Diagnosis and Management of Increased Intracranial Pressure in Patients with AIDS and Cryptococcal Meningitis

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This study was undertaken to characterize the laboratory and clinical course of patients with AIDS and cryptococcal meningitis who had normal or elevated cerebrospinal fluid (CSF) pressure. Data were obtained retrospectively from a randomized multicenter quasifactorial phase III study comparing amphotericin B with or without flucytosine in primary treatment of cryptococcal meningitis. CSF pressure was measured before treatment and at 2 weeks. Repeated lumbar punctures were done to drain CSF and to reduce pressure. Patients with the highest baseline opening pressures (≥250 mm H_2O) were distinguished by higher titers of cryptococcal capsular polysaccharide antigen in CSF; more frequently positive India ink smears of CSF; and more frequent headache, meningismus, papilledema, hearing loss, and pathological reflexes. After receiving antifungal therapy, those patients whose CSF pressure was reduced by >10 mm or did not change had more frequent clinical response at 2 weeks than did those whose pressure increased >10 mm ($P < .001$). Patients with pretreatment opening pressure <250 mm H_2O had increased short-term survival compared with those with higher pressure. We recommend that opening pressures ≥250 mm H_2O be treated with large-volume CSF drainage.

Cryptococcal meningitis is uncommon in immunocompetent hosts. Before the AIDS outbreak, clinical experience was <1000 patients per year in the United States. The AIDS pandemic has been associated with a dramatic worldwide increase in cryptococcosis. Before the introduction of protease inhibitor therapy, 5%–10% of HIV-seropositive patients developed cryptococcal meningitis, often as the AIDS-defining clinical illness [1]. Cryptococcal meningitis is now a less-frequent but still relatively common opportunistic infection associated with AIDS. Disease occurs late in the course of AIDS, with severe immune suppression. Widespread disease is usual; meningitis is the most common manifestation [2–4]. Most research attention has focused on selection of antifungal regimens for use in the acute or chronic phases of illness, and considerable progress has been made [5–7]. A variety of regimens have been tested, including amphotericin B desoxycholate, lipid formulations of amphotericin B, the triazoles fluconazole and itraconazole, and combinations of drugs combining either fluconazole or amphotericin B with flucytosine [8–16]. In noncomatose patients treated with amphotericin B at 0.7 mg/kg, mortality in the first 2 weeks has decreased to <10% [14].

AIDS patients with cryptococcal meningitis differ from their non–HIV-infected counterparts in that they have little inflammatory response in the CSF, large fungal burdens, and few mass lesions [6]. Increased CSF pressure has been observed in some of these patients [17]. In general, for patients with high CSF pressure associated with inflammatory changes of meningitis, treatment of high CSF pressure has been aimed at decompressing the CSF volume, either by ventricular drainage or by medical means such as acetazolamide or mannitol [18]. Corticosteroids have also been used, on the grounds that they sharply reduce monocyte/macrophage and polymorphonuclear leukocyte production of proinflammatory cytokines and subsequent excess fluid in the CSF space [19]. However, at the present time, the causes and consequences of elevated CSF pressure in AIDS patients with cryptococcal meningitis are un-

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clear. The present data are derived from a secondary evaluation of the role that elevated intracranial pressure plays in the clinical and mycological outcomes of initial treatment of cryptococcal meningitis in patients with AIDS. The primary study compared the efficacy of amphotericin B alone versus amphotericin B plus flucytosine during the first 2 weeks of therapy for 381 patients with AIDS and cryptococcal meningitis [14]. The study mandated measurement of CSF opening pressure at each lumbar puncture and documentation of medications and procedures through the course of therapy.

Methods

Study protocol. Mycoses Study Group (MSG) protocol 17/AIDS Clinical Trials Group (ACTG) protocol 159 was a prospective randomized comparison of amphotericin B (0.7 mg/kg/day) plus flucytosine placebo versus amphotericin B plus flucytosine (25 mg/kg every 6 h) for the first 2 weeks of therapy [14]. This was followed by rerandomization to either itraconazole or fluconazole at 400 mg/day through week 10. The criteria for diagnosis included HIV infection and a culture of CSF positive for *Cryptococcus neoformans.* The primary criteria for response included clinical stabilization or improvement of neurological symptoms and signs and a mycological response at 2 weeks of therapy (defined as culture of CSF negative for *C. neoformans*). Clinical success at 10 weeks was defined as resolution of fever, headache, and meningismus [14]. Mycological success was defined as a culture of CSF negative for fungi.

Pretreatment measurement of opening pressure was strongly encouraged, as was measurement of opening pressure during all subsequent lumbar punctures. A key procedure in this study was the lumbar puncture done after 2 weeks of treatment, when amphotericin B/flucytosine treatment was changed to antifungal triazole. This lumbar puncture marked completion of the most intense antifungal therapy and was the assessment point for the initial therapy.

The details of neurological examinations, a truncated mental status query, laboratory examinations, and clinical and mycological outcome are published elsewhere [14]. Data were collected locally and reviewed centrally by an end-point review panel blinded to treatment codes.

Investigators were provided the option of obtaining CT or MRI evaluation for potential focal lesions or raised intracranial pressure. Imaging was not required by the protocol. In the absence of focal lesions, treatment of elevated CSF pressure by lumbar drainage was encouraged. For this, a large-bore (18-gauge) needle was commonly used, and CSF was allowed to drain until a satisfactory closing pressure had been achieved, commonly <200 mm H_2O. Details on closing pressure or volume of CSF drained were not required by the protocol. The process was repeated as often as necessary to achieve a stable opening pressure acceptable to the physician. Lumbar (2 patients) or ventricular (4 patients) drains were occasionally used. After 4 days, if the pressure remained elevated, acetazolamide could be added at a dose of 250 mg/6 h orally. Corticosteroids were allowed at doses of up to 50 mg/day of hydrocortisone to alleviate reactions to the amphotericin B infusions. Autopsy data were recovered when possible, with particular attention to evidence of cryptococcosis in the CNS. When there were no autopsy data, the suspected cause of death was listed.

Statistical methods. Patients were grouped as to whether or not they had a pretreatment opening pressure measured, and those who did were further grouped into quartiles according to their opening pressure. This was done to provide a sufficient number of patients in each group to allow comparison over a broad range of opening pressures. Pressure groups were compared by the Kruskal-Wallis test for ordinal measurements and the χ^2 test for categorical measurements [20]. The Kaplan-Meier method was used for survival analyses, and the groups were compared by the log-rank test [21]. The nonprotocol use of dexamethasone and methylprednisolone was surprisingly frequent. Because of this, the most heavily enrolling sites were examined for disparity of use of steroids versus drainage for reduction of elevated CSF pressure. No site bias was found.

Results

Characteristics of patients according to their baseline opening pressure. Of the 381 patients, 221 had opening pressure measured at their pretreatment lumbar puncture and 160 had no opening pressure measured. The majority of patients who had pretreatment lumbar puncture, without opening pressure had this procedure done in an emergency room. The initial lumbar puncture was commonly done by physicians not involved with this study. One concern was the potential bias if this large group of patients for whom no pretreatment CSF opening pressure was measured had more severe disease than the group of patients who underwent opening pressure measurement.

Of note, among those patients who had pretreatment opening pressure measured, there was a higher percentage who had opening pressure measurement repeated at 2 weeks (73%) than there was among those who had no pretreatment opening pressure measured. Only 54% of patients with no pretreatment opening pressure measured had opening pressure measured at 2 weeks ($P = .0001$). The median pressure at 2 weeks was 230 mm H_2O for those who had pretreatment opening pressure measured versus 203 mm H_2O for those who did not (not significant). The general severity of illness, as measured by AIDS-defining infections, was similar for both groups. The median cryptococcal capsular polysaccharide antigen titers in CSF were significantly higher among those who had an opening pressure measurement at pretreatment lumbar puncture (1 : 2048) than among those who did not (1 : 1024; $P = .005$). There were no differences in mortality, clinical response, or mycological response in the 2 groups (data not shown). Other factors compared included age, ethnicity, level of consciousness, first AIDS-defining illness, signs and symptoms of cryptococcal meningitis, Karnofsky score, percentage of positive blood cultures, presence of extraneural sites of cryptococcosis, routine CSF chemistry determinations, complete blood cell counts, and renal function and liver function tests. Among these parameters, there was no evidence for significant differences between those

who did or did not have pretreatment opening pressure measurements. Among the 39 participating sites, there were differences in the number of patients with pretreatment opening pressure measured, ranging from none of 4 patients with opening pressure measured at 1 site to all of 5 patients with opening pressures measured at 2 other sites. We concluded that the group who had no pretreatment opening pressure measured did not have significant clinical differences (other than the ones listed) from those who did have pressure measured.

In table 1, the 221 patients who underwent pretreatment lumbar puncture with opening pressure measurement were further divided by quartiles according to the opening CSF pressure. We initially examined a cut point of 250 mm H_2O to distinguish higher versus lower pressures. Then, as previously noted, division by quartiles was done to have roughly equal groups for a more detailed comparison. Patients with pressures <190 mm H_2O were considered those with normal opening pressures. The other 3 groups had elevated pressures: 190–249 mm H_2O, 250–349 mm H_2O, and ⩾350 mm H_2O. Each group was compared with each other group and with the group who had no opening pressure measured. There were no differences among the quartiles in parameters reflecting the general severity of HIV infection. These included CD4 cell count, positive culture of blood, and other extrameningeal sites of dissemination (data not shown). Physical findings were recorded by the primary physician. Dilated eye examinations were at the discretion of the primary physician. Ophthalmology and neurology consultations were not routinely sought. The majority of patients with papilledema had measurement of opening pressure. Papilledema was significantly more frequent among patients with the highest CSF opening pressure (⩾350 mm H_2O) than among groups with lower CSF pressure and those with no pressure measured.

Hearing loss, as assessed by the primary physician, was also observed more frequently in those with pressures ⩾350 mm H_2O. Visual abnormalities were commonly encountered but were no more frequent among those with opening pressures ⩾350 mm H_2O. Other clinical correlates of high intracranial pressure included pathological reflexes and more frequent headache and meningismus (both $P < .01$). Headache was present in all 3 groups with the highest pressure as compared to the group with normal pressure. Meningismus was more frequent with in the group with the highest opening pressures (⩾350 mm H_2O). Fever and night sweats, which may reflect activity of host inflammatory responses, were significantly decreased among those with highest opening pressures. There were no differences among groups in the degree of inflammatory responses measured in the CSF; there was virtually no cellular response, depression of CSF glucose level, or increase in CSF protein level beyond normal ranges.

Table 1. Pretreatment clinical and laboratory findings for patients with AIDS and cryptococcal meningitis, grouped according to baseline CSF opening pressure.

	Baseline opening pressure, mm H_2O				
Finding	Not done (n = 160)	<190 (n = 52)	190–249 (n = 50)	250–349 (n = 59)	⩾350 (n = 60)
Opening pressure at 2 w	54	79	70	68	77
CD4 cell count/μL, median	21	18	17	18	18
Cryptococcemia	62	58	44	59	66
Extrameningeal foci	37	24	31	38	20
Headache	89	79	96	92	92
Meningismus	44	25	40	42	64
Papilledema	1	8	4	9	29[a]
Hearing loss	2	4	—	3	12[b]
Pathological reflexes	4	—	4	2	15[b]
Seizures	5	—	4	3	5
Other cranial nerve deficits	2	4	4	7	15[b]
Behavioral changes	17	19	22	21	32
Normal mentation[c]	88	98	88	93	82[a]
Visual changes	26	31	29	24	41
Fever	76	81	86	58	73[b]
Night sweats	32	41	62	24	28[b]
Cryptococcal antigen titer, median					
Serum	1 : 1037	1 : 4096	1 : 2048	1 : 16,384	1 : 8192
CSF	1 : 1024	1 : 512	1 : 1024	1 : 1048	1 : 8192[a]
Positive India ink smear of CSF	85	79	76	86	95
WBC in CSF, median cells/μL	6	4	8	6	11
Protein in CSF, median mg/dL	65	53	58	52	57
Glucose in CSF, median mg/dL	47	48	43	47	45

NOTE. Data are % of patients with finding except as indicated. Significance was determined by χ^2 for categorical measurements and by Kruskal-Wallis test for ordinal characteristics.

[a] $P < .001$.

[b] $P < .01$.

[c] Assessed by minimental examination.

The major laboratory differences among the 4 quartiles of patients were the parameters reflecting fungal burden, including the percentage of positive India ink smears and the titer of cryptococcal capsular polysaccharide antigen in the CSF but not in the blood. The fungal burden was much higher among those with elevated intracranial pressure, particularly those with pressures ⩾350 mm H_2O.

Coma was an exclusion for this study. Lesser degrees of mental impairment were permitted. The mini–mental status median score for those who had a baseline opening pressure measurement was 13, and the score of those who did not have an opening pressure measurement was 12. The difference was not significant. Although there were trends toward more problems in the highest pressure group, there were no differences among groups for behavioral changes. Therefore, the group with the highest baseline CSF opening pressures had evidence of a higher fungal burden and clinical neurological findings suggestive of increased intracranial pressure but no other evidence of more widespread disease.

Nature of the CNS lesion. Of the 221 patients with pretreatment opening pressures measured, 157 underwent cerebral radiographic imaging studies. Scans were interpreted at each institution, and a number of scans had incomplete data. The frequency of imaging studies was similar among all 4 quartiles of patients. The most common abnormalities included atrophy (19%), focal lesions (10%), white matter lesions (3%), and meningeal enhancement (3%). Three of the patients with focal lesions had mild ventricular enlargement, but there was no evidence for obstructive hydrocephalus.

Interventions. The protocol required 4 lumbar punctures at baseline, 2 weeks, 4 weeks, and 10 weeks. Aggressive draining of CSF was encouraged for patients with elevated opening pressure. Table 2 shows the number of patients in each group who had >4 lumbar punctures. More lumbar punctures were done for patients with baseline opening pressures ⩾350 mm H_2O than for the lower-pressure groups. Of the 60 patients with pretreatment opening pressures ⩾350 mm H_2O, 13 had extra lumbar punctures done, and the number of extra lumbar punctures in this group was 26 (14 of these were done in steroid recipients), many more than were done for any of the other 3 groups with baseline pressures measured. The timing of these procedures was at the discretion of the primary physician and was not designated specifically in the protocol. In addition, 2 patients had lumbar drains and 4 had ventriculoperitoneal shunts, all to treat sustained elevated intracranial pressure.

Corticosteroids were given to 150 patients (39% of the total of 381 patients), and 2 others received adrenocorticotropic hormone (1 for adrenal insufficiency). As shown in table 2, overall steroid use was not highly associated with CSF drainage or pressure quartile. Only 10 patients who received steroids underwent CSF drainage, whereas 140 other patients who received steroids did not have extra lumbar punctures for drainage.

Table 2. Interventions among patients with AIDS and cryptococcal meningitis, grouped by baseline CSF opening pressure.

	Baseline opening pressure, mm H_2O				
Intervention	Not done (n = 160)	<190 (n = 52)	190–249 (n = 50)	250–349 (n = 59)	⩾350 (n = 60)
>4 lumbar punctures in 10 weeks					
Steroids	0	2 (4)	1 (2)	2 (3)	5 (8)
No steroids	2 (1)	4 (7)	1 (2)	3 (5)	8 (13)
No. of extra lumbar punctures					
Steroids	0	2	1	4	14
No steroids	2	6	1	3	12
⩽4 lumbar punctures in 10 weeks					
Steroids	56 (35)	15 (29)	22 (44)	25 (43)	22 (37)
No steroids	102 (64)	31 (60)	26 (52)	29 (49)	25 (42)

NOTE. Data are no. (%) of patients except as indicated.

ACTG case records did not include a provision for indicating why corticosteroids were used. Therefore, data on specific indications for steroid use are limited to the 263 MSG participants. Of the 110 MSG participants who received steroids, 55 received hydrocortisone to prevent or suppress reactions to infusion of amphotericin B. Six others received dexamethasone or methylprednisolone for this purpose. These patients were similarly distributed across all quartiles of baseline opening pressures, as were those patients who had no opening pressure measured. Treatment for amphotericin B infusion reactions thus accounted for 55% of MSG patients given steroid therapy.

Of the MSG patients, 41 were given methylprednisolone or dexamethasone for other reasons than suppression of infusion reactions. Of these 41 MSG patients, 27 (66%) had a successful clinical response at 2 weeks versus 86% of 191 patients who did not receive high-dose steroids (P = .001). Mycological outcome was also worse among high-dose steroid recipients (41%) than among nonrecipients (62%; P = .001). Of the 41 high-dose steroid recipients, 31 had baseline opening pressures measured, and of these, 13 (42%) had pressures ⩾350 mm H_2O. Ten (77%) of these 13 patients were treated specifically for raised intracranial pressure. Four (31%) of these 13 high-dose steroid recipients died, versus only 1 (3%) of 39 who did not receive steroids and had pressures ⩾350 mm H_2O (P = .003). Only 5 patients with baseline opening pressures <350 mm H_2O received methylprednisolone or dexamethasone for raised intracranial pressure. Of the total of 41 MSG patients who received dexamethasone or methylprednisolone, 8 (20%) died within 2 weeks, versus 6 (3%) of the 13 patients who did not receive these steroids (P < .0001). For the 13 MSG patients with CSF pressure ⩾350 mm H_2O who underwent methylprednisolone therapy, the microbiological outcome was not affected. Therefore, the use of corticosteroids in pharmacological doses was not associated with a salutory clinical outcome. Indeed, for whatever reason, the use of high-dose corticosteroids was strongly associated with mycological failure, clinical failure, and early death. Finally, mannitol was used to treat 4 patients for

Table 3. Outcomes for 161 patients with AIDS and cryptococcal meningitis after 2 weeks of therapy, according to the change in their CSF opening pressure at follow-up lumbar puncture.

Outcome	CSF opening pressure		
	Decrease >10 mm (n = 81)	No change (n = 24)	Increase >10 mm (n = 56)
Clinical failure	2	4	20[a]
Mycological failure	33	21	43

NOTE. Data are % of patients. Data are limited to 161 patients who had measurements of opening pressure at baseline and at 2 weeks. Early deaths may bias this comparison. Mycologic failure is defined as positive culture of CSF at 2 weeks of treatment. Data are not related to pressure quartiles at initial lumber puncture but to change in pressure during therapy.

[a] $P < .001$.

raised intracranial pressure, and acetazolamide was given to 1 patient for the same reason.

Table 3 shows the 2-week outcome in terms of change in CSF pressure from baseline to the 2-week CSF pressure measurement for 161 patients with paired data. For those patients whose CSF pressure increased during the first 2 weeks of therapy, the clinical failure rate (persistence or worsening of signs and symptoms of fungal meningitis after 2 weeks of therapy) was significantly higher than for those patients whose pressure remained stable or decreased. However, there was no difference in the rate of CSF culture conversion at 2 weeks (microbiological failure was defined as a persistent positive result on culture of CSF).

The overall survival of patients is presented in table 4. The mean pretreatment opening pressure for survivors was 279 ± 10 mm H_2O, and for those who died it was 294 ± 17 mm H_2O ($P = .41$, two-sample t test). Analysis of Kaplan-Meier curves showed that there were statistically significant differences in survival between patients with CSF pressure <190 and ⩾250 ($P = .05$) or ⩾350 mm H_2O ($P = .008$). Also, there was a clear association of elevated baseline opening pressure with shortened long-term survival. The causes of death were attributed to multiple factors, and it was not clear what role cryptococcal meningitis played.

A similar question is whether the clinical response outcome can be predicted before initiation of treatment. If one examined outcome only with use of the initial CSF pressure measurement (table 4), the predictive value of this initial CSF pressure measurement for clinical failure, among 221 patients, did not indicate statistically significant differences among the 4 quartiles at 2 weeks ($P = .98$). However, the 2-week mycological responses (persistently positive results of CSF culture) were fewer in the group with initial pressures ⩾350 mm H_2O (45%; $P = .02$).

Patients who died had a median mental status score of 10, which is significantly lower than that for the entire study population ($P < .0003$). Among the fatalities, 21 deaths occurred early in the study up to day 15 (5.5%), and another 3.9% occurred between 2 and 10 weeks. Of the 21 patients who died during the initial 2 weeks of therapy, the median survival was 7 days. Twelve of these 21 patients had a baseline CSF pressure measured. Of these 12 patients, 6 had an opening pressure ⩾350 mm H_2O. Of these 6 patients with extremely high CSF pressure, 5 died on or before day 7 and 1 died on day 10. Six other patients had baseline opening pressures <350 mm H_2O, and of these, 1 died on day 6 and the others died between days 8 and 15. One patient, who had pretreatment opening pressure of 300 mm H_2O, died on day 12 with abnormal cranial nerve function and an opening pressure of 550 mm H_2O 2 days before death. Another patient, without a baseline opening pressure measurement, died on day 15 with an opening pressure of 600 mm H_2O. Thus, there is a suggested association of extremely high pretreatment CSF opening pressure with mortality in the first week of treatment. A review of case records showed that of the 21 deaths in the first 2 weeks, 4 patients' deaths were attributed to elevated CSF pressure, 6 to fungal meningitis, 4 to respiratory failure due to cryptococcosis, 2 to disseminated cryptococcosis, and 5 to causes unrelated to cryptococcosis. This last group included 3 of the 4 deaths among patients with CSF pressures <350 mm H_2O. A Cox proportional hazards model was used to analyze the effect of baseline opening pressure on survival; the relationship was found to be significant ($P = .001$). To evaluate whether the 2-week clinical and mycological outcomes or the baseline pressure independently were predictors of survival, an additional model was run. In this model,

Table 4. Outcome of treatment according to baseline CSF opening pressure for 221 patients with AIDS and cryptococcal meningitis.

Outcome	Baseline opening pressure, mm H_2O				
	<190 (n = 52)	190–249 (n = 50)	240–349 (n = 59)	⩾350 (n = 60)	P
No. of deaths					
Overall to 12 months	11	10	16	23	.004[a]
Week 0–2	1	0	5	6	
Week 2–10	1	1	2	3	
Median months to death	11	10	7	6	
Clinical response (% of patients)					
2 weeks	83	80	80	82	.98
10 weeks	67	76	77	60	.26
Mycological response (% of patients)					
2 weeks	69	64	47	43	.02
10 weeks	74	73	70	62	.55
Relapse[b]					
No. of patients	4	4	9	8	.1
Median months to relapse	5.3	4.5	4.1	4.1	.95

[a] Overall significance by Wilcoxon analysis of Kaplan-Meier life tables, with follow-up to 12 months. Patients in the lowest-pressure group had significantly higher survival: $P = .05$ vs. those with pressures of 250–349 mm H_2O and $P = .008$ vs. those with pressures ⩾350 mm H_2O (by Kaplan-Meier analysis). Patients with pressures of 190–249 mm H_2O also had increased survival compared with those in the highest-pressure group ($P = .02$). Among patients whose baseline CSF opening pressure was not measured, 9 died in the first 2 weeks and 5 died between weeks 2 and 10.

[b] Defined as signs of recurring headache associated with culture of CSF positive for *Cryptococcus neoformans,* except for 1 patient whose cultures were negative but who had appropriate clinical findings and increasing cryptococcal antigen titer in CSF.

both high baseline opening pressure ($P = .0001$) and a poor 2-week clinical outcome ($P = .0001$) were independent prognostic indicators for death.

Discussion

Cryptococcal meningitis has traditionally been considered typical of chronic granulomatous meningitis, in which there are foci of inflammation in the basilar meninges, occasionally cerebral mass lesions, but more generally a diffuse lymphocytic meningitis [22–25]. Tuberculous meningitis and coccidioidomycosis are others in this group. Meningeal inflammation is commonly associated with basilar meningitis, occasional vasculitis and focal mass lesions, and impairment of resorption of CSF in the arachnoid granulations. Although absorption of CSF is impaired, production continues, and according to Boyle's law, CSF pressure increases. Clinical manifestations of raised pressure may include headache, papilledema, and focal neurological signs, particularly of cranial nerves [26]. The pathophysiology of chronic granulomatous meningitis involves infiltration of tissue with lymphocytes and macrophages and sometimes granulomas [24, 27]. Disease is also associated with the local elaboration in the CSF of proinflammatory cytokines [28].

Treatment of elevated CSF pressure in granulomatous meningitis is aimed at decompressing the fluid, either by ventricular drainage or by medical means, such as treatment with acetazolamide or mannitol. These agents reduce secretion of the CSF or render the plasma relatively hypertonic, thus causing an osmotic gradient from the CSF to the plasma [18]. Corticosteroids have also been used, since these sharply reduce release of proinflammatory cytokines by monocytes/macrophages and polymorphonuclear leukocytes [19]. Granulomatous fungal meningitis has also been treated with corticosteroids for associated vasculitis (often manifested by focal cranial nerve damage) [24]. Although the value of corticosteroid therapy has best been shown in acute bacterial meningitis, there are studies suggesting benefit among more seriously ill patients with tuberculous meningitis, another form of granulomatous meningitis [29, 30].

The pathophysiology of cryptococcal meningitis may be more varied than that of other forms of granulomatous meningitis. Moreover, the recent explosion of reported cases of cryptococcal meningitis accompanying AIDS has created a situation in which a life-threatening CNS infection occurred without physicians understanding the pathophysiology or recognizing the frequency of increased intracranial pressure. In patients with AIDS, meningeal cryptococcosis appears to be distinct from the above-noted processes, in which there is an active host inflammatory response. When associated with AIDS, cryptococcal meningitis appears less like lymphocytic choriomeningitis and more like a massive fungal infestation with absent host immune response. The CSF contains large numbers of cryptococci, as reflected by high titers of cryptococcal capsular polysaccharide antigen and frequently positive India ink smears. This contrasts with the minimal to absent host cellular response. Cryptococci are thought to cause outflow obstruction mechanically, by blocking passage of CSF across arachnoid villi. In addition, aggregates of cryptococcal capsular polysaccharide accumulate in arachnoid villi, as well as in subarachnoid spaces leading to lymph channels as auxiliary pathways of CSF drainage. Patients in our series had elevated CSF pressure without evidence of obstructive hydrocephalus. This is consistent with communicating hydrocephalus. Another unique and perhaps critical factor may be the cerebral edema that accompanies cryptococcal meningitis. Formation of parenchymal edema may involve aggregates of cryptococcal capsular polysaccharide that interfere with the normal egress of interstitial fluid into the subarachnoid space. Goldman et al. [31] have found massive amounts of capsular polysaccharide in brains of experimentally infected mice. Humans with AIDS and cryptococcal meningitis may also have extensive deposition of capsular polysaccharide [32]. Alternatively, the polysaccharide may contribute to increasing the osmolality of the CSF and interstitial fluid, promoting fluid accumulation or retention.

In this large series, elevated intracranial pressure on admission was present among at least three-quarters of our patients who had pretreatment opening pressures measured. A primary reason for the lack of pretreatment opening pressure measurements for many patients was the performance of the procedure by nonparticipants in this study. This is likely to be even more frequent in the outside community. The fact that so many patients had baseline lumbar punctures without measurement of opening pressure indicates widespread and ongoing lack of awareness of the importance of raised intracranial pressure in AIDS patients with cryptococcal meningitis. A striking finding was that 60% of our patients with pressure measured had pressures $\geqslant$250 mm H_2O. Thirty percent had pressures $\geqslant$350 mm H_2O. Whereas recognized clinical signs and symptoms of elevated pressure were significantly more common in patients with these extremely high pressures, they were frequently absent even in patients with the highest pressures. Accordingly, in the AIDS patient with cryptococcal meningitis, absence of clinical clues does not exclude marked elevation of intracranial pressure. Direct measurement is required. The investigators were required to measure opening pressure during any lumbar puncture, but this was not appreciated by the many other physicians who performed the first diagnostic lumbar puncture. The 2-week follow-up lumbar puncture was critical to evaluation of therapy. However, 2-week lumbar punctures were performed for only 73% of those who initially had an opening pressure measured and 54% of those who did not.

Although neuroradiological studies were frequently undertaken, especially among symptomatic patients with elevated pressure, obstructive hydrocephalus was extremely rare, as were focal neurological abnormalities. In the current series, no major

adverse reactions were reported with repeated lumbar punctures for drainage. Sixteen patients complained of increased headaches, whereas more had dramatic relief of headache within minutes of the procedure.

Given the remarkably low mortality of patients in the first 2 weeks of therapy, an adverse influence of increased intracranial pressure is not immediately apparent. This is particularly impressive in view of the large numbers of patients with high pretreatment intracranial pressure. Nevertheless, very high pressure was associated with death in the first week of therapy. Of 21 patients who died on or before day 15 (median survival, 7 days; mean, 7.1 days), at least 3 were thought by their physicians, on clinical grounds, to have died from high intracranial pressure. It is likely that the majority of other deaths were caused by increased intracranial pressure that was not recognized. Mini–mental status scores indicated that patients who died had lesser integrative mental function than did those who survived. Comatose patients were excluded from this study, and presumably this would be an even higher risk group for raised intracranial pressure.

Initial raised CSF pressure correlated with papilledema, impaired hearing, pathological reflexes, and delayed CSF mycological clearance at 2 weeks. The last may have been due to the higher yeast burden in these patients. Extreme elevation of the CSF pressure was associated with increased mortality at 2 weeks, and the pressure did correlate with long-term clinical outcome. It is unclear whether late mortality was causally related to increased CSF pressure on admission or to yeast burden.

In addition to repeated lumbar punctures, corticosteroids were given to 150 patients; in the 110 cases for which the indication was listed, the majority of patients received low doses of hydrocortisone to alleviate or prevent infusion toxicities from amphotericin B. However, 41 patients received methylprednisolone or dexamethasone for other reasons than suppression of amphotericin B toxicity, and 13 of these had baseline opening pressures >250 mm H_2O. Ten of these patients had cerebral edema or raised intracranial pressure given as the reason for high-dose corticosteroids. In view of the absence of inflammatory changes in the CSF, we were surprised at the frequency with which corticosteroids were used at doses higher than those prescribed in the protocol. The use of high doses of corticosteroids for these patients was associated with significantly higher mortality than was seen among those with high CSF pressures who did not receive corticosteroids. Four additional patients received mannitol and 1 received acetazolamide, all for treatment of elevated CSF pressure.

This study was observational. As already noted, we were unable to assess changes in CSF pressure in the 160 patients who did not have pretreatment opening pressure measured. Of those for whom the gradient of pretreatment and 2-week opening pressures was recorded, 2-week clinical success (CSF culture conversion and clinical stabilization or improvement) was associated with reduction of elevated CSF pressure. Twenty-eight of our patients had repeated lumbar punctures to reduce CSF pressure, usually in the first 2 weeks of treatment. These included 18 of 119 patients with baseline opening pressures ⩾250 mm H_2O, so drainage was undertaken more commonly among those patients with markedly elevated pressure. The impact of reduction of CSF pressure by mechanical means may be somewhat clouded by the 7 patients who received mannitol and the 18 who received dexamethasone or methylprednisolone for treatment of increased intracranial pressure or cerebral edema. Nine of the 18 patients given dexamethasone or methylprednisolone for raised intracranial pressure also received extra lumbar punctures for CSF drainage. Nevertheless, the majority of patients with elevated CSF pressures either were not specifically treated or received CSF drainage alone.

This study emphasizes the importance of measurement of opening pressure at the time of lumbar puncture for all AIDS patients, often before the diagnosis of cryptococcal meningitis is confirmed. The benefits of CSF drainage were apparent to some patients within minutes of the procedure. Nevertheless, these observations also raise additional questions regarding optimal management of elevated CSF pressure. Issues include volume of CSF to be removed, frequency of CSF drainage, and alternatives to frequent lumbar puncture, including noninvasive medical techniques or drugs to reduce intracranial pressure.

In summary, elevated intracranial pressure is a common feature of cryptococcal meningitis occurring in patients with AIDS, being found in more than half of patients in whom pressure was measured. Although such patients often present with recognized signs and symptoms, the raised pressure is frequently clinically silent. Failure to address raised intracranial pressure may result in delayed clinical response and death. Elevated intracranial pressure is associated with massive fungal burden and usually absent host immune response. Focal lesions (which would be contra-indications to lumbar puncture) were uncommon, and obstructive hydrocephalus was not documented at baseline scans. CSF communication with the lumbar space was thus free. Treatment by mechanical decompression via lumbar drainage was not harmful and may have been helpful by removing not only fluid but also fungal polysaccharide. In the absence of evidence for a sound rationale that high-dose steroids play a useful role, we favor drainage of CSF, to be done as often as necessary to control CSF pressure. We do not recommend the use of high doses of corticosteroids.

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