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Cryptococcosis in HIV-infected hospitalized patients in Germany: Evidence for routine antigen testing

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Summary *Objectives:* To investigate the diagnostic value of routine cryptococcal antigen (CRAG) testing in HIV-infected patients in a low prevalence setting.
Methods: Retrospective single centre cohort study of a 10-year period (2005–2014).
Results: 5461 patients tested for CRAG were included. Cryptococcal antigenaemia was found in 1.6% and 1.1% of patients with CD4 counts of $\leq$100/μl and 101–200/μl, respectively. The positive predictive values for identifying clinically relevant cryptococcal disease was 96% and 100%, respectively. Half of the patients had a non-specific presentation and median time-to-diagnosis was high (5 days, range 1–44 days). The median time-to-diagnosis in direct admissions to our centre with routine CRAG testing was significantly shorter: 1 day (range: 1–17) vs. 7 days (range: 2–44), $p = 0.003$. Prevalence of cryptococcal antigenaemia was 2.8% in patients with pneumocystis pneumonia and median time-to-diagnosis of cryptococcosis was significantly longer in this subgroup (15 days; range: 1–44 vs. 3 days; range: 1–17; $p = 0.008$). CRAG titres $\geq$1:512 were associated with disseminated disease (OR 21.3, $p = 0.0008$, 95% CI 1.64–277), however, 10% of patients with disseminated cryptococcosis had CRAG titres <1:16.
Conclusion: Our data support routine CRAG testing in hospitalized HIV-infected patients with CD4 counts $\leq$200/μl, and/or pneumocystis pneumonia.

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Introduction

HIV-associated cryptococcosis is a serious disease with a significant morbidity and mortality and can present with a myriad of clinical symptoms.[1–3] The disease is rare in Western Europe and diagnostic delays are common.[4] Cryptococcal antigenaemia is defined as the presence of cryptococcal capsular polysaccharide antigen (CRAG) in the blood.[5] Cryptococcal antigenaemia can be the result of a clinically relevant cryptococcal infection, most frequently of the meninges. However, it can also be the sole finding in an asymptomatic patient in whom cryptococcal disease cannot be detected despite extensive investigations. The latter group of patients is classified as having asymptomatic cryptococcal antigenaemia (ACA). However, this term might be misleading in two ways. On the one hand, around 20% of patients with culture-proven cryptococcal meningitis lack classical neurological signs and symptoms such as headache or altered mental state[4] and might present "asymptomatically". On the other hand, patients without cryptococcal meningitis or overt signs of sepsis or organ involvement can be diagnosed as having ACA but do in fact have mild symptoms such as fever and malaise.[6–8] Therefore, an alternative term "isolated positive cryptococcal antigenemia" (IPCA) seems more appropriate for patients with cryptococcal antigenaemia after exclusion of cryptococcal meningitis, cryptococcaemia and organ manifestations.[9] Interestingly there is growing evidence that IPCA preceeds clinical infection.[10–12]

Data on the prevalence of cryptococcosis and cryptococcal antigenaemia in Western Europe is limited[13–16] and currently there are no recommendations for routine CRAG screening in this setting.

In this study we sought to determine the prevalence of cryptococcal antigenaemia and analyse the spectrum of the underlying cryptococcal diseases including IPCA in HIV-infected patients of predominately European origin stratified by levels of immunosuppression. We aim to contribute to future recommendations for CRAG testing in Europe.

Methods

Patients

We reviewed the medical records of adult HIV-infected patients hospitalized in the Department of Infectious Diseases of the Vivantes Auguste-Viktoria Klinikum (AVK) Berlin, Germany, who had received serum CRAG testing on admission between, 1st of March 2005 and 31st of February 2014. The department is a major HIV-medicine referral centre receiving around 950 HIV-infected patient admissions per year. The catchment population consists mainly of white male Europeans with a smaller fraction of patients from Sub-Saharan Africa and South-east Asia.

In line with the internal standard operating procedure all HIV-infected patients with low or unknown CD4 count received routine serum CRAG testing on admission. The results were generally available the morning of the next working day. This protocol was implemented for the whole study period. In practical terms, all patients admitted to the ward with i) a newly diagnosed HIV infection, ii) presumed opportunistic infection, iii) presumed failure of antiretroviral treatment, and finally iv) a CD4 cell count below 200/μl were tested for serum CRAG. The majority of the patients with immunologically and virologically controlled HIV disease, who were admitted to the ward with a non-HIV related problem, did not receive CRAG testing.

Latex agglutination test was used for CRAG testing during the whole study period. The test has been validated and widely used with high sensitivity (97–100%) and specificity (86–100%).[17,18] A commercial Latex Agglutination Test produced by IMMY Immunomycologics, Inc., Norman, OK, USA was used in the study period. The test was performed on whole blood and CSF samples by examined laboratory technicians. The test was reported as negative if the screening test performed on undiluted patient specimen read negative. The reactivity was graded from 0 ("negative") through 1+ ("weak") to ≥2+ ("strong"). All weakly reactive specimens (1+ reaction) were tested for prozone effect by titration, this was found in one specimen. All 2+ or stronger reactions were reported as positive. All positive specimens underwent a titration procedure. The titre was reported as the highest dilution still showing strong reaction. False-negative results are rare and might be caused by very low CRAG burden, early infection, presence of immune complexes, prozone effect and poorly encapsulated strains with low production of polysaccharide.[19] National Centre for Mycotic Disease, Canada evaluated Latex Agglutination Test Kit by Immunomycologics in a study in 1993 and found both the sensitivity and the specificity of 100%.[20]

For the patients with a positive serum CRAG titre we reviewed all their available medical records, including but not limited to admission notes, communications with general practitioners and referral letters.

Cryptococcal meningitis was defined in the majority by a positive cryptococcal CSF culture. Additionally, one patient was diagnosed based on a positive blood culture with a positive CSF India ink stain. Three patients were diagnosed based on a positive cryptococcal antigen (CRAG) titre in the CSF with a positive India ink stain and a meningeal syndrome that responded to antifungal therapy. One patient was diagnosed by a brain biopsy and one patient was diagnosed post-mortem.

Disseminated cryptococcosis was defined according to Infectious Disease Society of America (IDSA) criteria as involvement of at least 2 non-contiguous sites, or cryptococcaemia.[21]

Localized cryptococcosis without signs of dissemination was defined as pulmonary cryptococcomas, pneumonia with a pleural effusion, or focal lymphadenopathy diagnosed either by pleurocentesis or biopsy. With the additional requirement of both negative blood cultures and a CRAG titre <1:512.[21]

IPCA ("asymptomatic" cryptococcal antigenaemia) was defined as cryptococcal antigenaemia without cryptococcaemia or unequivocal organ manifestation after exhaustive investigations including lumbar puncture and thoracic imaging.