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BRIEF REPORT

Adjunctive Corticosteroid Therapy in the Treatment of Coccidioidal Meningitis

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Coccidioidal meningitis (CM) has high morbidity, and adjunctive measures to improve outcomes are needed. Using an established multicenter retrospective cohort study of CM (N = 221), we found that patients receiving adjunctive corticosteroids had a significant reduction in secondary cerebrovascular events (P = .0049). Those with CM-associated cerebrovascular events (8%) may benefit from short-term corticosteroids.

Keywords. coccidioidomycosis; meningitis; vasculitis; corticosteroids; stroke.

Coccidioidomycosis refers to the spectrum of disease caused by the dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii* [1]. The incidence of infection continues to increase and recent estimates suggest that >150 000 patients are infected yearly [2, 3]. Pulmonary infection is the most common clinical manifestation; however, the spectrum of disease ranges from asymptomatic exposure with subsequent immunity to severe and life-threatening disseminated disease [4].

Coccidioidal meningitis (CM) is the most feared complication of extrapulmonary dissemination [5]. Prior to the availability of effective antifungal therapy, 1-year mortality rates exceeded 90% and were 100% within 2 years of diagnosis [6]. The major complications of central nervous system (CNS) infection include basilar meningitis, encephalitis, space-occupying lesions, and vasculitis [7, 8]; such manifestations have been observed in up to 50% of patients who ultimately died from CM [9–11]. The incidence of CNS vasculitis in nonfatal CM is unknown, although presents clinically with signs and symptoms consistent with a cerebrovascular accident (CVA) secondary to vascular occlusion from the accompanying vasculitis. This condition remains a difficult and controversial management issue [1]. Some clinicians have advocated for the use of short-term corticosteroid therapy in an attempt to reduce the perivascular inflammation responsible for vasculitis [5], while others have questioned the efficacy of this approach given the well-known immunosuppressive effects of corticosteroids [12].

We sought to evaluate the possible benefits of corticosteroids in a retrospective cohort of patients with CM as adjunctive therapy to antifungal treatment in those who experienced a CVA attributed to underlying CM-associated vasculitis.

METHODS

This study was approved by the institutional review board of each institution. We were granted a waiver of consent given the retrospective nature of the project. We identified cases by searching hospital databases from the period 2005–2010. We manually reviewed patient medical records, and all patients with confirmed CM (2005–2010) were included for analysis [13]. Proven meningitis was defined as the presence of coccidioidal precipitin (immunoglobulin [Ig] M) antibody, or complement-fixing (IgG) antibody in the cerebrospinal fluid (CSF) in accordance with current guidelines [14], with concurrent changes in the white blood cell (WBC) count, protein level, and/or glucose level suggestive of CNS infection. A CM-associated CVA, for this study, was defined as a neurologic deficit without radiographic evidence of an alternative etiology [15] and coincident or immediately following (within 30 days) the initial diagnosis of CM.

Clinical variables collected included demographic data, patient symptoms and examination findings, serum coccidioidal antibody titers, CSF results, radiographic imaging of the CNS, and medications (including the timing, duration, and dosing of corticosteroid therapy).

All statistical analysis was performed using GraphPad Prism software version 6.04. Fisher exact test was performed to compare associations between clinical variables and the incidence of CNS infection. P values < .05 were considered statistically significant.

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RESULTS

A total of 221 patients with CM were identified (Table 1). The patients were predominantly male (166/221 [75%]) and white or Hispanic (157/221 [71%]). While human immunodeficiency virus (HIV) (24/221 [11%]) and diabetes mellitus (12/221 [5%]) were the most frequent comorbid conditions, no obvious immunologic impairment or comorbidity was seen in the majority of patients (173/221 [78%]).

A total of 18 patients experienced CM-associated CVA (8.1%). Patients without CM-associated stroke (n = 203) were not significantly different in age, sex, or ethnicity, nor did they have significant differences in comorbidities from those who did experience a CVA during treatment for CM. CSF parameters compared between those without a CVA and those with a CVA revealed no significant differences in median opening pressure (median, 19 [range, 11–53] vs 29 [range, 13–40] cm H_2O; $P = .61$), WBC count (median, 5 [range, 0–1375] vs 21 [5–36] cells/μL; $P = .34$), or glucose level (median, 58 [range, 15–564] vs 38 [range, 31–45] mg/dL; $P = .17$). CSF protein trended to be higher in patients who experienced a CVA (median, 38 [range, 15–564] vs 210 [range, 117–304] mg/dL; $P = .06$; Table 1). There was no difference in the incidence of CVA between immunocompetent and immunocompromised groups ($P = .77$). Patients who experienced a CVA also had a trend toward a higher incidence of concurrent hydrocephalus ($P = .11$)

Table 1. Clinical Variables of Patients With and Without Coccidioidal Meningitis–Associated Cerebrovascular Accidents

Variable	Without CVA (n = 203)	With CVA (n = 18)	*P* Value
Age, y, median (range)	46 (8–89)	41 (25–84)	.86
Sex, male, No. (%)	151 (74)	15 (83)	.40
Ethnicity, No. (%)			.76
Hispanic	71 (35)	7 (39)	.80
White	71 (35)	8 (44)	.45
Black	33 (16)	1 (6)	.32
Asian/Pacific Islander	17 (8)	1 (6)	>.99
Other/unknown	11 (5)	1 (6)	>.99
Comorbidities, No. (%)			
HIV	22 (11)	2 (1)	>.99
CD4 count <200 cells/μL	18 (9)	2 (1)	>.99
Diabetes mellitus	11 (5)	1 (6)	>.99
On immunosuppression (nontransplant)	11 (5)	0	.61
Transplant patients	1 (0.5)	0	…
Concurrent hydrocephalus	12 (6)	3 (17)	.11
CSF parameters, median (range)			
Opening pressure, cm H_2O	19 (11–53)	29 (13–40)	.61
CSF WBC, cells/μL	5 (0–1375)	21 (5–36)	.34
CSF protein, mg/dL	38 (15–564)	210 (117–304)	.06
CSF glucose, mg/dL	58 (9–135)	38 (31–45)	.17

Abbreviations: CSF, cerebrospinal fluid; CVA, cardiovascular accident; HIV, human immunodeficiency virus; WBC, white blood cell.

There were no demographic differences among patients who did or did not receive corticosteroids for CM-associated CVA. The majority of patients who experienced CM-associated CVA subsequently received corticosteroids (15/18 [83%]) at all sites contributing patients to this study (Table 2). Patients who received corticosteroids for secondary prevention were significantly less likely to develop additional CVA events (1/15 [6.7%]) compared to those who did not receive corticosteroid therapy (3/3 [100%]) ($P = .0049$). No deaths in this study were attributed to vasculitic events.

Corticosteroid regimens differed between sites. Dexamethasone was prescribed to 14 patients (doses between 8 and 40 mg/day for 10–21 days). The majority of these patients (9/14) received dexamethasone 10 mg intravenously once, followed by 4 mg 4 times daily. Steroid tapering ranged from 2 to 6 weeks. One patient received hydrocortisone (50 mg every 6 hours for 10 days).

Adverse events possibly related to corticosteroids occurred in 3 of 15 patients: hyperglycemia requiring insulin (resolved after steroid discontinuation), avascular necrosis of the tibia (managed nonsurgically), and superimposed aspiration pneumonia (which may or may not be related to receipt of corticosteroids). No steroid recipients exhibited clinical worsening of CM as deemed by site investigators.

DISCUSSION

The results of this study suggest that adjunctive treatment with corticosteroids may significantly reduce the risk of a second CVA in cases of CM-associated vascular events. The benefits of this approach have been proposed by others [5], although no formal studies have been conducted.

Table 2. Clinical Variables of Patients With Coccidioidal Meningitis–Associated Cerebrovascular Accidents, by Receipt of Corticosteroids

Variable	Receipt of Corticosteroids (n = 15)	No Corticosteroids (n = 3)	*P* Value
Age, y, median (range)	74 (63–91)	64 (63–70)	.63
Sex, male, No. (%)	12 (80)	3 (100)	>.99
Concurrent hydrocephalus	1	2	…
Second CVA[a]	1	3	.0049
Complications attributed to corticosteroids[b]	3	NA	…
Clinical worsening of meningitis attributed to steroids	0	NA	…

Abbreviations: CVA, cardiovascular accident; NA, not applicable.

[a]Second vascular events occurred 4 days following corticosteroid therapy in the treated patient, and 9, 10, and 15 days following the first event in the untreated group.

[b]One case each of: hyperglycemia, avascular necrosis of tibia, and superimposed bacterial infection.

Coccidioidal meningitis remains a highly morbid disease and treatment is challenging even for clinical experts with extensive experience in the treatment of coccidioidomycosis. Although CM is typically a basilar meningitis, vasculitic complications may be observed in other locations including the internal capsules, basal ganglia, brain stem, and cerebral cortex and manifest clinically as focal deficits secondary to infarction. Histologically, CM-associated vasculitis exhibits an inflammatory reaction involving the walls of small-/medium-sized vessels and the adjacent perivascular zone, and WBCs are hypothesized to remain attached to the vascular endothelium and propagate the inflammatory process responsible for vascular obstruction [9]. Organisms within or adjacent to the vessel wall have not been observed in carefully performed human and animal studies [9, 16], suggesting that inflammation is predominately driven by circulating immune complexes or soluble coccidioidal antigens. Similarly, inflammation in murine models of *Streptococcus pneumoniae* meningitis (another condition with proven benefits of adjunctive corticosteroid therapy) has been shown to be dependent on the presence of pneumococcal antigen, and neither the presence of viable/intact organisms nor their presence within the vessel wall are necessary for an exuberant inflammatory response [17, 18].

An animal model of CM-associated CVA has shown an increase in multiple inflammatory molecules [16, 19], and observations from archived human CSF obtained from patients undergoing treatment for CM have similarly shown increases in both tumor necrosis factor α and interleukin 1β [20]. In vitro studies and data from clinical trials have observed a significant reduction in these initial-phase and immunomodulatory cytokines with the use of glucocorticoids, providing biologic plausibility for their clinical benefit in CM [21, 22].

Although our results are significant, they should be interpreted with caution due to the small sample size and the retrospective nature of the study. Additionally, the current study examined adjunctive corticosteroid therapy only after a vascular event had been observed, and to our knowledge there are no data exploring the use of adjunctive corticosteroids coincident with the initial therapy of CM.

In our study, the number of immunocompromised patients was small, and concerns of further immunosuppression in this group (in the setting of ongoing CNS infection) may be valid. For example, although adjunctive corticosteroid therapy is considered standard of care during the treatment of bacterial and tuberculous meningitis [23, 24], in HIV-associated cryptococcal meningitis it has been associated with more adverse events and disability compared to placebo [25]. The rate of adverse reactions potentially associated with corticosteroid therapy in our study was elevated (20%), and were serious, although most side effects in our study were reversible and should be balanced against the risks of a second CVA in these patients.

In conclusion, our results suggest a benefit of corticosteroids in the treatment of coccidioidal-associated vascular events. The complications of CM, including vasculitis, are associated with high patient morbidity and mortality, and attempts to improve outcomes remain of paramount importance. Future studies should be performed prospectively to confirm our findings and should evaluate the role of corticosteroids as adjunctive agents during the primary treatment of CM.

Notes

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