Lacunar Stroke in Cryptococcal Meningitis: Clinical and Radiographic Features

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Objective: Cryptococcal meningitis carries a high mortality, and survivors are left with considerable neurologic sequelae and marked disability. We lack a clear understanding of the pathogenesis of neurologic sequelae and description of stroke features in this population. We aim to describe clinical and radiographic features and predictors of stroke in a cohort of patients with cryptococcal meningitis. *Methods:* We collected key information on patients diagnosed with cryptococcal meningitis at the University of Colorado Hospital between 2000 and 2018 (n = 42). Of those, 32 had neuroimaging studies available. Bivariate and risk ratio estimates regression models were performed to identify predictors of stroke. *Results:* We found a 26% ischemic stroke complication rate in individuals with cryptococcal meningitis. Most strokes were acute (75%), lacunar (100%), multiple (88%), bilateral (63%), and involving the basal ganglia (75%). Presence of malignancy (38% versus 8%, $P = .085$) was higher in stroke in individuals with cryptococcal meningitis, although not statistically significant. Every unit decrease in hemoglobin and serum sodium were predictors for 1.35 and 1.14 times increase in the risk of ischemic stroke, respectively. The presence of hyponatremia carried a RR of 5.7 (95% confidence interval, 1.7-34, $P = .005$). Cryptococcal meningitis lead to death in 19% of patients and a considerable rate of neurologic sequela among survivors. *Conclusions:* Cryptococcal meningitis carries a high risk of lacunar stroke, particularly in the basal ganglia. Cryptococcal meningitis-associated stroke is common and frequently associated with neurologic disability among survivors. We need to understand the possible role of malignancy, anemia, and hyponatremia in the onset of ischemic stroke.

Key Words: Cryptococcal meningitis—cryptococcus neoformans—stroke, lacunar—cerebral ischemia—risk factors

Ischemic stroke is a common complication of cryptococcal meningoencephalitis, affecting organ transplant recipients, patients with acquired immunodeficiency syndrome[1] and occasionally, immunocompetent patients. Cryptococcal meningitis carries a high mortality in up to 20% of individuals infected.[2] Among the survivors, an

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Received December 6, 2018; revision received December 28, 2018; accepted December 31, 2018.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article. Dr. Pate was supported in part by Grant Number D33HP31669 from the Health Resources and Services Administration (HRSA). Study data were collected and managed using REDCap, NIH/NCRR Colorado CTSI Grant Number UL1 TR002535.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.12.043

important rate of neurologic sequelae causes marked disability.[3] Meningitis survivors are more likely to develop hearing impairment, muscle weakness, and cognitive deficits.[4] Previous cohorts have shown rates up to 45% for long-term neurological deficits, such as cognitive impairment, vision loss, ataxia, deafness, and seizures.[5] *Cryptococcus spp.* reaches the central nervous system (CNS) by migration of infected macrophages into the brain, promoting disruption of the blood-brain barrier (BBB) and ultimately invading the microglia. Cerebral ischemia may occur during any stage due to progressive endarteritis of subarachnoid vessels caused by exudates, with subsequent thrombosis and occlusion. Lacunar strokes—resultant from a cryptococcal-mediated vasculopathy— complicate the course of cryptococcal meningitis, particularly among HIV-infected individuals.[6-8] We need a better understanding of prevalence in the United States (US), clinical features, and risk factors of lacunar stroke in patients with cryptococcal meningitis. This would translate into more effective preventive measures to decrease the incidence of this devastating complication. Our aim is to describe the clinical and radiographic features of strokes in a cohort of patients with cryptococcal meningitis at the US.

Methods

Ethics Statement

The present investigation is in health insurance portability and accountability act (HIPAA) compliance according to the Colorado Multiple Institutional Review Board (COMIRB) at the University of Colorado Denver. Analysis of clinical data has been performed under an approved protocol (COMIRB Protocol 15-1340).

Patients and Data Collection

We included all patients with a diagnosis of Cryptococcal meningitis treated at the University of Colorado Hospital in Aurora, Colorado between January 2000 and September 2018. Cryptococcal meningitis diagnosis was defined by a positive cerebrospinal fluid (CSF) cryptococcal antigen, a positive CSF cryptococcal culture, a positive blood cryptococcal culture with endophthalmitis or known history of cryptococcal meningitis. Cryptococcus infection was identified through Immuno-Mycologics Inc. (IMMY, OK) serum and CSF cryptococcal antigen tests (CrAg LFA —Cryptococcal Antigen Lateral Flow Assay) using semi-quantitative enzyme immunoassay. Confirmation was done through regular fungal culture. These tests, unfortunately, cannot distinguish the species or the genotype of the isolate. Blood cultures were processed using the BD BACTEC 9240 automated culturing system. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado-Denver.[9] The following data were retrospectively collected: demographics (sex, race, age, place of birth, place of residence, and occupation); symptoms (constitutional, headaches, altered mental status, respiratory abnormalities, fever, and others), medical history (smoking, lung disease, diabetes mellitus, hypertension, lupus, malignancy, sarcoidosis, cirrhosis, HIV infection, solid organ transplant, use of calcineurin inhibitors or corticosteroids, and prednisone dose); HIV (time since diagnosis, history of HIV antiretroviral drug resistance, antiretroviral therapy, CD4 count, and viral load); transplant (type and time since transplant); vital signs at collection times (systolic blood pressure, diastolic blood pressure, weight, pulse, temperature, and BMI); laboratory results (complete blood cell count, comprehensive metabolic panel, baseline renal function, lumbar puncture opening pressure, serum cryptococcal antigen, CSF cryptococcal antigen, CSF culture, blood culture, CSF cell count, CSF glucose, and CSF protein); and outcomes of cryptococcal infection: immune reconstitution syndrome (IRS), treatment regimen, death at 1 year, cognitive deficits, muscle weakness, speech difficulties, hearing impairment, MRI imaging results, use of ventriculoperitoneal shunts (VPS), new onset cryptococcal infection, and relapse. Presence of strokes was determined by a neuroradiologist examination of all available images. In patients with stroke, the following variables were collected: type of stroke, stage, type, and number of infarcts, location, laterality, and the presence of other imaging abnormalities: Cryptococcomas, hydrocephalus, meningeal enhancement, and basal exudates.

Operational Definitions

A detailed description of the definition of each variable has already been published.[10]

Statistical Analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The means and standard deviations for continuous variables were calculated. For categorical variables, frequencies and percentages were calculated. For categorical explanatory variables, Fisher's exact association test was used to test for association with stroke. Relative risks of stroke and their 95% confidence intervals (CI) were calculated using exact score-based methods. For continuous explanatory variables, generalized linear models were fit to estimate relative risks and test for association. Differences between stroke and nonstroke patients for the continuous variables were also investigated with T and Wilcoxon tests.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

Stroke Features in Patients with Cryptococcal Meningitis

We analyzed data from 32 patients with Cryptococcal meningitis, including 8 patients with Cryptococcal meningitis-associated stroke (Table 1). Twenty-six per cent of cryptococcal meningitis cases had associated strokes (Table 2). The strokes were typically multiple, ischemic, and lacunar. Most of the strokes were diagnosed during its acute phase and tended to affect the basal ganglia. Other common abnormalities observed among all patients were a meningeal enhancement, basal exudate, cryptococcomas, and perivascular enhancement (Fig. 1).

Clinical Differences Between Patients With and Without Stroke

The median age of patients with stroke and without stroke were 56 and 51 years, respectively. Patients were predominantly male and Caucasian in both groups. Constitutional symptoms and headaches predominated in both groups. Malignancy was more frequently present in patients with strokes (38% versus 8%, P = .085). Other prevalent comorbidities were essential hypertension (50% versus 23%, P = .195), HIV infection (38% versus 63%, P = .252), corticosteroid use (38% versus 17%, P = .3265), diabetes mellitus (25% versus 21%; P = 1.000), active smoking (25% versus 21%; P = 1.000), transplant status (13% versus 17%; P = 1.000), and lung disease (13% versus 13%; P = 1.000). Laboratory data showed normal means for white blood cells in both groups. Patients with strokes had more pronounced mean anemia (10 ± 2 g/dL versus 12 ± 2 g/dL, P = .020) and mean hyponatremia (132 ± 6 mmol/L versus 137 ± 4 mmol/L, P = .0645) and lower median CSF pleocytosis (85.0, IQR: (45.5-137.0) cells x 10^6/L

Table 1. *Clinical characteristics among patients with or without stroke*

Patient characteristics	N	Stroke (n = 8)	Nonstroke (n = 24)	P values
		Demographics		
Gender (men)	32	75% (6)	88% (21)	.578
Race (white)	32	88% (7)	58% (14)	.209
Age	32	56 ± 12	51 ± 14	.371
		Symptoms		
Constitutional	32	88% (7)	83% (20)	1.000
Headaches	32	50% (4)	58% (14)	.704
Altered mental status	32	38% (3)	29% (7)	.681
Fever	29	13% (1)	32% (7)	.391
		Past medical history		
Smoking (current)	32	25% (2)	21% (5)	1.000
Lung disease	32	13% (1)	13% (3)	1.000
Diabetes mellitus type 2	32	25% (2)	21% (5)	1.000
Malignancy	32	38% (3)	8% (2)	.085
HIV	32	38% (3)	63% (15)	.252
Transplant	32	13% (1)	17% (4)	1.000
Steroid	32	38% (3)	17% (4)	.327
Hypertension	30	50% (4)	23% (5)	.195
		Laboratory data		
WBC (4.0-11.1 × 10^9/L)	31	12 ± 14	5 ± 3	.141
Hemoglobin (14.3-18.1 g/dL)	31	10 ± 2	12 ± 2	.020
Na (133-145 mmol/L)	31	132 ± 6	137 ± 4	.065
OP (<20 cm H_2O)	19	27 ± 13	31 ± 13	.499
CSF WBC (0-5 × 10^6/L)	27	118 ± 128	146 ± 342	.298
CSF glucose (40-70 mg/dL)	27	36 ± 27	32 ± 14	.682
CSF protein (15-45 mg/dL)	27	146 ± 64	145 ± 141	.984
		Outcomes		
Death	32	13% (1)	21% (5)	.601
Ventriculo-peritoneal shunt	28	17% (1)	5% (1)	.389
Cognitive deficits	27	57% (4)	40% (8)	.662
Hearing impairment	26	29% (2)	21% (4)	1.000
Incoherent speech	27	14% (1)	10% (2)	1.000
Muscle weakness	27	57% (4)	50% (10)	1.000

Table 2. *Stroke features in cryptococcal meningitis*

Variable	% (N)
Frequency	25.8% (8)
Type of stroke—ischemic	100% (8)
Stages of infarcts	
Acute	75% (6)
Subacute	12.5% (1)
Chronic	25% (2)
Type of infarct—lacunar	100% (8)
Number of infarcts	
Single	12.5% (1)
Multiple	87.5% (7)
Location	
Basal ganglia	75% (6)
Frontal	25% (2)
Thalamus	12.5% (1)
Cerebellum	12.5% (1)
Brainstem	12.5% (1)
Laterality	
Right	0% (0)
Left	37.5% (2)
Bilateral	62.5% (5)
Other radiographic abnormalities	
Cryptococcomas	23.1% (3)
Hydrocephalus	7.7% (1)
Meningeal enhancement	92.3% (12)
Basal exudates	15.4% (2)

versus 38.0, IQR: (14.0-95.0) cells x 10^6/L, P = .298). CSF protein was similar between the 2 groups. Opening pressure was similarly elevated in both groups (27 ± 13 cm H_2O versus 31 ± 13 cm H_2O, P = .499).

We observed additional imaging abnormalities more frequently in the group with stroke: Cryptococcomas (13% versus 8%, P = 1.000), meningeal enhancement (50% versus 38%, P = .684) and basal exudates (13% versus 4%, P = .444). The difference in mortality was not statistically significant between groups (13% versus 21%, P = .601). Other adverse outcomes—although not statistically significant but clinically relevant—seemed to be greater among patients with strokes: VPS (17% versus 5%, P = .389), cognitive deficits (57% versus 40%; P = .662), hearing impairment (29% versus 21%, P = 1.000), speech difficulties (14% versus 10%, P = 1.000), and muscle weakness (57% versus 50%, P = 1.000).

The Relative Risk of Stroke in Patients With Cryptococcal Meningitis

The relative risk of stroke in the setting of malignancy was 3.24 (95% CI, 0.40-10.04, P = .09) and 5.71 (95% CI, 1.77-34.13, P = .006) for hyponatremia (sodium <133 mmol/L). Every unit (mmol/L) decrease in hemoglobin was associated with 1.35 times increase in the risk of ischemic stroke, (95% CI, 1.05-1.72, P = .03). Likewise, every unit decrease in sodium levels was associated with 1.14 times increase in the risk of ischemic stroke, (95% CI, 1.04-1.24, P = .05) (Table 3). Opening pressure, CSF glucose levels, and temperature were not associated with increased risk of stroke.

Discussion

In the present study, acute ischemic stroke developed in 26% of the cryptococcal meningitis cases. Strokes were ischemic, lacunar, multiple, and predominantly affected the basal ganglia. We found malignancy, anemia, and hyponatremia as potential clinical factors associated with a higher risk of stroke in patients with cryptococcal meningitis. We also determined that patients with cryptococcal meningitis-associated strokes suffered a higher rate of disabling neurological deficits.

Lacunar strokes are a well-recognized multifactorial entity with 25% 5-year mortality and associated vascular cognitive impairment.[11] Endothelial dysfunction and BBB disruption are the main pathogenic mechanisms. Infections, particularly tuberculosis and fungal meningitis are uncommonly recognized as an etiology for lacunar stroke. However, several case reports have described this complication in cryptococcal meningitis[6,12] and clinicians occasionally reached the diagnosis of CNS cryptococcosis after an initial stroke presentation.[13-15] Rates of ischemic stroke in patients with cryptococcal meningitis vary across series, ranging between 13% and 54%.[7,8,16,17] In the present study, strokes were predominantly ischemic and lacunar, most commonly compromising the territory of the medial lenticulostriate and thalamoperforating arteries. *Cryptococcus spp.* directly invades the brain endothelium mediating BBB disruption via secretion of vascular endothelial growth factor (VEGF).[18] *Cryptococcus spp.* also permeate the perivascular space of penetrating basal arteries and induce proliferation of endothelial cells leading to panarteritis, thrombosis, and occlusion. Venules congestion by thickened fibroid tissue and small vein occlusions has been proposed as an additional pathogenic mechanism.[13]

Anemia and malignancy—surrogates for chronic illnesses and protracted courses—may be preclinical markers for stroke in this population. Likewise, hyponatremia is commonly encountered in patients with large ischemic and hemorrhagic stroke due to cerebral salt wasting.

Additional clinical factors associated with risk of stroke in this setting include altered mental status, diabetes mellitus, smoking, previous stroke, older age, longer duration of illness, and a high burden of fungal disease evidenced by extensive meningeal enhancement, hydrocephalus, cryptococcomas, and basal exudates.[7,8,19] The present study highlights the clinical features of ischemic stroke resultant from cryptococcal meningitis in a US-based population. Our study suggests that stroke leads to worse outcomes in individuals infected.

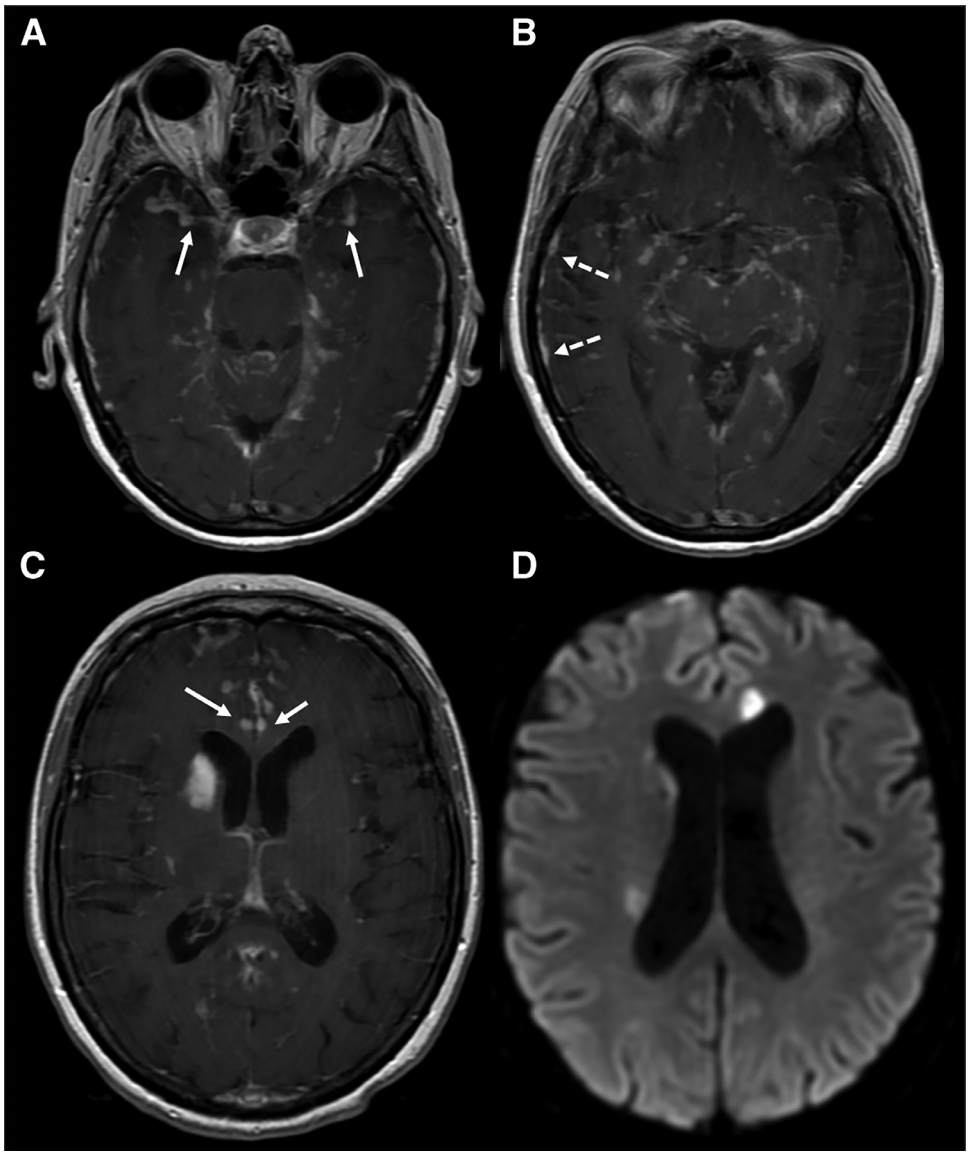

Figure 1. *MRI features of patients with cryptococcal meningitis associated strokes.*

Postcontrast images demonstrate characteristic leptomeningeal and perivascular enhancement. (A) Note enhancement along the bilateral MCA and ACA territories (arrows). (B) Although less commonly observed, note dural enhancement (dashed arrows). (C) Enhancing "cryptococcoma" in the right caudate head (arrows). (D) Diffusion-weighted image with small lesions exhibiting restricted diffusion.

There are several limitations to the analysis. The retrospective nature of the study, the small sample, and the possibility of selection bias may have influenced the reliability of predictors and variables analyzed.

We speculate that the occurrence of ischemic stroke in the setting of cryptococcal meningitis is a delayed manifestation of the infection mediated by the degree of immunosuppression and fungal burden. By the time neurologic

Table 3. *Relative risk models per 1-unit decrease*

Variable	Risk ratio estimate	95% confidence interval	*P* value
Hemoglobin (1 unit)	1.35	1.05-7.72	.03
Sodium (1 unit)	1.14	1.04-1.25	.05
Opening pressure (1 unit)	1.02	0.96-1.09	.45
CSF glucose (1 unit)	0.99	0.96-1.02	.65
Temperature (1 unit)	1.04	0.65-1.67	.86

symptoms developed, a neuroinvasion is already established even with negative CSF studies.[20] Since this devastating infectious vasculopathy is associated with disabling neurological deficits; increase recognition, prompt diagnosis, and early and targeted treatment are the cornerstone in the management of susceptible individuals.

Acknowledgments: The authors would like to thank Dr. Phillip Gorelick for providing insightful and constructive criticism during the elaboration of the manuscript.

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