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Is HIV-associated tuberculosis a risk factor for development of cryptococcal disease?

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Abstract

Cryptococcal meningitis (CM) and TB are leading causes of mortality in patients initiating ART in Africa. We hypothesized that a history of TB may predispose to development of CM and examined the association using multivariate logistic regression in a cohort of patients initiating ART. History of pulmonary TB was independently associated with development of CM (OR 6.6; 95% CI 1.3–32.7) after adjustment for covariates including CD4 counts. A number of potential mechanisms may underlie this association.

Keywords

Cryptococcus neoformans; cryptococcosis; Tuberculosis; Africa; antiretroviral therapy; HIV

Introduction

Cryptococcal meningitis (CM) is a leading cause of mortality in AIDS patients in the developing world [1]. However, the pathophysiology and natural history of infection with *Cryptococcus neoformans* remain poorly understood. Acute infections following heavy exposure are reported [2], but most HIV-related clinical disease is thought to result from reactivation of “latent” pulmonary infection acquired many years earlier [3]. The key

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Conflicts of Interest

The authors have no conflicts of interest

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predisposition to disease development is HIV-related loss of T-cell immunity [4]. However, other factors influencing either the acquisition of infection, re-activation and subsequent dissemination are unknown.

In Cape Town, South Africa, we have noted that a substantial proportion of patients with CM have a history of tuberculosis (TB). Together these are two leading causes of morbidity and mortality among patients accessing antiretroviral therapy (ART) in Africa [5] and a possible association between these diseases has previously been noted [6-8]. Although this might simply reflect a shared association with CD4 lymphocytopenia, we hypothesized that TB may directly affect risk of cryptococcal disease via a number of potential mechanisms. We therefore examined this relationship in a cohort of patients enrolling in an ART service in Cape Town [9-11].

Clinical data were collected from consenting patients with approval from the Research Ethics Committee of the University of Cape Town. Data from previous studies of TB [10] and cryptococcal disease [9] were available for sequential patients enrolling in this well-characterised ART cohort between September 2002 and April 2005. The main outcome was development of microbiologically confirmed CM during the first year of follow-up and the temporal association with a history of previous TB or prevalent TB (the latter defined as TB episodes which were either diagnosed or already being treated at enrolment). TB diagnoses were established as previously described in detail for this cohort [10]. Statistical comparisons were made using the χ^2 or Fisher's exact tests. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using logistic regression modeling.

Data were available for 707 patients of whom 26% were male. The median age was 33 years (IQR 28-38), 52% had stage 3 disease and 28% stage 4 disease. The median baseline CD4 count was 97 cells/ μ L (IQR 46-157) and viral load 76,803 copies/ml (IQR 33,167-191,030). Most patients (n=636; 90%) started ART, and of these, 28 (4%) were lost to follow up and 58 (9%) died during the first year of ART. Among these losses, very few patients (n=4) had detectable cryptococcal antigen detectable in serum at baseline and all remained free of cryptococcal disease prior to leaving the programme (after a median of 47 days). All those lost to follow-up or who died were therefore assumed not to have CM at the end of the 1-year study and all 707 patients were included in the analysis.

A history of pulmonary TB (PTB) was recorded in 45% (n=308) of the cohort, and extrapulmonary TB (EPTB) in 8% (n=55). These episodes (PTB and EPTB) occurred within 2 years prior to enrollment in 66% (n=241), between 3 and 5 years in 26% (n=95), and more than 5 years earlier in 7% (n=27). Prevalent TB was present in 19% (n=137). CM developed in 2% (n=13) of the cohort a median of 35 days after initiating ART; 6 of these had a history of previous CM a median of 140 days prior to enrollment.

Of patients who developed CM, 85% (n=11) had a history of TB (all PTB). This preceded the initial episode of CM in 5 of the 6 relapse cases, and only one patient was on rifampicin at the time of relapse. In univariate analysis, a history of previous TB was associated with development of CM (OR 4.94; 95% CI 1.1-22.4, p=0.039). When restricted to PTB, the association was stronger (OR 6.87; 95% CI 1.5-31.2, p=0.013) and when restricted to PTB within two years prior to enrollment, the odds ratio was 8.7 (95% CI 2.4-32.0, p=0.001). Prevalent TB was not significantly associated with CM (OR 0.75; 95% CI 0.16-3.4, p=0.7). Multivariate analysis revealed that both baseline CD4 cell count and history of PTB within the preceding 2 years were strong and independent predictors of the development of CM (PTB within 2 years OR 6.6, 95% CI 1.3-32.7, p=0.02, see table).

Despite the common association between CD4 lymphocytopenia and development of TB and CM, our data suggest that a history of PTB within the last 2 years may be an

independent risk factor for subsequent development of CM. The observation that prevalent TB episodes were not significantly associated may relate to the fact that any impact on cryptococcal disease risk during the period of follow-up is likely to have been curtailed by the rapid ART-induced restoration of immune function and the resulting protection against CM.

A number of possible mechanisms may underlie the observed association between these two diseases. *Cryptococcus neoformans* is ubiquitous, and exposure through inhalation of fungal spores is common [12, 13] and yet only approximately 10% of AIDS patients develop cryptococcal disease [4]. This suggests CD4-independent factors may also be important. A shared immunological deficit may allow entry and/or dissemination of both *Mycobacterium tuberculosis* and *Cryptococcus neoformans*. Defects in pulmonary innate immune function, for example, may underlie high rates of both TB and cryptococcal disease in gold-miners with silicosis [14]. Vitamin D-deficiency is associated with defects in production of cathelicidins by macrophages; these are known to be involved in innate responses to both organisms [15, 16]. Post-tuberculous lung disease is a strong risk factor for respiratory infections, including low-grade pathogens [17], and might serve as either a portal of entry for new infection, impair clearance, promote re-activation of latent infection or facilitate its dissemination. Convincing evidence exists for latent cryptococcal infection in animal models [18] and humans [19] and reactivation of infections after at least 9 years [3]. Although factors leading to reactivation remain largely unknown, the development of an immunosuppressive phenotype that accompanies active TB [20] could conceivably promote cryptococcal reactivation. Studies are required to explore these various hypotheses.

Patients enrolling in ART cohorts are subject to survival biases and observed associations may be subject to residual confounding. The specificity of the observed association has not been demonstrated and it is possible that the risk of serious opportunistic diseases other than CM may also be increased following episodes of TB. Thus, the observed association requires confirmation in prospective studies. The association was nevertheless robust and the temporal relationship plausible. This finding is supported by data showing that cryptococcal disease is an important cause of late mortality in African patients receiving TB treatment [21]. Not only must clinicians be vigilant to the possibility of cryptococcal disease in patients with a recent history of TB, it also may be appropriate to screen such patients for subclinical disease using cryptococcal antigen tests prior to ART initiation.

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Table

Univariate analysis and Multivariate model examining the relationship between previous history of TB and subsequent development of CM.

Cryptococcal meningitis	Odds ratio	95% CI	P value
<i>Univariate analysis</i>			
Age (10 years increments)	1.19	0.6 – 2.2	0.6
Sex (female vs male)	0.79	0.2 – 2.6	0.7
CD4 count (50 cells/ μ L increments)	0.39	0.2 - 0.7	0.005
Viral load (Log ₁₀ copies/ml increments)	3.52	1.0 – 12.4	0.05
History of TB (PTB + EPTB)	4.94	1.1 – 22.4	0.04
History of PTB (all cases)	6.87	1.5 – 31.2	0.01
History of PTB (previous 2 years)	8.70	2.4 – 32.0	0.001
History of EPTB	-----*	-----	0.61
Prevalent TB	0.75	0.2 – 3.4	0.7
<i>Multivariate model[†]</i>			
Age (10 year increments)	0.93	0.4 - 2.1	0.9
Sex (female vs male)	1.03	0.3 - 3.8	1.0
CD4 count (50 cells/ μ L increments)	0.41	0.2 - 0.9	0.02
Viral load (Log ₁₀ copies/ml increments)	1.87	0.5 – 6.7	0.3
History of PTB			
- previous 2 years	6.6	1.3 - 32.7	0.02
- 3-5 years ago	1.99	0.2 - 23.4	0.6
Prevalent TB	0.89	0.2 - 4.4	0.9

* No cases of EPTB occurred in patients developing CM, hence an odds ratio is not presented. If the 0 cell is replaced with 0.5 the OR = 0.4, p=0.61 on Fisher's exact test.

[†] Variables were included in the logistic regression model if they were significantly associated with the primary outcome in bivariate analysis (p<0.2) or if they were deemed clinically relevant based on previous literature. CD4 count, viral load and age were included as continuous variables, the remainder as dichotomous variables. PTB = pulmonary TB. EPTB = extrapulmonary TB. History of TB over 5 years previously was not included in the final model due to small numbers (27), and as it occurred in none of the patients who subsequently developed disease.