

**Symptomatic cryptococcal antigenemia presenting as early cryptococcal meningitis with
negative CSF analysis.**

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Summary- Blood CrAg testing should be considered in all severely immunocompromised HIV-infected individuals who are hospitalized with suspected meningitis. Fluconazole monotherapy is inadequate for individuals with neurologic symptomatic cryptococcal antigenemia.

Abstract:

Background: Individuals with cryptococcal antigenemia are at high risk of developing cryptococcal meningitis if untreated. The progression and timing from asymptomatic infection to cryptococcal meningitis is unclear. We describe a sub-population of individuals with neurologic symptomatic cryptococcal antigenemia, but negative CSF studies.

Methods: We evaluated 1201 HIV-seropositive individuals hospitalized with suspected meningitis in Kampala and Mbarara, Uganda. Baseline characteristics and clinical outcomes of participants with CNS-symptomatic cryptococcal antigenemia and negative CSF CrAg were compared to participants with confirmed CSF CrAg+ cryptococcal meningitis. Additional CSF testing included microscopy, fungal culture, bacterial culture, TB culture, multiplex FilmArray PCR (Biofire), and Xpert MTB/Rif (Cepheid).

Results: We found 56% (671/1201) of participants had confirmed CSF CrAg+ cryptococcal meningitis, and 4% (54/1201) had neurologic symptomatic cryptococcal antigenemia with negative CSF CrAg. Of those with negative CSF CrAg, 9% (5/54) had *Cryptococcus* isolated on CSF culture (n=3) or PCR (n=2), and 11% (6/54) had confirmed tuberculous meningitis. CSF CrAg-negative patients had lower proportions with CSF pleocytosis (16% vs 26% with ≥ 5 white cells/mcL) and CSF opening pressure $>200\text{mmH}_2\text{O}$ (16% vs 71%) compared with CSF CrAg+. No cases of bacterial or viral meningitis were detected by CSF PCR or culture. In-hospital mortality was similar between symptomatic cryptococcal antigenemia (32%) and cryptococcal meningitis (31%) ($P=.91$).

Conclusions: Cryptococcal antigenemia with meningitis symptoms was the third most common meningitis etiology. We postulate this is early cryptococcal meningoencephalitis. Fluconazole monotherapy was suboptimal, despite *Cryptococcus*-negative CSF. Further studies are warranted to understand the clinical course and optimal management of this distinct entity.

Keywords: Cryptococcal meningitis, HIV; Diagnosis; Fungal Antigen; Aseptic Meningitis

Introduction

Cryptococcal meningitis is the most common cause of meningitis in Sub-Saharan Africa and accounts for 15% of HIV/AIDS-related deaths globally [1-3]. Cryptococcal antigenemia, which precedes the development of cryptococcal meningitis, has a prevalence of 8.8% among HIV-infected Ugandan adult outpatients with CD4 T-cell counts <100 cells/ μ L, and this prevalence is two-fold greater among those hospitalized [4, 5]. Globally, the cryptococcal antigenemia prevalence is estimated at 6% in HIV infected individuals with CD4 T-cell counts <100 cells/ μ L [1].

Current World Health Organization (WHO) guidelines recommend screening all antiretroviral therapy (ART) naïve HIV infected individuals with CD4 T-cell counts <100 cells/ μ L for cryptococcosis using a serum or plasma cryptococcal antigen (CrAg) test, followed by pre-emptive antifungal therapy if CrAg positive to diminish the risk of developing cryptococcal meningitis [6, 7]. If untreated, patients with cryptococcal antigenemia progress to develop meningitis symptoms within a median of 22 days (by latex agglutination) [8]. However, the exact timing of developing meningitis symptoms in individuals with a positive serum CrAg versus the ability to detect cryptococcal antigen in cerebrospinal fluid (CSF) remains unclear. The optimal treatment for this group of patients has not been defined.

We characterized high-risk patients who were hospitalized with symptoms of meningitis including headache, neck pain, vomiting, and/or fever with a positive whole blood CrAg test, but with negative CSF evaluation (negative CrAg and no other bacterial, viral, mycobacterial or fungal etiology identified; hereafter referred to as 'symptomatic antigenemia' group). We compared this neurologic symptomatic antigenemia group to patients with confirmed CSF CrAg+ cryptococcal meningitis in terms of clinical presentation and hospital outcomes.

Methods

Study Participants

As part of screening for enrollment into the “Adjunctive sertraline for treatment of HIV-associated cryptococcal meningitis” (ASTRO-CM) clinical trial (ClinicalTrials.gov: NCT01802385) [9], we prospectively consented 1,201 HIV-infected adults presenting with suspected meningitis to evaluate for the etiology of meningitis at Mulago National Referral Hospital and Mbarara Regional Referral Hospital in Uganda. Study participants were HIV-infected adults (≥ 18 years) with signs/symptoms of meningitis, who provided written informed consent for lumbar puncture, diagnostic testing, and collection of research data. We excluded individuals with past history of cryptococcal meningitis and females who were pregnant. Ethical approvals were obtained from the Uganda National Council of Science and Technology (UNCST), Mulago Hospital Research and Ethics Committee, and University of Minnesota.

Study Procedures

First, symptomatic hospitalized persons with suspected meningitis underwent finger stick testing of whole blood with the CrAg lateral flow assay (LFA) (Immy, Norman, Oklahoma, USA) [10]. Second, lumbar punctures were performed with CSF tested using CrAg LFA to establish a diagnosis of cryptococcal meningitis. All CrAg testing was independently repeated in the microbiology laboratory to confirm the point-of-care CrAg result. Tuberculous meningitis (TBM) was diagnosed by Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), mycobacterial growth indicator tube (MGIT) culture, or acid-fast bacilli smear [11]. Multiplex PCR (FilmArray Meningitis/Encephalitis Panel, BioFire Diagnostics, LLC, Salt Lake City, Utah) was also performed on a subset of samples to evaluate for potential viral and bacterial etiologies of meningitis [12]. Quantitative fungal cultures were performed on whole CSF, and plates were incubated at 30°C for 10 days on Sabouraud Dextrose Agar (SDA), as previously described [13, 14]. The overall stepwise diagnostic algorithm is presented in **Supplemental Figure 1**.

Statistical Analysis

We analyzed data based on CSF CrAg test results. Individuals with first episode cryptococcosis were included in comparative analyses. We compared baseline characteristics and clinical outcomes of individuals in the symptomatic cryptococcal antigenemia group with the cryptococcal meningitis group. We compared continuous variables with Wilcoxon rank sum tests and compared categorical variables with Fisher's exact tests. *P*-values <.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results:

Between August 2013 and May 2017, we consented 1,201 HIV-infected participants hospitalized with suspected meningitis for lumbar puncture. All participants first received a CrAg LFA test on finger stick whole blood. Of these, 60% (725/1201) had a positive blood CrAg test. Of those with a positive blood CrAg, 93% (671/725) had positive CSF CrAg and confirmed cryptococcal meningitis, and 7.4% (54/725) had negative CSF CrAg. Of the 574 participants with first episode of meningitis and a positive CSF CrAg, 0.9% (5/574) had cryptococcal meningitis and microbiologic-confirmed TB meningitis co-infection (**Figure 1**).

Among the 54 participants with negative CSF CrAg, 3 (6%) subsequently grew *Cryptococcus* on CSF culture (Range, 10 – 95 CFU/mL) with negative multiplex PCR, and two patients (13% of 15 tested) had *Cryptococcus* DNA detected by multiplex PCR with sterile cultures (**Table 1**). Six participants (11%) were diagnosed with TBM using Xpert MTB/Rif (n=5), acid fast bacilli smear microscopy (n=1) and/or mycobacteria culture (n=3). There were no cases of viral or bacterial meningitis diagnosed among this group based on CSF profile, multiplex PCR, or bacterial culture. Thus, 43 were included in the final symptomatic antigenemia group for analysis.

Participants in the symptomatic antigenemia group and the cryptococcal meningitis group had similar baseline characteristics (**Table 2**). The CD4 T-cell counts in the symptomatic antigenemia group (median 29 cells/ μ L, IQR, 7-69) were not statistically different from the cryptococcal

meningitis group (median 16 cells/ μ L, IQR, 6-48; $P=.16$). Headache was a less common symptom in the symptomatic antigenemia group than the cryptococcal meningitis group, (84% versus 98%; $P<.01$). The proportion of participants on antiretroviral therapy in the symptomatic antigenemia group did not differ from the cryptococcal meningitis group (53% versus 52%; $P=.84$). No participant initiated or changed antiretroviral therapy during hospitalization. A significantly higher proportion of participants in the symptomatic antigenemia group had normal CSF white blood cell counts (<5 cells/ μ L) compared to the cryptococcal meningitis group (84% vs 64%; $P<.01$). Similarly, the median CSF opening pressure was 127 mmH₂O (IQR 93-157) in the symptomatic antigenemia group compared to 270 mmH₂O (IQR 180-400) in the cryptococcal meningitis group ($P<.01$). Among those in the symptomatic antigenemia group, 16% (5/32) had elevated CSF opening pressure >200 mmH₂O.

Of six symptomatic antigenemia participants with TB meningitis co-infection, CSF was more inflammatory compared to symptomatic antigenemia participants without TB meningitis. Participants with TB meningitis co-infection presented more frequently with abnormal CSF pleocytosis ≥ 5 white cells/ μ L (67% vs 16%, $P=.02$), however, the proportions presenting with elevated protein >45 mg/dL (60% vs 37%, $P=.37$), and opening pressure of >200 mmH₂O (50% vs 16%, $P=.33$) were similar when compared to those with symptomatic antigenemia.

Among the 96% (585/612) with known in-hospital outcomes, early mortality did not differ in the symptomatic antigenemia group 32% (11/34) who were treated with fluconazole monotherapy (initially 800mg/day) versus 31% (173/551) in the cryptococcal meningitis group who were treated with combination amphotericin B and fluconazole ($P=.91$). Among patients in the symptomatic antigenemia group, the median time to in-hospital death was 7 (IQR, 4 to 18 days, max, 31 days), and a further 21% had unknown outcome (e.g. fled from the hospital / lost to follow up). Thus, outcomes in this symptomatic antigenemia group, who generally appeared less ill at baseline, were suboptimal when receiving fluconazole monotherapy.

Discussion:

We identified a group of HIV-infected individuals with cryptococcal antigenemia and symptomatic meningitis but without microbiologic evidence of CSF infection. We propose that these persons most likely have early cryptococcal meningitis. In the absence of testing blood for CrAg and only testing CSF, we would have missed their diagnosis. Likely these missed diagnoses commonly occur in immunocompromised populations throughout the world. These neurologic “symptomatic antigenemia” patients had relatively milder symptoms at baseline, normal CSF opening pressures, and slightly higher CD4 T cell counts, yet they still had 32% known early in-hospital mortality with the WHO and U.S. recommended fluconazole monotherapy for CrAg antigenemia. While anecdotally recognized over the past ~4 decades, this is the first cohort describing this population and the prevalence (1 in 25 adults presenting with meningitis symptoms in Uganda).

There are two important lessons from our findings. First, diagnostic testing of immunocompromised individuals with suspected central nervous system (CNS) infection should always include blood testing of cryptococcal antigen, particularly in the absence of an identified CSF pathogen. Second, CNS cryptococcosis is a meningoencephalitis where early in infection, yeasts can be present in the brain parenchyma without CSF involvement. Untreated, eventually CSF involvement will occur based on the natural history of *Cryptococcus neoformans*. [8]. A South African autopsy study reported intra-parenchymal *Cryptococcus* in the brains of patients with cryptococcal antigenemia who received preemptive fluconazole therapy and later died [15].

Second, the current guidelines recommending fluconazole therapy for isolated cryptococcal antigenemia are inadequate [7, 16, 17]. While these guidelines may be adequate for asymptomatic antigenemia, for persons with symptomatic CNS disease and no other identifiable cause of symptoms, patients should be approached similarly to CNS infection, with consideration of more aggressive management with amphotericin-based therapy or combination fluconazole and flucytosine. Of notable concern is the similar in-hospital mortality among these those with symptomatic antigenemia as compared with symptomatic cryptococcal meningitis patients. Despite the fact that these symptomatic antigenemia patients were identified early during the continuum of cryptococcal disease while progressing to overt cryptococcal meningitis, we observed unacceptably high early mortality

(32%). The proximal cause of death was unclear, based on the available data. Even with preemptive fluconazole monotherapy in asymptomatic cryptococcal antigenemia persons screened in a multi-site cryptococcal screening and treatment program in Kampala Uganda, 28% were symptomatic at the time of clinic return [18]. Of these symptomatic cryptococcal antigenemia persons identified in outpatient clinics, 54% were dead or lost at 6 months [18]. Fluconazole monotherapy even at 1200mg/day for CNS disease has been associated with a 68% mortality in a recent Ethiopian study [19].

Therefore, given the implementation of national cryptococcal antigen screening programs where patients with symptomatic cryptococcal antigenemia will increasingly be identified, we posit that treating individuals with symptomatic cryptococcal antigenemia with a short course of amphotericin-based therapy could potentially improve their clinical outcomes. However, the dose and duration should be the subject of future research. We would also recommend an enhanced diagnostic approach, especially considering that 11% of those with symptomatic antigenemia had confirmed TB meningitis co-infection. A further proportion may have had TB meningitis missed on CSF testing, thus cryptococcal antigenemia alone still requires comprehensive diagnostic evaluation. CSF culture detected *Cryptococcus* in 3 false negative CSF CrAg tests among 1201 (0.25%) CSF processed; all of whom had their cryptococcal infection detected by blood CrAg testing. In comparison, in the absence of blood CrAg testing, 4.2% (51/1201) would have not had their cryptococcal infection detected by standard CSF culture, CrAg testing, and microscopy. Thus, we strongly recommend an enhanced diagnostic work up for all immunocompromised patients with suspected CNS infection to include blood cryptococcal antigen testing.

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Conflict of interest:

All authors have no financial conflict of interest to declare.

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Figure 1: Study population: 1,201 individuals with suspected meningitis were screened with a blood CrAg test. Overall, 40% (476/1,201) were CrAg negative in blood and excluded from this analysis; all whom were also CSF CrAg negative. Overall, 671 individuals were blood and CSF CrAg positive were diagnosed with cryptococcal meningitis. Of 574 with first episode cryptococcal meningitis, 5 had tuberculous meningitis co-infection and were excluded from this analysis. Of the 54 blood CrAg positive and CSF CrAg negative, 3 were later diagnosed by CSF culture and 2 by PCR with cryptococcal meningitis, 6 were diagnosed with microbiologically confirmed tuberculous meningitis (TBM), and 43 had neurologic symptomatic cryptococcal antigenemia.

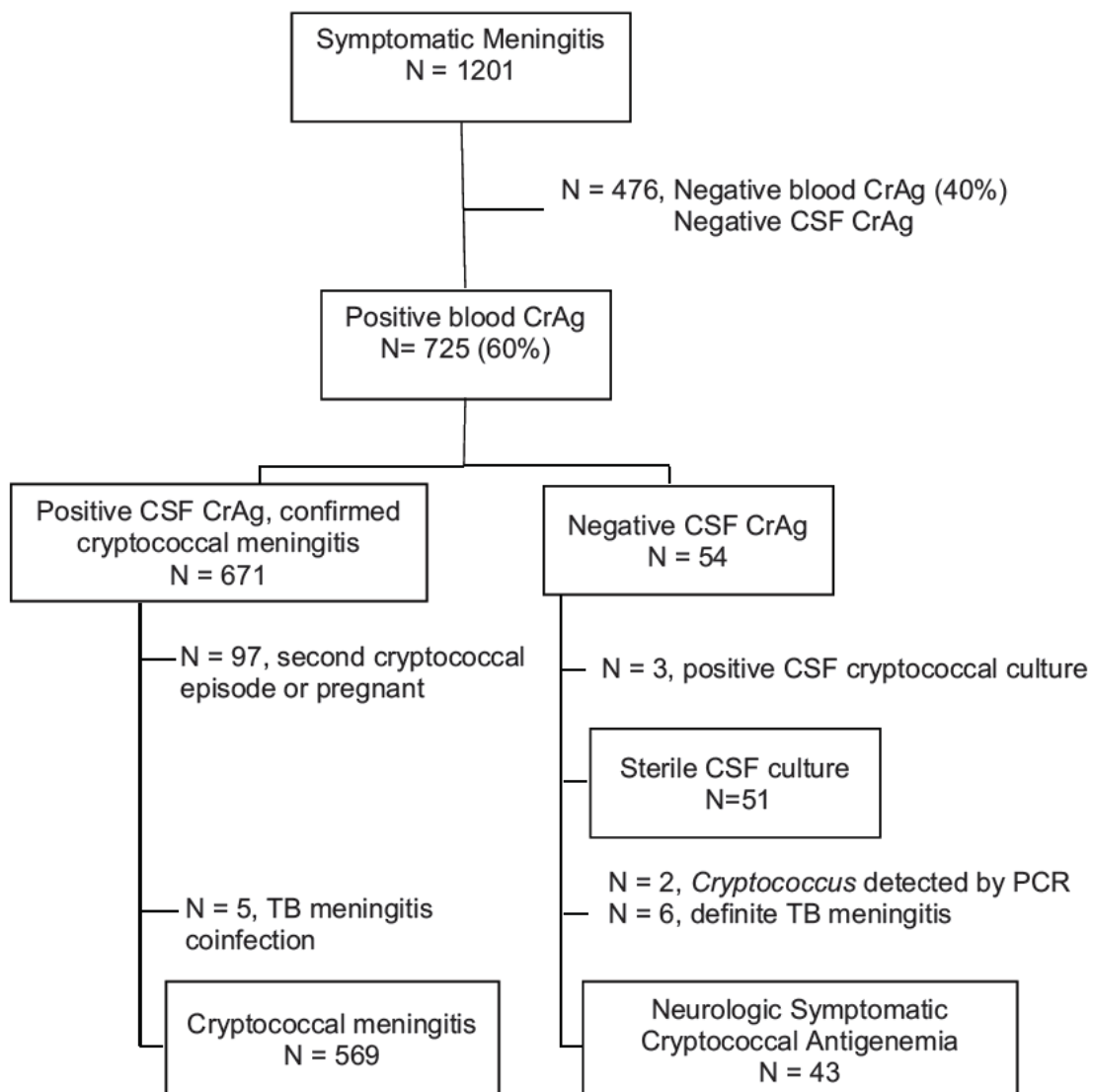


TABLE 1: ALTERNATIVE DIAGNOSES

Diagnostic Testing	Blood CrAg positive & CSF CrAg negative (N=54)	Blood & CSF CrAg positive (N=574)
CSF CrAg positive on repeat testing in laboratory	0	573
CSF <i>Cryptococcus</i> culture positive	3 (6%)	500 (88%)
CSF PCR performed	15 (28%)	86 (15%)
Positive for <i>Cryptococcus</i>	2 (13%)	55 (64%)
Positive for HHV6*	1 (7%)	--
Diagnosed with TBM	6 (11%)	5 (1%)
Positive CSF AFB smear	1 of 47	0 of 14
Positive CSF MTB culture	3 of 33	1 of 43
Positive CSF Xpert MTB/Rif	5 of 48	4 of 46

* additional PCR testing was negative for: *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus (CMV), enterovirus, herpes simplex virus 1 and 2, human parechovirus, varicella zoster virus (VZV)

TABLE 2: BASELINE CHARACTERISTICS OF STUDY POPULATION

Characteristics	Neurologic Symptomatic Cryptococcal antigenemia group (n=43)	Cryptococcal Meningitis group (n=569)	P-value
Men	44% (29%, 59%)	59% (55%, 63%)	0.06
Age, years	38 (30, 45)	35 (29, 40)	0.13
Receiving ART	53% (39%, 68%)	52% (48%, 56%)	0.84
Fever	56% (41%, 71%)	49% (44%, 53%)	0.36
Headache	84% (73%, 95%)	98% (96%, 99%)	<0.01
Photophobia	12% (2%, 21%)	27% (23%, 30%)	0.03
Seizures	5% (0%, 11%)	14% (12%, 17%)	0.07
Cough	21% (9%, 33%)	20% (17%, 24%)	0.91
Abnormal Lung Exam	26% (13%, 39%)	15% (12%, 18%)	0.06
Glasgow Coma Score < 15	48% (33%, 63%)	42% (38%, 46%)	0.47
Hemoglobin, g/dL	10.6 (8.2, 11.9)	11.4 (9.9, 12.9)	<.01
CD4 T cells/ μ L	29 (7, 69)	16 (6, 48)	0.16
Creatinine, mg/dL	0.7 (0.2, 1.1)	0.7 (0.6, 0.9)	0.59
CSF white cells <5 cells/ μ L	84% (73%, 95%)	64% (60%, 68%)	<0.01
CSF protein, mg/dL	31 (22, 67)	43 (21, 94)	0.19
CSF protein <45 mg/dL	63% (48%, 78%)	51% (47%, 56%)	0.15
Opening Pressure, mmH ₂ O	127 (93, 157)	270 (180, 400)	<0.01
Any abnormal: CSF white cells, Protein, or Opening Pressure	44% (29%, 59%)	83% (80%, 86%)	<0.01

Proportions (95% confidence intervals) displayed are out of N with data in group; Median (IQR)

displayed for continuous variables; P-values are from Wilcoxon Rank Sum tests for continuous variables, and Fisher's exact tests for categorical variables. Persons with TBM co-infection are excluded.