Shunting in cryptococcal meningitis

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OBJECTIVE Patients with cryptococcal meningitis often develop symptomatic intracranial hypertension. The need for permanent CSF diversion in these cases remains unclear.

METHODS Cases of cryptococcal meningitis over a 5-year period were reviewed from a single, large teaching hospital. Sources of identification included ICD-9 codes, operative logs, and microscopy laboratory records.

RESULTS Fifty cases of cryptococcal meningitis were identified. Ninety-eight percent (49/50) of patients were HIV positive. Opening pressure on initial lumbar puncture diagnosing cryptococcal meningitis was elevated (> 25 cm H₂O) in 33 cases and normal (≤ 25 cm H₂O) in 17 cases. Thirty-eight patients ultimately developed elevated opening pressure over a follow-up period ranging from weeks to years.

Serial lumbar punctures for relief of intracranial hypertension were performed in 29 cases. Thirteen of these patients ultimately had shunting procedures performed after failing to improve clinically. Two factors were significantly associated with the need for shunting: patients undergoing shunt placement were more likely to be women (5/13 vs 0/16; $p = 0.01$) and to have a pattern of increasing CSF cryptococcal antigen (10/13 vs 3/16 cases; $p = 0.003$). All patients re-presenting with mycological relapse either underwent or were offered shunt placement.

CONCLUSIONS Neurosurgeons are often asked to consider CSF diversion in cases of cryptococcal meningitis complicated by intracranial hypertension. Most patients do well with serial lumbar punctures combined with antifungal therapy. When required, shunting generally provided sustained relief from intracranial hypertension symptoms. Ventriculoperitoneal shunts are the favored method of diversion. To the authors' knowledge, the present study is the largest series on diversionary shunts in primarily HIV-positive patients with this problem.

<http://thejns.org/doi/abs/10.3171/2015.4.JNS15255>

KEY WORDS cryptococcal meningitis; shunt; lumbar puncture; headache; infection

CRYPTOCOCCAL meningitis is a major opportunistic infection seen commonly in the immunocompromised, particularly in those infected with HIV.²⁶ Elevated CSF pressures are often seen in these patients. Significant neurological decline can occur if elevated CSF pressures are inadequately managed.^{28,29,33,39} Various treatment strategies to address intracranial hypertension in this setting have been described, including medical management, serial lumbar punctures, external lumbar and ventricular drain placement, and either ventricular or lumbar shunting.²⁶ The literature remains unclear as to when each approach is indicated and how often patients require neurosurgical intervention. The present study offers a retrospective review of our experience at a single institution over a 5-year period.

Methods

A retrospective electronic chart review was conducted of records from a single large teaching hospital of 586 beds

serving a major metropolitan area. Using ICD-9 codes, patient admission and discharge diagnoses of cryptococcal meningitis between September 2008 and February 2013 were identified. Lists of positive CSF cultures and cryptococcal antigens were also obtained for this time period to identify infected persons. Individual patient encounters were then inspected for pertinent data regarding diagnosis, management pattern, and outcome. The review was approved by the Baylor College of Medicine institutional review board.

The open-source R software package (<http://www.rproject.org/>) was used to calculate 2-sided Fisher's exact test p values to analyze contingency tables of comparison groups, Welch's variant 2-sample t -test p values for comparison of distribution means, Wilcoxon rank-sum p values for comparison of distribution medians of cryptococcal antigen levels, and Pearson correlation coefficients for regression analyses. For analysis of statistical significance, a p value threshold < 0.05 was used.

ABBREVIATIONS HAART = highly active antiretroviral therapy; IRIS = immune reconstitution inflammatory syndrome.

SUBMITTED February 2, 2015. **ACCEPTED** April 9, 2015.

INCLUDE WHEN CITING Published online October 30, 2015; DOI: 10.3171/2015.4.JNS15255.

Results

Fifty cases of cryptococcal meningitis were identified, some of which were initially diagnosed prior to the study period. The average age was 39 years (range 22–57 years), and with the exception of a single case, study patients (49/50) were HIV positive. The patient without HIV infection was infected with *Cryptococcus gattii*; the rest of the patients were infected with *C. neoformans*. Eighty-six percent (43/50) of patients had confirmation by positive CSF culture, 10% (5/50) had only positive CSF cryptococcal antigen tests, and 4% (2/50) were diagnosed at outside facilities with diagnosis records unavailable for retrospective review.

The 4 most common presenting symptoms included headache in 72% (36/50) of patients, nausea and vomiting in 42% (21/50), altered mental status in 26% (13/50), and meningismus in 20% (10/50). Quantitative cryptococcal antigen titer level from CSF on initial lumbar puncture diagnosing cryptococcal meningitis ranged from 1:32 to 1:65,536 (normal is nonreactive). Quantitative cryptococcal antigen level adjusted logarithmically did not correlate with opening pressure ($r = 0.16$, $p = 0.28$). Table 1 summarizes patient demographic data.

The Infectious Diseases Service was consulted in all cases. Patients received dual induction therapy with flucytosine in combination with either amphotericin B deoxycholate (Fungizone) or liposomal amphotericin B (AmBisome) in 90% (45/50) of cases. Table 2 summarizes antifungal management. Among the 5 patients who did not receive standard induction therapy, there were 3 cases of early discharge due to death or discharge against medical advice. Fluconazole was used alone in another case because of severe renal failure and what was believed to be very mild cryptococcal meningitis. It is unclear why 5-flucytosine was not given with amphotericin B in the remaining case.

When feasible, CSF cultures were taken on diagnosis, 2 weeks later, and during additional lumbar punctures per-

formed for therapeutic CSF drainage. Lumbar puncture opening pressures were measured with the patient in the lateral decubitus position with hips and knees extended. Ten percent (5/50) of patients had culture-confirmed mycological relapse. In all 5 cases, relapse was attributed to a history of medication noncompliance. In an additional 9 cases, relapse was suspected on clinical grounds without positive fungal cultures. Among these 9 cases, 3 patients had a history of medication noncompliance and 4 were ultimately believed to have immune reconstitution inflammatory syndrome (IRIS) due to highly active antiretroviral therapy (HAART).

All 50 patients underwent noncontrast CT head imaging. Per the subjective read of the neuroradiologist, only 12 persons demonstrated ventriculomegaly. In 1 patient, there was obstructive hydrocephalus secondary to severe cerebral swelling around the fourth ventricle. Ten of the persons with ventriculomegaly also had concomitant intracranial hypertension. The majority (28/38, 74%) of patients who developed elevated opening pressures had no changes in ventricular morphology. The presence of ventriculomegaly as determined by the neuroradiologist did not significantly correlate with altered mental status presentation.

On review, examination for papilledema was not consistently documented. In those with intracranial hypertension, 5 patients had documented papilledema and 4 of these 5 had opening pressures exceeding 47 cm H₂O.

Altogether, 42% (21/50) of cases were treated exclusively with medical management centered on antifungal therapy, 32% (16/50) were treated with medical management plus serial lumbar punctures, and 26% (13/50) had neurosurgical management with ventriculoperitoneal or lumboperitoneal shunts. Figures 1 and 2 present flow charts categorizing interventions and outcomes.

Opening Pressures and Therapeutic Drainage

Opening pressure on initial lumbar puncture diagnosing cryptococcal meningitis was elevated (> 25 cm H₂O) in 33 cases and normal (≤ 25 cm H₂O) in 17 cases. Approximately 30% (5/17) of patients with initially normal opening pressures later had elevated opening pressures on subsequent lumbar punctures over a period of weeks to years.

TABLE 1. Summary of demographic and presentation data in 50 patients with cryptococcal meningitis

Variable	No. of Pts (n = 50)	%
Mean age, yrs	39	NA
Sex		
M	43	86
F	7	14
HIV status		
Positive	49	98
Negative	1	2
Presentation		
Headache	36	72
Nausea, vomiting	21	42
Seizure	6	12
AMS	13	26
Meningismus	10	20
Syncope	4	8

AMS = altered mental status; NA = not applicable; Pts = patients.

TABLE 2. Summary of antifungal and intracranial hypertension management

Type of Management	No. of Pts	%
Antifungal*		
Fungizone, AmBisome, flucytosine, fluconazole	28	56
Fungizone, flucytosine, fluconazole	16	32
AmBisome, flucytosine, fluconazole	1	2
Other	5	10
Intracranial hypertension		
Medical only	21	42
Serial LPs	16	32
Shunt	13	26

LP = lumbar puncture.

* Fungizone refers specifically to amphotericin B deoxycholate and AmBisome to liposomal amphotericin B.

FIG. 1. Flow chart summarizing management and outcomes in patients diagnosed with cryptococcal meningitis who initially presented with normal opening pressures. All patients who received shunts were managed preoperatively with serial therapeutic lumbar punctures. One patient with delayed intracranial hypertension received a shunt within 1 month of diagnosis of intracranial hypertension. ICH = intracranial hypertension; OP = opening pressure on lumbar puncture.

The remaining 12 patients with normal opening pressures on initial and subsequent lumbar punctures were treated with antifungal management only. Nine patients with elevated opening pressures were also managed medically, without serial lumbar punctures or surgical interventions. In most of these latter cases, opening pressures

were only marginally high and symptoms of headache were less pronounced.

Acetazolamide and mannitol were not used for medical management of intracranial hypertension. Corticosteroids, primarily prednisone, were used in the setting of IRIS, which was ultimately diagnosed in 28% (14/50) of

FIG. 2. Flow chart summarizing management and outcomes in patients diagnosed with cryptococcal meningitis who initially presented with elevated opening pressures. All patients who received shunts were managed preoperatively with serial therapeutic lumbar punctures.

patients. This usually presented with relapsed symptoms of headache, nausea, and vomiting, as well as elevated opening pressures weeks to months after initiation or re-initiation of HAART.

Serial lumbar punctures for relief of intracranial hypertension were performed in 29 cases. Drainage was performed with the goal of reducing closing pressure to less than 50% of opening pressure or to less than 25 cm H₂O, whichever was higher. Thirteen of these patients ultimately required ventriculoperitoneal or lumboperitoneal shunt placement. In the 16 cases managed with serial lumbar punctures alone, 14 patients had a good response to therapeutic serial lumbar puncture drainage and were discharged to home. The remaining 2 patients were discharged to hospice.

Shunt Placement

Neurosurgery consult was sought in 44% (22/50) of cases, with nearly 60% (13/22) of these patients ultimately undergoing either ventriculoperitoneal or lumboperitoneal shunt placement. Shunts were considered when patients did not obtain adequate relief of headache after lumbar puncture drainage, had persistently elevated opening pressures after at least 3 taps, or could no longer tolerate further lumbar punctures. In the 9 patients who were seen by neurosurgery but not treated with shunt placement, 3 patients did not have intracranial hypertension and 5 improved with serial lumbar punctures.

Table 3 describes characteristics of patients who underwent shunt placement. There was a median of 7 lumbar punctures performed prior to shunt placement (range 2–32). This was not statistically different than the number of lumbar punctures recorded for patients undergoing serial lumbar punctures alone. Reviewed lumbar puncture counts were based primarily on laboratory records of collected CSF samples. This undercounts lumbar punctures performed for therapeutic nondiagnostic drainage. One patient had at least 32 lumbar punctures performed prior to shunt placement. Most of these taps were performed at an outside facility prior to transfer to our institution for shunt insertion.

The time from diagnosis of intracranial hypertension to date of shunt placement was a median of 27 days. Nine of 13 shunts were placed within 2 months of diagnosis of intracranial hypertension. In patients who received shunts more than 2 months after development of intracranial hypertension, 2 patients underwent shunt insertion during periods of mycological relapse secondary to medication noncompliance and 1 patient had suspected IRIS after re-initiating HAART.

In patients who received shunts, fixed medium-pressure valve ventriculoperitoneal shunts were placed in 69% (9/13) of patients and lumboperitoneal shunts in the remainder. In all but 1 case, symptoms of intracranial hypertension improved with shunt placement. Fifty-four percent (7/13) of patients were discharged and remain alive with clinical follow-up of more than 1 year. Two of 13 patients who had shunt insertion required repeat surgery for shunt revision. The first developed a subdural hematoma secondary to overdrainage and required high-pressure valve substitution. The second was found to have a malfunction-

ing shunt during a readmission for mycological relapse. This shunt was successfully explanted.

Patients Receiving Serial Lumbar Punctures Versus Shunt Placement

Patients who underwent serial lumbar punctures and then had shunts placed were compared with patients receiving serial lumbar punctures only (Table 4). Two factors were more common in patients who underwent a shunt procedure. Patients who received shunts were more likely to be women (5/13 vs 0/16; $p = 0.01$). Additionally, patients who underwent a shunt procedure were significantly more likely to have an increased CSF cryptococcal antigen level after diagnostic lumbar puncture (10/13 vs 3/16 cases, $p = 0.003$).

Mortality

There were 13 deaths during the study period and all occurred among HIV-infected patients. Eight deaths were secondary to concomitant infection related to immunodeficiency or after changes in code status due to respiratory failure or progression of terminal AIDS. Two patients with opening pressures in the upper normal range were given comfort care only at the request of their families after their altered mental status failed to improve. Two deaths were attributed directly to disseminated cryptococcal infection, with 1 of these 2 patients refusing an offer of a shunt for treatment of intracranial hypertension. The remaining death occurred in the outpatient setting for unknown causes 4 months after discharge diagnosis of cryptococcal meningitis.

Discussion

Cryptococcosis is a major opportunistic pathogen worldwide, and is particularly common in the immunocompromised HIV-positive population. Although the widespread use of HAART has lowered the incidence of cryptococcosis, the incidence and mortality of this infection remain high in areas with uncontrolled HIV disease and among patients with limited access to HAART.²⁶

Intracranial hypertension is well reported in both HIV-positive and -negative patients who develop cryptococcal meningitis.^{8,13} Symptoms include headache, nausea, vomiting, and altered mental status. In a large series of 221 patients, Graybill et al.¹³ demonstrated that more than 50% (119/221) of patients had opening pressures ≥ 25 cm H₂O on initial lumbar puncture. Failure to address the consequences of intracranial hypertension can be significantly detrimental.^{1,8,11,24} Current guidelines strongly emphasize measuring opening pressure on initial diagnostic lumbar puncture, and performing serial lumbar puncture drainage for pressure and symptom control.²⁶ Papilledema, when documented, was associated with high opening pressures in this series, consistent with prior work by Graybill et al.¹³

Neurosurgeons are often asked to consider permanent or temporary methods of diversion in these cases. Despite elevated opening pressures, many of these patients do not demonstrate ventriculomegaly by imaging.^{13,26,33,34,36} In this series, 28 of 38 patients with elevated opening pressures had no changes in ventricular morphology.

TABLE 3. Patients who received permanent diversionary shunts*

Age (yrs)/ Sex	HIV	OP (cm H ₂ O)	No. of Preceding Taps	Days to Shunt	Shunt Outcome	Follow-Up (days)	Final Status	Mycological Relapse	IRIS	Ventriculomegaly w/ shunt	Shunt Type	Revision	Comments
51/M	Yes	36	3	6	Improved	28	Hospice	No	Yes	Yes, unchanged w/ shunt	Ventricular	No	Shunt for persistently elevated OPs. Had a difficult postop extubation complicated by aspiration pneumonia. Eventually discharged to hospice.
36/M	No	47	5	7	Improved	10	Alive	No	No	Yes, improved after shunt	Ventricular	No	C. gattii infection. Shunt for mild communicating hydrocephalus and persistently elevated OPs w/ headache. Headaches significantly improved.
50/M	Yes	41	6	8	Improved	1512	Alive	Yes, due to noncompliance	No	No	Ventricular	No	Headaches and elevated OPs persisted despite daily serial LPs. Improved w/ shunt, but re-presented w/ mycological relapse secondary to noncompliance. Improved w/ medical management.
35/M	Yes	44	4	12	Improved, but required revision	383	Alive	No, but clinical relapse	No	Yes, unchanged w/ shunt	Ventricular	Yes	Shunt for somnolence and lethargy associated w/ intracranial hypertension. Improved after shunt, but subsequently developed overdrainage subdural hematoma. Treated successfully w/ revision to high-pressure valve.
45/M	Yes	55	14	27	Improved	261	Hospice	Yes, due to noncompliance	Yes	No	Ventricular	No	Noncompliant w/ multiple mycological relapses initially managed w/ serial LPs. Shunt after developing somnolence requiring intubation. Mental status subsequently improved. Pt later discharged to hospice after developing respiratory complications.
34/F	Yes	Height	32	56	Improved	17	Deceased	No	No	No	Ventricular	No	Refractory intracranial hypertension despite numerous therapeutic LPs. Improved after shunt. Died later of septic shock secondary to gram-negative pneumonia.
28/F	Yes	55	3	120	Improved	23	Deceased	No	No	Yes, improved after shunt	Ventricular	No	Initially managed w/ serial LPs at an outside facility. Presented w/ cerebellar swelling and obstructive hydrocephalus, which were much improved after shunt. Died later of septic shock.
30/M	Yes	32	9	136	Improved, but shunt later explanted	1485	Alive	Yes, due to noncompliance	No	Yes, after shunt removal	Ventricular	Yes	Noncompliant w/ multiple mycological relapses. Intracranial hypertension improved w/ shunt. Recurrent symptoms revealed malfunctioning shunt. Shunt explanted after ventriculostomy trial revealed normal pressures.
38/M	Yes	55	7	138	Improved	292	Alive	No, but clinical relapse	Yes	No	Ventricular	No	Initially managed w/ serial LPs, but re-presented w/ symptoms of intracranial hypertension believed to be secondary to IRIS. Improved w/ shunt.
33/F	Yes	55	2	4	Improved	1671	Alive	No	No	No	Lumbar	No	Had persistently high OPs after 2 LPs. Shunt performed in lieu of daily LPs. Headaches significantly improved.
43/F	Yes	30	15	27	Improved	750	Alive	No	Yes	No	Lumbar	No	Shunt after headaches failed to improve following serial LPs. Re-presented w/ multiple reoccurrences of headache. Diagnosed w/ IRIS.

(continued)

TABLE 3. Patients who received permanent diversionary shunts* (continued)

Age (yrs)/ Sex	HIV	OP (cm H ₂ O)	No. of Preceding Taps	Days to Shunt	Shunt Outcome	Follow-Up (days)	Final Status	Mycological Relapse	IRIS	Ventriculomegaly	Shunt Type	Revision	Comments
24/F	Yes	35	7	52	Unchanged	1066	Hospice	No, but clinical relapse	Yes	No	Lumbar	No	Initially managed w/ serial LPs, but continued to present w/ recurrent headache believed to be due to IRIS. Shunt placed, but headaches persisted. Eventually discharged to hospice.
22/M	Yes	40	13	281	Improved	701	Alive	Yes, due to noncompliance	Yes	No	Lumbar	No	Noncompliant w/ multiple mycological relapses. Lumbo-peritoneal shunt placed for persistent headache. Initially improved, but re-presented w/ persistent headache believed to be due to IRIS. Ventricular shunt offered, but pt refused.

OP = opening pressure.

* Sorted by shunt type and days to shunting after diagnosis of intracranial hypertension. Except where specifically noted, "Preceding Taps" column does not include lumbar punctures performed at outside facilities.

† LPs were performed at an outside institution and OPs were not available for review.

Treating Elevated Pressures

Various treatment strategies to address elevated intracranial pressure in the management of cryptococcal meningitis have been proposed. Medical management alone using acetazolamide and steroids is not helpful.^{13,22} In HIV-negative patients, ventriculoperitoneal shunting is well described by multiple authors and has had excellent results.^{6,10,11,15,19,25,27,28,33,35–37} In HIV-positive patients, however, the use of shunting to treat intracranial hypertension has been surprisingly sparse. Rather, there has been a greater emphasis on the use of serial lumbar punctures and lumbar drains for therapeutic relief of CSF pressure. Table 5 summarizes selected published data on HIV-infected patients with cryptococcal meningitis who received shunts.

In 1998, for example, Fessler et al.¹² presented a prospective series identifying 10 HIV-positive patients with cryptococcal meningitis and elevated opening pressures ≥ 20 cm H₂O on diagnostic lumbar punctures. All had symptoms of intracranial hypertension. Nine patients underwent a short trial of serial lumbar punctures for up to 72 hours and as frequently as twice daily, but all failed to demonstrate sustained relief from symptoms of headache, nausea, vomiting, and altered mental status. All 10 patients subsequently underwent lumbar drainage via an external lumbar drain. Although all 10 patients had significant relief in symptoms, 8 patients could not be weaned off external lumbar drainage without recurrence of symptoms. Lumboperitoneal shunts were then placed in these patients, with good response.

More recently, a large retrospective analysis by Bicanic et al.⁴ in 2009 demonstrated significant value of multiple scheduled lumbar punctures performed within the first 2 weeks of cryptococcal meningitis treatment. Elevated opening pressures were treated with therapeutic drainage of up to 30 ml of CSF to achieve a closing pressure below 20 cm H₂O, or less than 50% of opening pressure. Under this protocol, there were no major differences in outcome based on initial opening pressures. With 10 weeks of follow-up, only 4 patients required therapeutic lumbar puncture drainage after Day 14. One patient ultimately required 5 days of drainage via lumbar drain. No shunts were placed.

This is the largest series in which permanent diversionary shunts were placed for the management of intracranial hypertension secondary to cryptococcal meningitis in primarily HIV-positive patients. This higher rate of shunting may be partly attributed to a high rate of clinical and mycological relapse of 28% (14/50) of patients and may reflect the medication noncompliance of our subpopulation. Fifty percent (7/14) of these patients with relapsed symptoms of intracranial hypertension ultimately received shunts. Of the 5 patients presenting with culture-confirmed mycological relapse, permanent shunts were implanted in 4 and offered to the fifth patient, who was ultimately given comfort care at the request of the family.

Shunt Placement in the Immunocompromised

As described by Woodworth et al.,⁴⁰ there may be multiple conjectural reasons for hesitation regarding shunt placement in HIV-infected patients. First, implanted shunts might be more susceptible to infection in the immu-

TABLE 4. Patients with intracranial hypertension who had either serial lumbar punctures alone or serial lumbar puncture followed by shunt placement

Variable	Serial LP (n = 16)	Shunt (n = 13)	p Value
No. of male pts (%)	16 (100)	8 (62)	0.01
Mean age, yrs (SD)	42 (8.8)	36 (9.2)	0.07
Mean no. of LPs (SD)	5.4 (2.0)	9.2 (8.1)	0.12
At diagnosis			
Mean OP (SD)	42 (10.1)	37 (14.1)	0.28
Median CSF cryptococcal Ag	4096	4096	0.72
Mean CSF protein (SD)	88.3 (57.7)	59.8 (35.0)	0.12
At time of elevated ICP			
Mean OP (SD)	42 (9.5)	44 (9.5)	0.55
Median CSF cryptococcal Ag	4096	2048	0.33
Mean CSF protein (SD)	88.3 (57.7)	59.6 (35.6)	0.12
Documented papilledema (%)	2 (13)	3 (23)	0.63
Ventriculomegaly (%)	2 (13)	5 (38)	0.19
At time of intervention			
Culture-confirmed mycological relapse (%)	0 (0)	3 (23)	0.08
Clinical relapse or IRIS (%)	6 (38)	3 (23)	0.45
Cryptococcal Ag pattern			
Median CSF cryptococcal Ag, maximum*	4096	8192	0.37
Increasing CSF cryptococcal Ag (%)*	3 (19)	10 (77)	<0.01
4-fold rise in CSF cryptococcal Ag (%)	1 (6)	5 (38)	0.06

Ag = antigen; ICP = intracranial pressure.

* CSF cryptococcal Ag, maximum refers to the maximum CSF cryptococcal antigen level seen on any lumbar puncture. Increasing CSF cryptococcal Ag refers to the number of patients demonstrating rising cryptococcal antigen levels in CSF on lumbar puncture after initial diagnostic lumbar puncture.

nocompromised, particularly through hematogenous seeding during periods of sepsis. In a recent large retrospective series of ventricular access device infection in premature neonates; however, sepsis alone without meningitis was not found to be a risk factor for device infection.³⁰ Second, HIV-positive cases of cryptococcal meningitis generally have high titers of cryptococcal capsular polysaccharide due to massive fungal infestation with absent host immune response.^{8,13} This high level of CSF polysaccharide may increase the risk of mechanical shunt obstruction, but has not been specifically reported in this population. Third, shunting of infected CSF to an otherwise uninfected peritoneum may theoretically allow for systemic progression of *Cryptococcus*. To our knowledge, no such cases have been reported.

In this series, CSF shunting was overall well tolerated. Despite immunodeficiency, there were no cases of shunt infection. There were no cases of cryptococcal spread to the peritoneum. Two patients required repeat surgery for shunt revision. One patient developed an over-shunting subdural collection that was addressed definitively with shunt-valve revision. The second patient was found to have an obstructed shunt that was successfully explanted with no further need for CSF diversion. Four of the 5 deaths in patients who received shunts were secondary to severe medical comorbidities and terminal progression of immunodeficiency. It is unclear what role intracranial hyperten-

sion played in the remaining death because that patient refused further workup.

It is our preference to offer shunt placement in patients with inadequate relief of intracranial hypertension symptoms after at least 3 lumbar punctures and initiation of appropriate antifungal therapy. Additionally, whether due to mycological relapse or to IRIS, patients with recurrent episodes of symptomatic elevated intracranial pressure may benefit from the sustained relief offered by shunting. As highlighted by previous authors, shunting during active fungal infection is not an issue if antifungal therapy has been started prior to implantation.^{25,26}

IRIS is a clinical diagnosis representing exuberant tissue inflammation in patients experiencing rapid improvement in cellular immunity after initiation of HAART. CSF cultures are generally negative. In a recent prospective series, 22.5% of treated patients with cryptococcal meningitis developed IRIS within 12 weeks of starting HAART.⁷ Cerebral edema can be severe and associated with intracranial hypertension.⁴¹ Current infectious disease guidelines advocate for the use of corticosteroids such as prednisone to control the inflammatory response.²⁶ Shunting when corticosteroids prove insufficient is not well described but was useful in this series.

Although we have placed lumboperitoneal shunts during our early experience with this problem, as well as in the management of pseudotumor cerebri due to the lack

TABLE 5. Summary of English-language literature on HIV-infected patients with cryptococcal meningitis complicated by elevated intracranial pressures

Authors & Year	No. of Pts	Serial LP	Lumbar Drain	EVD	LP Shunt	VP Shunt	Deaths	Comments
Denning et al., 1989	24	—	—	—	—	1	3	Four pts were HIV negative. Only 11, including the 1 pt w/ a shunt, had sustained response to cryptococcal treatment.
van Gemert et al., 1991	1	1	1	—	—	—	1	Case report of single pt who improved significantly w/ lumbar drainage. Died after removal of drain of unspecified cause w/ active cryptococcal disease.
Malessa et al., 1994	8	1	1	—	—	—	3	Five pts had signs of intracranial hypertension. One of these died of cerebral herniation. Another was managed successfully w/ LPs and drainage before later dying of respiratory infection.
Bach et al., 1997	5	—	—	—	1	4	—	No ventricular changes on imaging. All pts improved w/ shunt placement.
Fessler et al., 1998	10	10	10	—	8	1	—	Prospective trial. Pts had shunts placed after being unable to be weaned off lumbar drains.
Niño Oberto et al., 1999	2	2	—	—	2	—	—	Both pts improved w/ lumboperitoneal shunts.
Stevens et al., 1999	3	3	—	—	—	1	3	The pt w/ the shunt lived the longest. All 3 died w/ active cryptococcal disease.
Mylonakis et al., 1999	1	1	—	—	—	1	1	Case report of single pt. Improved definitively w/ VPS during active infection.
Graybill et al., 2000	221	26	2	—	—	4	60	Outcome of pts who received drain & shunt not specified. Forty-nine deaths occurred in pts w/ OP ≥ 19 cm H ₂ O.
Antinori et al., 2000	2	2	—	—	—	—	2	Report in reply to Graybill et al. of 2 pts w/ severely elevated ICP w/o radiographic changes. Both died of presumed herniation. Authors speculate that herniation occurred because of LP drainage. Counter-reply by Graybill et al. speculates that deaths may have occurred secondary to inadequate drainage.
Calvo et al., 2003	10	2	—	5	—	6	3	Five of 6 pts w/ shunts had good recovery whereas the other was left moderately disabled. Three deaths occurred in the group w/o shunts. Two of these occurred despite EVD. Two of 5 EVD pts had ventriculitis.
Sun et al., 2004	35	9	1	—	—	1	2	Nine pts had "extremely high" ICP (>35 cm). A median of 3.5 LPs to get ICP <40 cm H ₂ O w/ range of 1–27 LPs were performed.
Macswen et al., 2005	1	1	1	—	—	—	—	Improved significantly w/ lumbar drainage. Failed initial wean attempt at 7 days prior to drain removal at Day 13.
Woodworth et al., 2005	2	—	1	—	—	2	—	Both received shunts during active infection and improved significantly w/ follow-up >12 mos.
Manosuthi et al., 2008	601	—	54	—	—	—	3	Lumbar drains in place for a median of 7 days. Three lumbar drains had bacterial infections. There were 3 deaths among the 54 pts.
Bicanic et al., 2009	163	163	1	—	—	—	42	20% of pts had OPs >35 cm H ₂ O. All pts had at least 3 scheduled LPs. Only 4 pts required therapeutic LP drainage after Day 14. One required 5 days of drainage via lumbar drain.
Liao et al., 2012	19	5	5*	*	†	5†	1	Nos. from HIV-infected cohort.
Vidal et al., 2012	98	40	6	2	1	9	29	OPs >50 cm H ₂ O collected on or after 7 days after admission associated w/ higher mortality.
Meda et al., 2014	35	35	—	—	—	—	—	Compared w/ historical controls, pts receiving serial LPs had reduced mortality and improved short-term survival. Neurosurgical interventions not discussed.
Present study, 2015	50	28	—	—	4	9	13	One HIV-negative pt received a shunt. Two of 13 deaths were directly attributed to cryptococcal infection. One ventricular drain was placed diagnostically in a pt w/ previous shunt placement to assess viability of shunt independence.

EVD = external ventricular drain; VP = ventriculoperitoneal; — = not specified or 0.

* Type of temporary drain not specified.

† Type of permanent shunt not specified.

of ventriculomegaly, we now favor ventriculoperitoneal shunts exclusively. Lumboperitoneal shunts are often more technically difficult to place, particularly in obese patients. They are also more challenging to assess for failure because they cannot be easily tapped or palpated at the bedside. Even in cases where the ventricles are small, we have had good success using image navigation systems to place ventriculoperitoneal shunts, negating some of the purported technical advantages of lumbar shunt placement. Other authors have echoed similar difficulties with lumboperitoneal shunts.⁴⁰ Additionally, although the number of patients is too small for definitive assertion, patients suffering from IRIS seem to have better symptomatic relief with ventriculoperitoneal shunts than with lumboperitoneal shunts. More experience is needed to confirm this conjecture.

Impact of Sex

Of the 7 women in this series of 50 patients, 5 ultimately received shunts after serial lumbar puncture drainage failed, and 2 were treated with medical management only. It is not clear why female patients were more likely to receive shunts. There were no statistical differences in cryptococcal antigen levels or opening pressures based on sex. Perhaps there are similarities here with the pathophysiology of pseudotumor cerebri that reflect sex-specific responses to intracranial hypertension. Some cryptococcal meningitis series have demonstrated male sex as an overall negative prognostic factor,³ but to our knowledge none have correlated sex with need for CSF diversion.

Role of Lumbar and Ventricular Drains

In cases where clinical response to serial lumbar punctures is insufficient, we favor shunt placement over trials of external lumbar or ventricular drains. External drains generally require immobilization and demand a higher level of nursing comfort level because the open drain must be actively managed and monitored. In a large series by Manosuthi et al.,¹⁸ lumbar drains were in place for a median of 7 days. In comparison, recovery from shunt placement is generally on the order of a few days and requires only routine postoperative care. Additionally, in the series by Fessler et al.,¹² there was an 80% rate of conversion to implanted shunts, bringing into question the durability of external lumbar drainage to offer sustained relief.

Infectious considerations are also particularly important in this population afflicted by immunodeficiency. In the cryptococcal meningitis series by Calvo et al.,⁵ there was a 40% rate of ventriculitis in patients with external ventricular drains. Lumbar and ventricular drains are generally placed at the bedside and do not achieve the same standards of antisepsis required by intraoperative placement of shunts.

Conclusions

In cases where opening pressure is high, serial lumbar punctures combined with antifungal therapy are an effective first step in controlling intracranial hypertension in patients with cryptococcal meningitis. When clinical response is insufficient, however, ventriculoperitoneal shunt-

ing is an effective next step. To our knowledge, this is the largest series on shunting in primarily HIV-positive patients with cryptococcal meningitis. We speculate that this may partly reflect a higher rate of medication noncompliance and subsequent readmissions for relapse.

In this series, nearly 30% of patients with cryptococcal meningitis underwent long-term CSF diversion. All patients in this series who were readmitted with mycological relapse underwent or were offered shunt placement. Patients who underwent serial lumbar punctures and then had shunts placed were statistically more likely to have had a pattern of increasing CSF cryptococcal antigen levels than patients who had serial lumbar punctures alone. After shunt insertion, patients generally had sustained relief from symptoms of intracranial hypertension, particularly headache. Ventricular shunts are favored over other methods of permanent or temporary CSF drainage.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Gopinath, Cherian. Acquisition of data: Cherian. Analysis and interpretation of data: Cherian. Drafting the article: Cherian. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Gopinath. Statistical analysis: Cherian. Administrative/technical/material support: Gopinath. Study supervision: Gopinath.

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