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RISK FACTORS FOR CRYPTOCOCCAL MENINGITIS — A SINGLE UNITED STATES CENTER EXPERIENCE

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Abstract

Cryptococcal meningitis carries a high mortality. Further understanding of immune suppression factors associated with neuroinvasive infection will improve risk stratification and enhance early diagnosis and treatment with antifungal therapy. The aim of the study was to corroborate established or find novel clinical predictors for cryptococcal meningitis. We performed a matched case-control study of *Cryptococcus* infection in immunocompromised patients with or without cryptococcal meningitis. All patients with a diagnosis of cryptococcal disease were collected at University of Colorado Hospital between 2000 and 2015 (n=51). Thirty patients were diagnosed with cryptococcal meningitis. We built a logistic regression model for risk factors associated with cryptococcal meningitis. The single predictor univariate model found that a positive blood culture, positive serum cryptococcal antigen, current malignancy, and headaches were significantly associated with cryptococcal meningitis (p= 0.02). In the adjusted multivariate model, central nervous system disease was significantly associated with a diagnosis of HIV infection (OR: 24.45, 95% CI: 1.62 – 350.37; p=0.022) and a positive serum cryptococcal antigen test (OR: 42.92, 95% CI: 3.26 – 555.55; p=0.0055). In patients with HIV infection or a positive serum cryptococcal antigen, the pre-test probability of neuroinvasive *Cryptococcus* infection is increased and an aggressive diagnostic evaluation should be conducted to exclude infection and consider empiric therapy.

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Conflicts of Interest:

No conflict of interest were reported by the authors.

Keywords

Cryptococcal antigens; cryptococcal meningitis; *Cryptococcus neoformans*; Fungemia; HIV; risk factors

Introduction

It is estimated that cryptococcal infection causes approximately 3,400 hospitalizations every year in the U.S.A. alone [1]. Cryptococcal central nervous system (CNS) infection carries a high mortality of approximately 20 % in immunosuppressed patients [2]. *Cryptococcus* neoformans/*C. gattii* species complex are the main agents of cryptococcosis. Although infections with *C. gattii* have been described in the U.S.A [3], they are relatively rare in our region (Mountain West). It is recognized that initial pulmonary exposure through inhalation of spores precedes CNS infection [4, 5]. Dissemination following pulmonary infection is associated with higher mortality [2]. HIV infection with or without AIDS, solid organ transplantation, systemic lupus erythematosus (SLE), malignancy, sarcoidosis, and cirrhosis are immunosuppressive settings known to increase the risk for *Cryptococcus* dissemination and neuroinvasion [6–10]. Likewise, the presence of fever, headaches, altered mental status (AMS), weight loss, high dose steroid use or evidence of pleural effusion or pulmonary parenchymal infiltrates favor dissemination of *Cryptococcus* infection in patients with pulmonary disease [11, 6, 12, 13]. Other host factors associated with extra-pulmonary Cryptococcosis are male gender, fungemia, smoking, diabetes and Hispanic ethnicity [14–18]. Many of these predictors of cryptococcal meningitis have not been confirmed. Moreover, characterization of additional clinical features of neuroinvasive disease may permit better prediction of CNS dissemination. Finally, few cohort reports have taken place in the U.S.A. The aim of the study was to perform a matched case-control study of cryptococcal infected immunocompromised patients with or without cryptococcal meningitis infection to corroborate established or find novel clinical predictors for CNS cryptococcal infection.

Methods

Ethics statement

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

Patients and data collection

All patients with culture that grew *Cryptococcus* or with positive serum antigens detected were collected at University of Colorado Hospital through the microbiology laboratory between January 2000 and April 2015. Respective medical reports were accessed to collect clinical and laboratory variables for all patients. The following data was collected: demographics (gender, race, age, and occupation); symptoms (constitutional, headaches, altered mental status, respiratory abnormalities, fever, and others); medical history (smoking,

lung disease, diabetes mellitus, malignancy, sarcoidosis, cirrhosis, HIV infection, solid organ transplant, use of calcineurin inhibitors or steroids 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); absence of presence of cryptococcal meningitis, laboratory results (complete cell count, comprehensive metabolic panel, baseline renal function, lumbar puncture opening pressure, serum cryptococcal antigen, cerebrospinal fluid (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 and attributable death, cognitive deficits, use of ventriculoperitoneal shunts (VPS), new onset cryptococcal infection, and relapse.

Definitions

Occupation was recorded as written in the history and physical (H&P) report. An occupation was labeled outdoor if it was performed primarily in the open air. Symptoms and past medical history were recorded as written in the initial H&Ps (by medicine residents, attending physicians and/or sub-specialties consults notes). Abstracted constitutional symptoms included weakness, weight loss, fatigue, fever, myalgias, night sweats, and malaise. Recorded respiratory symptoms included cough, shortness of breath, congestion, sore throat and chest pain. Other recorded symptoms included rash, pruritus, and gastrointestinal (GI) complaints (diarrhea, flank pain, hematochezia, nausea, vomiting). Fever was defined in the initial H&P as temperature >37.7 °C. Smoking history was considered current or any former use of tobacco. Lung diseases included chronic obstructive pulmonary disease (COPD), pulmonary embolism, pneumonia, bronchiectasis, obstructive sleep apnea and lung neoplasm. Malignancy included current hematologic or solid organ neoplasms. Prednisone dose was calculated in milligrams and for those on non-prednisone steroids an equivalence converter was used to calculate the corresponding prednisone dose. HIV resistance was defined as written in the HIV provider history note or by the presence of any major mutations on a standard HIV genotype. 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. CD4 count, viral load, and laboratory data were obtained at the time of diagnosis with the cryptococcal infection. IRS was defined per previous published guided criteria [19]. Cryptococcal meningitis was defined as a positive cryptococcal CSF antigen study or positive CSF culture or a positive blood cryptococcal culture with endophthalmitis or known history of cryptococcal meningitis. Standard treatment for cryptococcal meningitis was defined as at least 14 days of amphotericin B plus flucytosine. *Cryptococcus* attributable death was defined as mortality with *Cryptococcus* infection considered to be the direct cause of death. Residual cognitive deficits were speech or gait abnormalities documented in follow-up assessments more than three months after the episode of cryptococcal meningitis. New onset infection was defined as first episode of cryptococcal infection. Relapse was any episode of recurrence of infection following clinical and microbiological pathogen control.

Statistical analysis

Statistical analyzes were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). The medians for continuous variables with Inter Quartile Range (IQR) were calculated. For categorical variables, the frequencies and percentages were calculated. We used data from 51 patients, (20 of whom did not contract CNS disease, 30 of whom did contract CNS disease) and one with absent cryptococcal meningitis outcome data. Using previous research [2, 6, 20, 9, 17], we ranked the primary predictor variables by order of clinical importance: HIV infection, use of steroids, transplant, cirrhosis, sarcoidosis, and type 2 diabetes (in order of ranking). There were several combinations of these predictors for which there were no data. To avoid over-parameterization, sarcoidosis, and type 2 diabetes were removed from the list. We created a single predictor model for the remaining variables. Selecting variables having a significance at the 0.02 alpha level, we fit a logistic regression model. We used backward elimination to create our final model that best predicted cryptococcal meningitis in the cohort of 50 patients with cryptococcal infection.

Results

Total cohort with *Cryptococcus* infection

A total of 51 patients with *Cryptococcus* infection were obtained (Table 1). The median age was 53.6 years. Patient were predominantly male and Caucasian, and about half had an outdoor occupation. Constitutional symptoms and fever were present in 33 (66%) and 11 (23%) of the patients respectively. The most prevalent comorbidities were smoking (52%), HIV infection (46%), steroid use (29%), malignancy (28%), transplant (18%) and diabetes (16%). Among patients with HIV, the mean time since diagnosis was 5.9 years with only 12% of patients receiving highly active antiretroviral therapy (HAART). Of those on HAART at diagnosis, therapy was started within the year prior to *Cryptococcus* infection. In the HIV infected group (n=23), prior to cryptococcal infection the median CD4 count and viral loads were 56 cells/μL and 81×10^3 copies/ml respectively. Significantly abnormal laboratory data included anemia (median hemoglobin of 11.9 g/dl), lymphopenia (median lymphocyte count of 0.9×10^9/L), and hypoalbuminemia (median albumin of 3.1 g/dl). IRS developed as a complication in 10% of the patients.

CNS disease (cryptococcal meningitis)

In the 30 patients with cryptococcal meningitis, the need for VPS and the presence of cognitive deficits were seen in 8% and 40%, respectively. There was an overall 33% crude mortality with an 18% *Cryptococcus* attributable mortality. Patients with cryptococcal meningitis had higher mortality attributed to cryptococcal infection (27% vs. 5%). Eighty eight percent of infections were new onset and 14% represented relapses. Among patients with cryptococcal meningitis, there was an increase in opening pressure (median of 24 cm H_2O). The positivity rate for serum cryptococcal antigen, CSF cryptococcal antigen, blood culture and CSF culture was 91%, 83%, 54% and 72% respectively. CSF studies revealed a mildly lymphocytic predominant pleocytosis (CSF white blood cell count (WBC) median of 57×10^6/L), hypoglycorrhachia (CSF glucose median of 39.5 mg/dl) and elevated CSF protein (median 89 mg/dl).

Predictors of CNS disease

A single predictor univariate model for all variables found: significant at the 0.05 level: CSF glucose (OR: 0.93, 95% CI: 0.87 – 0.99; p=0.022), and lung disease (OR: 0.21, 95% CI: 0.046 – 0.93; p=0.04). Significant at the 0.02 level: blood culture positive for *Cryptococcus* (OR: 15.17, 95% CI: 1.72 – 133.53; p=0.014), serum cryptococcal antigen (OR: 18.33, 95% CI: 3.15 – 106.70; p=0.001), malignancy (OR: 0.15, 95% CI: 0.04 – 0.61; p=0.007), and headaches (OR: 26.92, 95% CI: 3.16 – 229.32; p=0.003) (Table 2). In the single predictor models using primary predictors (described in previous studies), only HIV was found to be statistically significant (OR: 3.66, 95% CI: 1.01 – 13.22; p=0.0476). In addition to HIV infection, we saw a significant association between serum cryptococcal antigen, and CNS Disease (Table 3). The odds ratio of developing cryptococcal meningitis in patients who have HIV was 24.45, 95% CI= (1.6252, 350.3704), p-value= 0.0223 and 42.92, 95% CI= (3.2616, 555.5556), p-value= 0.0055 in patients with positive serum cryptococcal antigens.

Discussion

In this mixed population in a low cryptococcal meningitis prevalence U.S.A setting —0.4–1.3 per 100,000 people [21] — the presence of cryptococcal serum antigen showed the highest sensitivity for detecting cryptococcal meningitis. Based on these findings, a positive serum test should prompt immediate evaluation of CSF and initiation of empirical cryptococcal meningitis therapies in high-risk patients. This study also supported the male predominance documented with cryptococcal infections. As revealed in other studies, HIV infection, steroids use, and malignancy were also common predisposing factors for cryptococcal meningitis. The HIV infected patients in our cohort were characterized by profound CD4 depletion, high viral loads, and the majority of patients were not taking antiretroviral therapy. The significant presence of immunosuppression contributed to the development of this opportunistic infection. In the entire cohort, lymphopenia was a predominant laboratory abnormality along with markers of chronic illness including hypoalbuminemia and anemia. The mortality in our series of about 30% is in accordance with other studies [22–24]. The observed high rate of sequelae —up to 40% of cognitive deficit — is an uncommonly reported concerning finding. Despite meningeal and central invasion, a weak immune response was echoed by the disproportionately low CSF white count observed. Finally, we found additional clinical factors such as headaches, lung disease and hypoglycorrhachia as potential markers for cryptococcal meningitis.

The pathogenesis of cryptococcal meningitis is complex and the mechanisms of neuroinvasion remain elusive. One recognized enhancer of neuroinvasion is impaired cell-mediated immunity (CMI). HIV infection, associated with CMI depression, is one of the most predominant conditions driving the risk for cryptococcal meningitis [1]. Within this vulnerable population with CMI dysfunction, we lack clinical indicators to predict accurately an increased risk of cryptococcal meningitis. Clinical indicators can be divided as (1) preceding modulators increasing the risk of cryptococcal meningitis (e.g. male gender, smoking, steroid use, fungemia, and increased pulmonary tissue invasiveness) or (2) consequence of an already established cryptococcal meningitis pathophysiology (e.g. fever, weight loss, headaches, cryptococcemia, and AMS). Positive *Cryptococcus* blood culture or

a positive cryptococcal serum antigen test are well-recognized markers for cryptococcal meningitis. In HIV infected persons, serum antigen testing has been recommended as a screening test in some settings [25, 26]. We confirmed the presence of some of the already described factors in a low prevalence setting in the U.S.A.

Cryptococcosis is estimated to have an overall annual age-adjusted mortality of 0.07 per 100,000 population in 2010 in the U.S.A. [21]. Mortality is highly associated with HIV infection, cirrhosis, malignancy and autoimmune disorders. Globally, the burden of disease is even more worrisome. Cryptococcal meningitis is estimated to affect approximately 1 million persons each year and caused approximately 625,000 deaths [27]. Factors associated with increased mortality include AMS and bacterial co-infections among HIV-negative patients. Other mortality associates include older age, syncope, pneumonia, respiratory failure, ICU admission, fluconazole based therapy, high intracranial pressure and CSF fungal burden (among HIV+ infected patients) [28–30, 24, 2].

This study has multiple limitations. Its retrospective nature limit us to prove the CNS invasion predictors described. Selection bias is also a risk. Other potential factors could have been missed due to the relatively low number of patients studied. This retrospective review of cases of cryptococcal infection at a single institution showed a strong predictor risk rate of cryptococcal meningitis with the diagnosis of HIV/AIDS and a positive cryptococcal serum antigen. These findings highlight the importance of having a high clinical index of suspicion in patients with immunosuppression as well as to have a low threshold to screen patients with a serum cryptococcal antigen even in low prevalence settings. Prospective larger studies are needed to enhance the characterization of clinical predictors of cryptococcal meningitis among vulnerable immunosuppressive populations in the U.S.A.

Cryptococcal meningitis can have devastating consequences. Patients are at risk for mortality and disabling sequela. In patients with known immunosuppressive conditions, the presence of an HIV diagnosis, headaches, active malignancy, lung disease, hypoglycorrhachia or a positive serum cryptococcal antigen should alert the possibility of cryptococcal meningitis and trigger aggressive diagnostic workups to rule out disease and to consider empiric antifungal therapy.

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Table 1

Clinical characteristics in cases of *Cryptococcus* infection

Patient characteristics	Number	Total Count (%)	Count (%), Median (IQR)	
			Non-CNS (n=20)	CNS (n=30)
Demographics				
Gender (Male)	50	41 (82%)	14 (70%)	**27 (90%)**
Race (White)	48	32 (67%)	13 (68%)	**19 (66%)**
Age	51	53.6 (21.6)	60.2 (15.9)	**48.2 (25)**
Occupation (outdoor)	26	14 (54%)	6 (67%)	**8 (47%)**
Symptoms				
Constitutional	50	33 (66%)	11 (55%)	**22 (76%)**
Headaches	50	18 (36%)	1 (5%)	**17 (59%)**
AMS	50	10 (20%)	1 (5%)	**9(31%)**
Respiratory	50	22 (45%)	14 (70%)	**8 (28%)**
Other Symptoms	50	15 (30%)	3 (15%)	**12 (41%)**
Fever	47	11 (23%)	2 (11%)	**9 (32%)**
Past medical history				
Smoking (Former and current)	48	25 (52%)	9 (47%)	**16 (55%)**
Lung disease	50	10 (20%)	7 (35%)	**3 (10%)**
DM2	50	8 (16%)	4 (20%)	**4 (13%)**
Malignancy	50	14 (28%)	10 (50%)	**4 (13%)**
Sarcoidosis	50	1 (2%)	0 (0%)	**1 (3%)**
Cirrhosis	50	5 (10%)	2 (10%)	**3 (10%)**
HIV	50	23 (46%)	5 (26%)	**17 (57%)**
Transplant	49	9 (18%)	4 (21%)	**5 (17%)**
Steroid	49	14 (29%)	4 (21%)	**10 (33%)**
Prednisone dose (mg)	13	12.5 (10)	20 (40)	**11.25 (7.5)**
CNI	49	7 (14%)	3 (16%)	**4 (13%)**
HIV and Transplant				
Time since HIV Diagnosis (y)	20	5.9 (17.7)	5.1 (6.6)	**9 (18.5)**
HIV resistance	6	3 (50%)	1 (100%)	**3 (60%)**
HAART	22	6 (12%)	1 (5%)	**5 (17%)**
Time since HAART (y)	12	0 (0.3)	0 (4.1)	**0 (0.4)**
Viral load (10^3 copies/ml)	19	81 (211)	39 (187)	**83 (137)**
Type of SOT (Kidney)	10	6 (60%)	2 (40%)	**4 (80%)**
Time since Transplant (y)	9	1.1 (1.3)	0.9 (1.2)	**1.1 (3.2)**
CD4 (cells/μL)	24	56 (117)	14 (92)	**60 (123)**
Laboratory data				
WBC (4.0–11.1 × 10^9/L)	50	6.1 (4.5)	5.9 (4.3)	**6.5 (4.5)**
Hemoglobin (14.3–18.1 g/dl)	50	11.9 (4.5)	12.2 (3.9)	**11.2 (3.3)**
Platelets (150–400 × 10^9/L)	50	193 (165)	216.5 (98)	**165 (179)**

Patient characteristics	Number	Total Count (%)	Count (%), Median (IQR)	
			Non-CNS (n=20)	CNS (n=30)
Lymphocytes (1.0–4.8 × 10^9/L)	48	0.9 (1)	0.9 (0.8)	**0.8 (1.8)**
Monocytes (0.2–0.9 × 10^9/L)	48	0.4 (0.5)	0.5 (0.4)	**0.4 (0.6)**
Neutrophil (1.8–6.6 × 10^9/L)	48	3.6 (3.3)	4.2 (3.1)	**3.6 (3.5)**
Eosinophil (0.0–0.4 × 10^9/L)	48	0 (0.1)	0 (0.1)	**0 (0.1)**
Na (133–145 mmol/L)	49	135 (6)	137 (5)	**135 (6)**
Creatinine (0.7–1.3 mg/dl)	49	1 (0.7)	0.9 (0.4)	**1.2 (0.8)**
Baseline Creatinine	49	1 (0.3)	0.9 (0.1)	**1.1 (0.6)**
Corrected Ca (8.6–10.3 mg/dl)	47	9.4 (0.8)	9.3 (0.7)	**9.5 (0.8)**
Albumin (3.5–5.7 g/dl)	47	3.1 (1)	2.8 (1.4)	**3.2 (0.8)**
Alk. Phosphatase (39–117 U/L)	46	68.5 (35)	68.5 (30)	**68 (39)**
AST (12–39 U/L)	46	25.5 (17)	26 (11)	**25 (25.5)**
ALT (7–52 U/L)	46	24 (21)	22 (11)	**24.5 (25)**
Total Bilirubin (0.1–1.3 mg/dl)	46	0.7 (0.7)	0.7 (0.6)	**0.7 (0.8)**
Opening Pressure (<20 cm H_2O)	16	24 (23)	13.5 (0)	**24 (23)**
Serum cryptococcal antigen	39	26 (67%)	6 (35%)	**20 (91%)**
CSF cryptococcal antigen	24	20 (67%)	NA	**20 (83%)**
Blood culture	41	16 (39%)	1 (7%)	**14 (54%)**
CSF Culture	25	18 (58%)	NA	**18 (72%)**
CSF WBC (0–5 × 10^6/L)	31	35 (130)	1 (3)	**57 (150)**
CSF PMN (0–2 × 10^6/L)	31	1.5 (32.5)	0 (0)	**5.9 (42.8)**
CSF LYM (0–4 × 10^6/L)	31	10.7 (31.9)	0.7 (2.4)	**20.6 (32.4)**
CSF MONO (0–2 × 10^6/L)	31	1.8 (34.5)	0.1 (0.6)	**7.6 (36)**
CSF glucose (40–70 mg/dl)	30	42.5 (21)	62 (30)	**39.5 (20.5)**
CSF protein (15–45 mg/dl)	31	66 (84)	40 (10)	**89 (82)**
Outcomes				
IRS	49	5 (10%)	2 (11%)	**3 (10%)**
Treatment (AF)	47	24 (51%)	1 (6%)	**23 (79%)**
Death	49	16 (33%)	7 (37%)	**9 (30%)**
Attributable death	49	9 (18%)	1 (5%)	**8 (27%)**
Cognitive deficits	42	10 (24%)	0 (0%)	**10 (42%)**
VPS	43	2 (5%)	0 (0%)	**2 (8%)**
New onset	50	44 (88%)	20 (100%)	**24 (80%)**
Relapse	36	5 (14%)	0 (0%)	**5 (21%)**

*CNS: Central nervous system; AMS: altered mental status; DM2, diabetes mellitus type 2, CNI: calcineurin inhibitors; y: years; HAART: highly active antiretroviral therapy, SOT: solid organ transplant; CSF: cerebrospinal fluid; IRS: immune reconstitution syndrome; AF: Amphotericin B plus Flucytosine; VPS: ventriculoperitoneal shunt

Table 2

Single predictor models of risk factors for cryptococcal meningitis.

Characteristic	Odds Ratio (95% Confidence Intervals)	p-value
HIV infection	3.6616 (1.0143, 13.2183)	0.0476
Headaches	26.9168 (3.1593, 229.3184)	0.003
Corticosteroid use	1.8750 (0.4744, 7.4105)	0.3622
CSF glucose	0.9292 (0.8728, 0.9894)	0.022
Lung disease	0.2063 (0.0458, 0.9301)	0.040
Blood culture	15.1666 (1.7227, 133.5252)	0.014
Malignancy	0.1538 (0.03910, 0.6053)	0.007
Transplant	0.7500 (0.1672, 3.3646)	0.7015
SCA	18.3333 (3.1499, 106.7027)	0.001
Cirrhosis	1 (0.1445, 6.9212)	1.0000

SCA: Serum cryptococcal antigen.

Table 3

Adjusted model parameter estimates for cryptococcal meningitis.

Characteristic	Odds Ratio (95% Confidence Intervals)	p-value
HIV infection	24.4500 (1.6252, 350.3704)	0.0223
Corticosteroid use	8.6655 (0.5558, 135.1351)	0.1193
Transplant	2.4284 (0.1795, 33.8983)	0.4984
Cirrhosis	14.1844 (0.5029, 400)	0.1156
SCA	42.9185 (3.2616, 555.5556)	0.0055

SCA: Serum cryptococcal antigen.