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Research article

Asymptomatic cryptococcal antigenemia is associated with mortality among HIV-positive patients in Indonesia

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Abstract

Introduction: Previous studies, mostly from Africa, have shown that serum cryptococcal antigenemia may precede the development of cryptococcal meningitis and early death among patients with advanced HIV infection. We examined cryptococcal antigenemia as a risk factor for HIV-associated mortality in Indonesia, which is experiencing a rapidly growing HIV epidemic.

Methods: We included ART-naïve HIV patients with a CD4 cell count below 100 cells/μL and no signs of meningitis in an outpatient HIV clinic in Bandung, West Java, Indonesia. Baseline clinical data and follow-up were retrieved from a prospective database, and cryptococcal antigen was measured in stored serum samples using a semiquantitative lateral flow assay. Cox regression analysis was used to identify factors related to mortality.

Results: Among 810 patients (median CD4 cell count 22), 58 (7.1%) had a positive cryptococcal antigen test with a median titre of 1:80 (range: 1:1 to 1:2560). Cryptococcal antigenemia at baseline was strongly associated with the development of cryptococcal meningitis and early death and loss to follow-up. After one year, both death (22.4% vs. 11.6%; $p = 0.016$; adjusted HR 2.19; 95% CI 1.78–4.06) and the combined endpoint of death or loss to follow-up (67.2% vs. 40.4%; $p < 0.001$; adjusted HR 1.57; 95% CI 1.12–2.20) were significantly higher among patients with a positive cryptococcal antigen test.

Conclusions: Cryptococcal antigenemia is common and clinically relevant among patients with advanced HIV in this setting. Routine screening for cryptococcal antigen followed by lumbar puncture and pre-emptive antifungal treatment for those who are positive may help in reducing early mortality.

Keywords: cryptococcal antigenemia; meningitis; AIDS; antigen testing; lateral flow assay; Indonesia.

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Introduction

Cryptococcal meningitis is a major cause of subacute meningitis and death in patients with advanced HIV infection, affecting an estimated one million people each year, especially in sub-Saharan Africa [1,2]. Cryptococcal meningitis is usually diagnosed by microscopic detection or culture of cryptococcus from cerebrospinal fluid (CSF), or detection of cryptococcal antigen in CSF or serum [3–5]. Serum cryptococcal antigen has also been found in HIV patients without clinical meningitis. In a cohort in South Africa, cryptococcal antigen screening adequately identified patients at risk for cryptococcal meningitis and death [6]. Therefore, pre-emptive antifungal treatment for patients with asymptomatic serum cryptococcal antigenemia has been advocated [7,8]. Besides the South African study, several studies, most of them smaller, have been published from Uganda, Thailand and Cambodia [3,9–13]. We report the largest cohort study so far, from Indonesia, which has one of the most rapidly growing HIV epidemics in Asia [14]. Most HIV patients in Indonesia present with advanced disease, and early mortality is very high [15]. We determined the prevalence of serum cryptococcal antigenemia and its effect on mortality among ART-naïve patients with a CD4 count below 100 cells/μL.

Methods

Setting and design

The study was conducted in Hasan Sadikin Hospital, the top referral hospital which serves the 42 million people of West Java Province, Indonesia. Since December 2004, integrated in- and outpatient services are provided for HIV-positive individuals. Services include HIV counselling and testing, HIV treatment and management of opportunistic infections. Since September 2007, patients are included into a cohort study and characterized prospectively using a standard questionnaire, physical examination and laboratory examination. Baseline blood samples are archived for all patients. Patients on ART generally visit the clinic monthly, with scheduled clinical and laboratory follow-up, including the measurement of CD4 cell count and plasma HIV-RNA [16]. Patients with symptoms suggesting central nervous system infection are referred to a neurologist for further investigations. CSF, if taken, is examined for *M. tuberculosis,* bacteria and cryptococcus [17]. Cryptococcal meningitis is diagnosed if cryptococcus is found in CSF, either with direct India ink staining or culture, or if cryptococcal antigen testing is positive. Patients diagnosed with cryptococcal meningitis are treated with