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Symptomatic relapse of HIV-associated cryptococcal meningitis in South Africa: the role of inadequate secondary prophylaxis

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Abstract

Objectives—Cryptococcal meningitis is the commonest cause of adult meningitis in Southern Africa. A sizeable proportion of this disease burden is thought to be due to symptomatic relapse of previously treated infection. We carried out a study to examine the contribution of inadequate secondary fluconazole prophylaxis to symptomatic relapses of cryptococcal meningitis.

Design—A prospective observational study.

Setting—GF Jooste Hospital, a public sector adult referral hospital in Cape Town.

Subjects—Patients presenting with laboratory confirmed symptomatic relapse of HIV-associated cryptococcal meningitis between January 2007 and December 2008.

Outcome measures—Relapse episodes were categorized into 1) patients not taking fluconazole prophylaxis, 2) immune reconstitution inflammatory syndrome (IRIS) and 3) relapses occurring prior to ART in patients taking fluconazole. In-hospital mortality was recorded.

Results—There were 69 relapse episodes, accounting for 23% of all cases of cryptococcal meningitis. 43%(n=30) of relapse episodes were in patients not taking fluconazole prophylaxis, 45%(31) were due to IRIS and 12%(8) were in patients pre-ART taking fluconazole. Patients developing relapse due to inadequate secondary prophylaxis had severe disease and high in-hospital mortality (33%). Of the 30 patients not taking fluconazole, 47% (14) had not been prescribed secondary prophylaxis by their healthcare providers. Importantly, we documented no relapses due to fluconazole resistance in this cohort of patients who has received amphotericin B as initial therapy.

Conclusions—Large numbers of relapses of cryptococcal meningitis are due to failed prescription, dispensing, referral for or adherence to secondary fluconazole prophylaxis. Interventions to improve the use of secondary fluconazole prophylaxis are essential.

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Introduction

Cryptococcal meningitis in now the commonest cause of adult meningitis in southern Africa 1 2 and is a major burden on local healthcare services 3. Treatment remains unsatisfactory, with acute mortality in recent series from Africa ranging from 30-50%, even with optimal therapy 4 5. As a result, cryptococcal meningitis is a major cause of mortality in African HIV-infected patients, accounting for 13-44% of all deaths 6-8. Recently published estimates from the Centres for Disease Control and Prevention (CDC) show that cryptococcal meningitis is responsible for 504,000 deaths in sub-Saharan Africa annually 9.

A sizeable proportion of the cryptococcal disease burden is thought to be due to symptomatic relapse of previously treated infection. Recent work has highlighted the contribution made by immune reconstitution syndrome (IRIS) and fluconazole resistance to relapse in South African patients taking secondary fluconazole prophylaxis 10-12.

Without secondary prophylaxis at least 50-60% of patients will have disease relapse 13-15. When used properly secondary fluconazole prophylaxis is highly effective, increasing recurrence-free survival by over 13-fold at 6 months 16 17. Fluconazole has been freely available in South Africa since 2001 through Pfizers donation programme, and current South African guidelines for the treatment of HIV-associated cryptococcal meningitis recommend fluconazole consolidation treatment for all patients following initial amphotericin B therapy, then secondary fluconazole prophylaxis either lifelong, or until the CD4 count is >200 for 6 months on ART 18. Emerging evidence however suggests that the use of secondary fluconazole prophylaxis in South Africa is poor, with only 31.5% of initial prescriptions re-filled at 2 months, and only 6% of patients returning for fluconazole at 1 year 19.

To examine the contribution of inadequate fluconazole prophylaxis to symptomatic relapses of cryptococcal disease we carried out a prospective observational study at GF Jooste Hospital, a public sector adult referral hospital in Cape Town serving a population of 1.3 million (including a large part of Khayelitsha township, population 400 000, with HIV antenatal seroprevalence of 32.7% in 2006 20). Cryptococcus is the commonest cause of meningitis at the hospital, accounting for 63% of microbiologically confirmed cases 21, and the disease burden is high, with over 100 India ink positive cases per year 22.

Methods

Participants

The study was approved by the Research Ethics Committee of the University of Cape Town. Between January 2007 and December 2008 all patients presenting to GF Jooste Hospital with a laboratory confirmed diagnosis of cryptococcal meningitis were prospectively identified. Cases of symptomatic relapse were defined as occurring in patients with the following characteristics: (1) a previous laboratory confirmed case of cryptococcal meningitis, and (2) recurrence of typical cryptococcal meningitis (CM) symptoms, and (3) CSF India ink, antigen test (CRAG) and/or culture positive for *C. neoformans* at this presentation and (4) no alternative diagnosis. A patient could be classified as having more than one relapse episode, provided that there had been a resolution of symptoms and at least 1 month between episodes. During the study period the standard treatment of cryptococcal meningitis at the hospital consisted of two weeks of amphotericin B, at a dose of 1mg/kg, followed by fluconazole 400mg daily as consolidation treatment for 8 weeks, then long term secondary prophylaxis with fluconazole 200mg daily, as per current guidelines 18. As part of ongoing clinical studies 8 of the patients included here had also received additional induction treatment during their initial episode (2 received flucytosine, 4 received IFNγ and flucytosine, and 2 received fluconazole).

Procedures

Details of previous episodes of cryptococcal meningitis, current medications, including anti-retroviral therapy (ART) and anti-fungal medications, and self-reported adherence to medications were recorded. Where patients were not taking fluconazole secondary prophylaxis, the reason for this was ascertained by review of discharge scripts from the initial episode and by interview of the patient, and categorized into patient non-adherence, or failure on the part of healthcare providers to provide the appropriate medication. In patients taking fluconazole prophylaxis, episodes were categorized into either IRIS or non-IRIS relapses, with IRIS defined as (1) microbiologically confirmed first episode of CM and (2) resolution of CM symptoms before starting ART, and (3) self-reported adherence to fluconazole and ART, and (4) recurrence of CM symptoms after initiation of ART, and (5) no alternative diagnosis, including fluconazole resistance, found on laboratory testing and clinical review. All patients had a full clinical work up including lumbar puncture, cell counts, protein and glucose quantification, bacterial cultures and TB cultures where appropriate, and fluconazole mean inhibitory concentrations (MICs) in cases where fluconazole resistance was queried. CM-IRIS cases were further categorized as either CSF culture negative or positive.

During the last 12 months of the study patients were also interviewed by a research nurse to determine levels of knowledge about secondary fluconazole prophylaxis, and what education they had been given on discharge from hospital about the importance and correct usage of such prophylaxis. Additional demographic, clinical and laboratory data, including HIV status, CD4 counts, CSF findings and fluconazole mean inhibitory concentrations (MICs), where available, were obtained from patient hospital notes and computerized laboratory records. In-hospital mortality was recorded for all patients. Fluconazole MICs were determined using Etests (AB Biodisk). Plates were incubated at 35°C for 48h, and MICs were the lowest concentration at which the elliptical inhibition zone intercepted the scale on the strip. Etests have been shown to yield results in good agreement with the broth microdilution method 23. A definitive breakpoint-MIC has yet to be established. Given this, results were interpreted on the basis of the best available evidence using the following criteria: susceptible, MIC of ≤8 mg/mL; dosedependent susceptibility, MIC of 16-32 mg/mL; and resistant, MIC of ≥64 mg/mL 10 24-26.

Analysis

Data were analysed using Stata version 10 (StataCorp). Continuous variables were described as medians with interquartile ranges, and compared using the median test. Categorical data were described using proportions and compared using Pearson's χ^2 test or Fisher's exact test. Statistical significance was defined as $P<0.05$. Odds ratios for mortality with 95% CIs were calculated using logistic regression analysis.

Results

Patients

During the 2-year study period there were 300 episodes of laboratory confirmed cryptococcal meningitis. Of these 300 episodes, 69 were episodes of symptomatic relapse, occurring in 57 patients (6 patients had 2 episodes, one had 3 and one had 5), accounting for 23% of all laboratory confirmed cases of cryptococcal meningitis. Forty three percent (n=30) of relapse episodes were in patients not taking fluconazole prophylaxis, 45% (n=31) of episodes were due to IRIS, and the remaining 12% (n=8) were relapses in patients taking fluconazole prophylaxis, but prior to starting ART (see figure 1). Education of patients about the need for ongoing fluconazole prophylaxis was poor, with 38% (9) of 24 patients questioned (12 IRIS cases, 11 not taking fluconazole and 1 relapse on fluconazole prior to

ART) reporting having received no information about the requirement for fluconazole secondary prophylaxis. There was a correlation between education and adherence to fluconazole. Of the 9 who received no education, 7 were non-adherent (78%), versus 4 of the 15 (27%) who were educated. P=0.015.

Patient demographic, clinical and laboratory features of the relapse episodes are shown in table 1. Overall in-hospital mortality was 23%. Factors significantly associated with in-hospital mortality by univariate analysis were abnormal mental status (OR 7.2, 95% CI 2.1-25.0) and high fungal burden, evidenced by India ink positivity (OR 5.0, 95% CI 1.02-24.1).

Inadequate secondary fluconazole prophylaxis

Patients developing symptomatic relapse of cryptococcal meningitis due to inadequate fluconazole prophylaxis had severe disease, with a high proportion of abnormal mental status (30%), high fungal burdens (70% India ink positive) and high in-hospital mortality (33%). Patients not taking fluconazole were 2.5 times more likely to die in-hospital than those on appropriate fluconazole prophylaxis (OR, 95% CI 0.8-8.0, p= 0.11, univariate analysis).

Of the 30 patients not taking fluconazole, 16 (53%) had been prescribed fluconazole but were non-adherent to therapy. The remaining 14 (47%) had either not been prescribed secondary prophylaxis on discharge from hospital after their initial episode of cryptococcal meningitis, had not been appropriately referred to primary care, or the prescription had not been continued by their primary care providers.

IRIS

Patients developing symptomatic relapse of cryptococcal meningitis due to IRIS had milder disease, with a lower proportion of abnormal mental status (19%) and lower fungal burdens (55% India ink positive) than the other relapse cases, and low in-hospital mortality (13%), although these differences did not reach statistical significance. IRIS episodes occurred a median of 61 days (IQR 31-146) after commencing ART. CSF cryptococcal cultures were positive in 12 (39%) of the IRIS episodes. Fluconazole MICs were performed on 10 of these samples. None of the samples had an MIC ≥ 64 μg/ml suggesting fluconazole resistance. One had an MIC = 32 μg/ml indicating dose dependent susceptibility, raising the possibility that decreased fluconazole susceptibility was a factor in this case, while the remaining 9 all had MICs ≤ 8 μg/ml indicating susceptibility to fluconazole. Although neither a documented immunological or virological response to ART, nor a decrease in fungal burden despite worsening symptoms were required for a diagnosis of IRIS, these were recorded in all but two of the patients. In each of the 19 of 31 IRIS cases where CD4 and viral load data was available, all patients showed a marked decrease in viral load, and rising CD4 counts. In terms of decreasing fungal burden, 19 of 31 cases were culture negative, having been culture positive during the initial episode. A further 4 of the culture positive cases had a low fungal burden as evidenced by the fact that they were India Ink negative at the relapse presentation, 2 more had very scanty growth at the relapse presentation, and 2 had a documented decrease in CLAT titre. Of the two patients who did not have either a documented immunological and viral response, or a documented decrease in fungal burden despite worsening symptoms, a diagnosis of IRIS was clinically made, after ruling out other potential diagnoses, including possible fluconazole resistance (both had fluconazole MICs indicating susceptibility and were reportedly adherent to their medication).

Relapses prior to ART

Eight patients developed symptomatic relapse episodes while reporting adherence to appropriate secondary fluconazole prophylaxis, but before commencing ART. Of these, 4 were early relapses (within 1 month of discharge), and probably represent failure to respond to initial treatment rather than true relapse. The remaining 4 cases occurred at 50, 70, 104 and 196 days after the initial episode. Fluconazole MICs were performed in 2 of the 4 cases, and were both ≤ 8 μg/ml. In 3 of these 8 cases treatment of the initial episode of cryptococcal meningitis was inadequate (1 patient received fluconazole monotherapy, 2 had less than 2 weeks of amphotericin B). Two of the three patients who received inadequate initial therapy relapsed early (at 21 and 26 days post initial diagnosis) supporting the suggestion that these early relapses represented failure of initial treatment. The third relapsed at 50 days.

Discussion

Symptomatic relapse cases account for a large proportion (23%) of all cryptococcal meningitis cases admitted to our hospital. Almost half (43%) of these episodes occur in patients not taking secondary fluconazole prophylaxis, and outcomes in these patients are poor, with one third dying in hospital. Much of this morbidity, mortality and the associated costs to the health service are entirely preventable. Evidence for the efficacy of fluconazole consolidation and maintenance therapy is strong 16 17 27, treatment guidelines are clear 18, and the drug is made freely available to the South African public healthcare sector. That so many patients are presenting with symptomatic relapses while not taking fluconazole demonstrates a failure of the health care services, and highlights inadequacies in patient education, discharge planning and communication between secondary and primary providers. In 47% of these cases fluconazole had not been prescribed or dispensed by healthcare providers, or patients had not been properly referred to primary care services for continuation of their fluconazole. In the remaining cases patient non-adherence, in part, reflects a lack of patient education surrounding the importance of secondary prophylaxis, 38% of patients questioned reporting having received no education in this regard. Factors likely contributing to the inadequate patient education, and poor prescription, dispensing of, and referral for fluconazole in our setting, in common with many public sector health care facilities in South Africa, are heavy workloads, high turnover of junior staff, and language barriers.

Even with appropriate secondary fluconazole prophylaxis not all cases of symptomatic relapse can be prevented. Forty five percent of relapse cases in this study were due to IRIS, and 12% occurred in patients prior to ART despite taking fluconazole. Crypococcal IRIS is well recognized, and reported to occur in 6-30% of patients with cryptococcal meningitis following commencement of ART 28 29. IRIS accounted for 10% (31 of 300) of all cryptococcal meningitis episodes at our hospital, occurring at a median of 61 days after commencing ART, consistent with data from three recent South African cohorts where the median time to onset of IRIS symptoms after starting ART was 1- 2 months 10 12 30.

Compared to the non-IRIS relapse cases in this cohort the patients presenting with IRIS had less severe clinical disease, lower fungal burdens and a lower mortality of 13%.

There were few cases of symptomatic relapse in this cohort occurring in patients taking fluconazole and prior to commencing ART. Once very early relapses (within one month), which probably represented ongoing manifestations of the initial presentation, were excluded, only 4 patients fitted into this category. These cases may represent true failures of fluconazole prophylaxis, although poor fluconazole adherence is a possibility, as we only

assessed adherence by self-report. In the two cases without MICs available, fluconazole resistance cannot be excluded as a factor.

Of note, no fluconazole resistant isolates of *Cryptococcus neoformans* (MIC ≥ 64 μg/ml) were seen during the entire two-year study period, which contrasts markedly with an earlier study involving patients from the same hospital 10. Between 2003 and 2005, after patients not taking fluconazole secondary prophylaxis were excluded, 32 relapse episodes in 27 patients were reported. 21 of these were culture positive, of which 14 had isolates with resistance to fluconazole (MIC ≥ 64 μg/ml), and a further 2 had isolates with dose dependent susceptibility (MIC 16-32 μg/ml) 10. An explanation for this disparity is the switch to amphotericin B as initial treatment at our hospital, in early 2005. At the time of the earlier study (2003-5) the standard initial therapy for cryptococcal meningitis was fluconazole monotherapy 400mg/day. Clearance of cryptococci from the CSF has been shown to be very slow with fluconazole 4, a fungistatic agent, and the use of fluconazole as initial therapy may have promoted the development of drug resistance due to ongoing high fungal burdens and drug exposure over prolonged periods 31. The fungicidal effects of amphotericin B, leading to faster clearance of cryptococci from the CSF 4, followed by a switch to fluconazole once the fungal burden has been markedly reduced, appears to have minimized the risk of developing later fluconazole resistance.

Our study had several limitations, notably the reliance of patient self-reporting of both fluconazole adherence, and of education received relating to secondary prophylaxis on discharge from hospital after the initial meningitis episode. While the number of patients developing relapse prior to ART while reporting adherence to fluconazole was small, and false reporting of non-adherence is unlikely, non-adherence to fluconazole can also not be entirely ruled out as a factor in some of the culture positive IRIS cases.

In conclusion relapses of previously treated disease constitute a significant proportion of the cryptococcal meningitis disease burden. A switch from fluconazole to amphotericin B as initial treatment has been associated with virtual elimination of the problem of secondary fluconazole resistance at our centre, however large numbers of relapses are due to inadequate use of secondary fluconazole prophylaxis, and are entirely preventable. Efforts need to be made to strengthen both patient and provider knowledge about the importance of secondary fluconazole prophylaxis in treatment of cryptococcal meningitis and improve health system performance in this regard.

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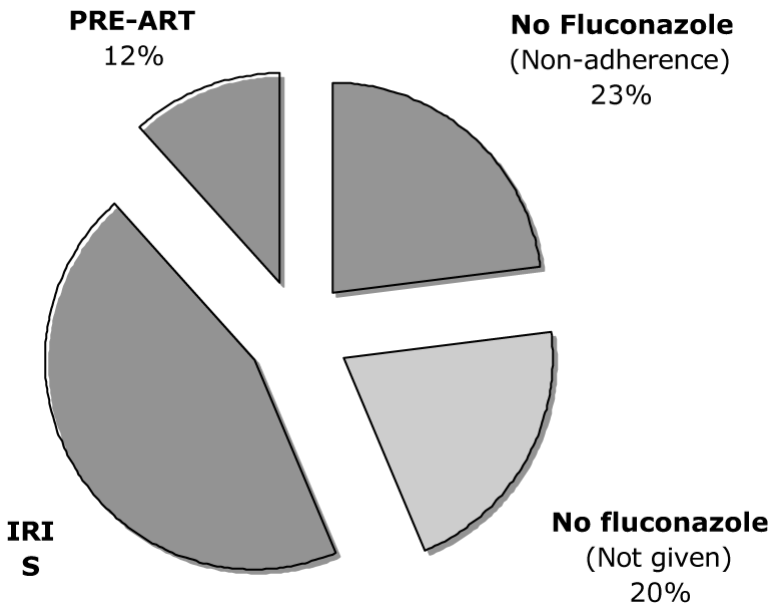

Figure 1. Causes of Symptomatic Relapse

Causes of symptomatic relapse of cryptococcal meningitis, divided in to immune reconstitution inflammatory syndrome (IRIS) in patients taking ART, absence of fluconazole secondary prophylaxis (subdivided into patient non-adherence and not given - either not prescribed, not dispensed, or not continued at primary care level), and relapses in patients taking fluconazole prior to starting ART.

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Table 1

Demographics, clinical features and outcomes of 69 episodes of symptomatic relapse of cryptococcal meningitis

	IRIS (n=31)	**No fluconazole (n=30)**	**Pre-ART, on fluconazole (n=8)**	***P value*** *
Age (years)	33 (29-42) **	35 (28-42)	33 (26-39)	*0.63*
Sex (% male)	52%	50%	50%	*0.99*
CD4 count (cells/μl) ***	77 (15-130)	46 (20-154)	60 (39-109)	*0.84*
Time from initial episode - relapse (days)	87 (56-146)	103 (67-156)	48 (23-96)	*0.28*
On TB treatment	37% (11)	46% (12)	25% (2)	*0.53*
Abnormal mental status (%) ****	19% (6)	30% (9)	25% (2)	*0.63*
CSF lymphocytes (x10^6/L)	7 (4-65)	8 (1-58)	6 (1-56)	*0.99*
CSF protein (g/dL)	1.08 (0.8-1.6)	0.97 (0.5-2.0)	0.4 (0.3-0.8)	*0.07*
CSF glucose (mmol/L)	2.0 (1.5-2.7)	2.0 (1.2-2.7)	2.6 (1.5-3.1)	*0.28*
India Ink positive (%)	55% (17)	70% (21)	88% (7)	*0.17*
In-hospital mortality	13% (4)	33% (10)	25% (2)	*0.17*

* P-values were calculated using Pearson's χ^2-test or the median test.

** Continuous variables are expressed as median (inter-quartile range).

*** CD4 cell count at time of relapse or most recent count within 6 months prior to relapse.

**** Abnormal mental status was defined as any reduction in level of consciousness (confusion or Glasgow coma score < 15) or a history of seizures.