. In fact, extremely increased ICP without hydrocephalus associated with cryptococcal meningitis can also be resolved using VP shunting (*11*).

External lumbar drainage *via* daily lumbar puncture, insertion of a lumbar drain, or placement of a VP shunt is recommended if focal neurologic signs and altered consciousness are not noted and radiographic images reveal no space-occupying lesions (*3*). However, frequent lumbar punctures and large-volume drainage in the face of elevated ICP have raised concerns among clinicians about the risk of brain herniation (*7*). Lumbar shunts in patients with HIV-associated cryptococcal meningitis have been described with slightly greater frequency. However, Woodworth *et al*. (*9*) suggested that these shunts are more prone to failure compared to VP shunts. Fessler *et al*. (*12*) studied the role of lumbar peritoneal shunts in the treatment of 8 patients with HIV-associated cryptococcal meningitis. They found that nearly half of the lumbar shunts failed. One of these patients responded favorably after a switch to VP shunting and the patient benefited from long-term shunting. In another study of cryptococcal meningitis in HIV-infected patients, Stevens *et al*. (*8*) suggested that managing elevated ICP with a VP shunt in this patient population may result in better long-term outcomes. The current findings corroborate these observations because most of the current patients have had a satisfactory course several months after VP shunt placement.

The current findings suggest that VP shunts remove a large amount of CSF and lower ICP, thereby significantly improving outcomes for patients with HIV-associated cryptococcal meningitis and persistently increased ICP. The benefits of placing VP shunts (long-term symptom control, elimination of the use of a percutaneous spinal catheter and the associated risk of infection, ability to provide care outside a hospital setting) in this patient population may outweigh the risks of potential infection, cryptococcal dissemination, and shunt obstruction. The limited sample in the current report implies that larger prospective studies are needed to better assess the potential utility of VP shunts in these patients. However, the placement of VP shunts in this patient population may be a reasonable and effective treatment modality with potentially beneficial outcomes.

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