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Identification of *Cryptococcus* Antigen in HIV-positive Turkish Patients by Using the Dynamiker® Lateral Flow Assay

Running Title: CrAg prevalence in HIV-positive adults in Turkey

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CrAg-positive patients, the median CD4 level was 666 cells/μL (115–1,344 cells/μL), with a median viral load of 23 copies/mL (0–3.69×10^6 copies/mL). In HIV-positive CrAg-negative patients, the median CD4 level was 633 cells/μL (31–2,953 cells/μL) and the median viral

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CrAg-LFA became available in 2011 and has since then been used worldwide; currently, it is considered an ideal diagnostic test for CrAg detection.[5–7,16] IMMY CrAg-LFA has been approved by the US Food and Drug Administration (FDA) for use with both serum and CSF, and has also received the Conformité Européenne mark for serum, plasma, and CSF, thus complying with the essential requirements of the European Conformity Directives.[3,17] Recently, Datcu et al.[18] and Ding et al.[19] compared the new Dynamiker®- and IMMY-CrAg LFA tests using both serum and CSF samples of patients with suspected or confirmed cryptococcosis and reported that the sensitivity and specificity of the Dynamiker® LFA test were 100% and 89.5–90%, respectively. A similar study also reported that the Kappa values for CSF and serum samples for Dynamiker® CrAg-LFA test were 0.972 and 0.955, respectively.[20] Furthermore, the Dynamiker® CrAg-LFA test is approved by the FDA, and most importantly, these studies provided clinical validation of the Dynamiker® LFA test.[18–20]

CrAg-LFA meets the requirements of low-income countries and the World Health Organization (WHO) affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users (ASSURED) criteria for diagnostic tests.[16,17,21,22] CrAg is detectable in serum between 5 and 234 (median 22) days before the onset of cryptococcal meningoencephalitis (CM) symptoms, which emphasizes the necessity of screening for serum CrAg as an independent predictor of CM and death.[23] Furthermore, the WHO recommends screening for CrAg for all human immuno-deficiency virus (HIV)-seropositive individuals with a CD4 cell count < 100 cells/μL.[22] Therefore, testing of plasma or serum samples with CrAg-LFA may potentially identify patients with asymptomatic infection who should receive pre-emptive fluconazole.[22,24]

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In Turkey, *Cryptococcus* was first isolated in 1959 from a patient with intestinal infection,[25] and only 66 registered cases of CM were reported from that time until 2017; of these cases, only 14 were patients with HIV/acquired immune-deficiency syndrome (AIDS).[26] Considering the undiagnosed and/or underreported HIV/AIDS cases and the published incidence rates, 106 patients with CM can be expected in Turkey each year (0.13/100,000 individuals).[26] Currently, however, there are no data on the prevalence of cryptococcal antigenemia or CrAg testing recommendations in Turkey, despite a growing number of HIV-positive individuals. Although it was reported that, in 2001–2013, the global annual number of HIV infections decreased by 38%, followed by a significant decline in AIDS-related deaths, the trends regarding new HIV infections differ among regions and countries.[27] In Turkey, 19,748 HIV-positive patients (24/100,000 individuals) were reported from 1985 to 2018, and the number of diagnosed HIV carriers (including 1,772 AIDS patients) dramatically increased (by 450%) after 2012.[28] Therefore, it is very important to identify the potential risk of CM prior to the onset of symptoms based on the presence of CrAg detected by sensitive tests.

The aim of this study was to determine the prevalence of asymptomatic *Cryptococcus* antigenemia in Turkey among adult HIV-positive patients and HIV-negative individuals by using the Dynamiker® CrAg-LFA test.

MATERIALS AND METHODS

Collection and storage of clinical samples

Prior to implementation, the protocol for this study was approved by the Ethics Committee of the Faculty of Medicine of the University of Çukurova, Adana, Turkey. This study was performed in compliance with the Declaration of Helsinki. Overall, 254 HIV-positive adult

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patients who were admitted to the outpatient clinic of the Çukurova University Medical Faculty Department of Infectious Diseases and Clinical Microbiology between June 2018 and February 2019 were included in the study. One hundred age- and sex-matched HIV-negative adult patients not receiving any immunosuppressant drugs were also enrolled as controls. During admission, the patients provided written, informed consent, upon which 5 mL of blood was drawn from each patient, centrifuged at 3,500 rpm for 10 min, and then the separated serum was transferred into a 1.5-mL Eppendorf tube. The samples were preserved at –80°C until analysis.

Collection of patient information

For each patient included in the study, the HIV-positive patient form was obtained; it included demographic information, CD4 cell count, anti-retroviral therapy (ART) status, HIV-RNA levels, active complaints, and findings of physical and radiological examinations.

Identification of CrAg in serum samples using LFA

Serum samples were incubated at 26°C for 30 min and then examined for the presence of CrAg using the Dynamiker® CrAg-LFA kit (Dynamiker Biotechnology Co. Ltd., Tianjin, China). According to the manufacturer's recommendations, 80 μL of each serum sample was slowly added to the sample application pad; after 15 min, test results were read and recorded. Presence of two red lines, test line (T) and control line (C), indicates cryptococcal antigen; while appearance of a single control line (C) and no red test line (T) indicates the absence of cryptococcal antigen. One test per patient was performed. The projected cost of the CrAg-LFA screening was 8.5 USD/test.

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Statistical analysis

All analyses were performed using the SPSS Statistics version 20.0 statistical software package (IBM, Armonk, NY). Categorical variables (CrAg-LFA positivity rates among HIV-positive and -negative patients) were expressed as numbers and percentages and the difference between groups was compared using chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

The results of the LFA test indicated that among the 254 HIV-positive patients, 28 (11%; 23 men and 5 women) with a median age of 39.1 years (range: 21–63 years) were CrAg-positive, whereas 226 (89%; 191 men and 34 women [gender of one patient not recorded]) with a median age of 39.2 years (range: 18–75 years) were CrAg-negative (Table 1). There were no CrAg-positive cases among the 100 HIV-negative individuals (82 men and 18 women; median age, 42.3 years; range: 18–67 years) (Table 1). Statistical analysis revealed that CrAg positivity was significantly higher in HIV-positive patients than in HIV-negative individuals (x^2=11.970; P<0.05). The difference in demographic characteristics between the groups was not statistically significant (P>0.05).

The median CD4 count in HIV-positive CrAg-positive patients was 666 cells/μL (range: 115–1,344 cells/μL). Interestingly, 27 of 28 CrAg-positive patients had a CD4 count > 200 cells/μL, while none of those with a CD4 count < 100 cells/μL was CrAg-positive. Among the 28 patients, 6 were newly diagnosed with HIV and their blood samples were taken before the start of ART, whereas 22 patients had been receiving ART for at least 7 months. In 10 patients, the HIV-RNA test was negative, and in 18 patients, 20 to 3.69×10^6 copies/mL of virus RNA were detected.

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The median CD4 count in 226 HIV-positive CrAg-negative patients was 633 cells/μL (range: 31–2,953 cells/μL); among them, 38 were newly diagnosed with HIV and were not receiving ART. In 88 patients, the HIV-RNA test was negative, and in 136 patients, the HIV-RNA levels (not recorded in the system for two patients) ranged from 20 to 1.95×10^6 copies/mL; for two patients, HIV-RNA levels were not detected. The differences in CD4 counts and HIV-RNA levels (copies/mL) between HIV-positive CrAg-positive and CrAg-negative patients were not statistically significant (x^2=0.134; P>0.05).

The geographical distribution of the 28 CrAg-positive HIV-positive patients is shown in Fig. 1. Fifteen patients were from Adana and 13 from nearby cities and towns. No apparent relationship between the presence of antigenemia and location was found.

DISCUSSION

We here found an unexpected high rate of seropositivity in HIV-positive patients (11%) and a lack of positivity in HIV-negative controls by using the Dynamiker® CrAg-LFA test in which results can be obtained in 15 min. Unlike the WHO recommendation,[22] most of our HIV-positive patients with CD4 counts > 200 cells/μL were seropositive, revealing the importance of screening tests in this high-risk group. However, among CrAg-positive patients, we were unable to find any proven contact with the reservoir of these pathogens.[1] By showing that CrAg can be detected before the onset of symptoms, the obtained data will aid in general efforts to reduce CM and related deaths and allow timely precaution measures to be taken.

CM in AIDS patients accounts for approximately 15% of AIDS-related deaths worldwide;[29] therefore, it is recommended that CrAg should be considered as an indicator of CM risk and associated fatality even in asymptomatic patients.[10,13,24] LFA was used to identify CrAg in HIV-positive individuals in various studies (Table 3),[30–44] which usually

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included patients with CD4 counts < 200 cells/μL who had not received ART. In asymptomatic HIV-positive patients, the prevalence of cryptococcal antigenemia varies between 1.6% (Ethiopia)[24] and 16.7% (Northeast Nigeria),[40] which is comparable with our result of 11%. However, the rate of antigenemia is significantly higher in HIV-positive individuals with cryptococcosis or CM; thus, 72% was reported in Uganda[36] and 95% in Brazil.[33]

Previous researches indicate that CrAg detection is usually performed in CSF, serum, complete blood, plasma, urine[30–44] (Table 3), and saliva.[45] In terms of monetary value, CrAg-LFA-based screening was shown to be highly cost-effective (2.71 USD/test) and was predicted to result in a 40% reduction in *Cryptococcus*-associated mortality in Uganda, with potential application in most areas of sub-Saharan Africa.[46] The cost of CrAg-LFA screening is also relatively low in other countries: 3.84–6.03 USD/test in South Africa,[47] 4.13 USD/test in Vietnam,[35] and 8 USD/test in Brazil;[33] it was estimated as 8.5 USD/test in the present study. However, CrAg-LFA testing was reported to be more expensive in Australia (18 USD/test).[12] Furthermore, in Turkey, the commercially available CrAg tests such as LA and EIA costs 8.5 USD/test and 14.2 USD/test, respectively. The monetary value of the LFA test is also another advantage of the test for developing countries.

Nevertheless, CrAg screening of patients at risk of *Cryptococcus* infection is not available in Turkey and the rates of asymptomatic cryptococcosis are unknown. In the present study, we attempted the first step toward determining the prevalence of asymptomatic antigenemia in Turkey and detected CrAg in 11% of HIV-positive patients, which is an unexpectedly high rate. However, there were no CrAg-positive individuals among HIV-negative controls, which is consistent with the following: (i) CM is rare among immunocompetent patients, (ii) HIV-

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immunosuppressant drugs in the current study, and (iii) low incidence of cryptococcosis in Turkey.[26]

The current study had several limitations. First, we determined only CrAg presence (qualitative read-out) but not its titers (quantitative read-out) in serum because of a specific testing procedure; nevertheless, this particular limitation should not undermine the major conclusions of the study. Second, we analysed only patients with HIV and did not consider other diseases such as leukemia/lymphoma that require immunosuppressant treatment and increase the risk of CM in HIV-negative individuals. Third, using another FDA-approved commercial kit was not possible due to limited funds. Finally, the patient group was heterogeneous in terms of the ART status and CD4 counts, and the 28 CrAg-

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TABLE and FIGURE TITLES:

TABLE 1 Characteristics of HIV-positive and HIV-negative patients according to CrAg-LFA results

TABLE 2 Studies that used LA and/or EIA with LFA to diagnose cryptococcosis[5–15]

TABLE 3 Studies that used LFA to identify CrAg in HIV-positive patients[30–44]

FIGURE 1 Geographical distribution of the 28 CrAg-positive HIV-positive patients

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TABLE 1 Characteristics of HIV-positive and HIV-negative patients according to CrAg-LFA results

Characteristics	**HIV-positive (*n*=254)**		**HIV-negative (*n*=100)**	
	CrAg+	**CrAg-**	**CrAg+**	**CrAg-**
Median age (range, years)	39.1 (21–63)	39.2 (18–75)	–	42.3 (18–67)
Gender				
Men	23	191	0	82
Women	5	34	0	18
CD4 count (cell/μL)				
< 100	0	4	–	–

CrAg, Cryptococcal antigen; LFA, Lateral Flow Assay; ART, Anti-retroviral therapy.

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TABLE 2 Studies that used LA and/or EIA with LFA to diagnose cryptococcosis.[5–15]

Author	Ref.	Country	Number of samples		Disease				LFA				LA				EIA		
			Serum	CSF	Yes		No		Positive		Negative		Positive		Negative		Positive		Negative
					S	CSF	S	CSF	S	CSF	S	CSF	S	CSF	S	CSF	S	CSF	S

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TABLE 3 Studies that used LFA to identify CrAg in HIV

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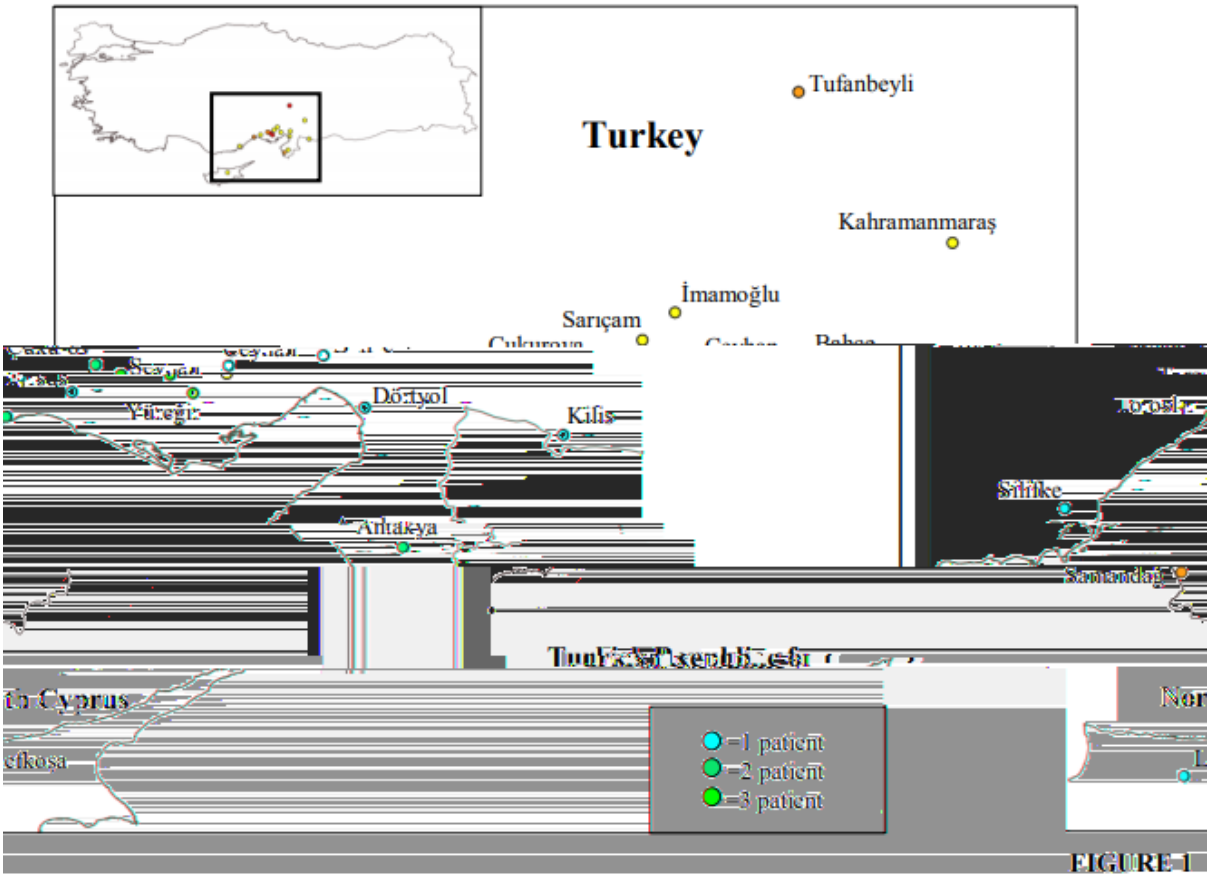

FIGURE 1

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