RESEARCH ARTICLES

Epidemiology of Cryptococcal antigenemia among HIV infected patients in southwestern Nigeria

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Abstract

Cryptococcosis is a life-threatening fungal infection that presents diversely with no specific pathognomonic features. Cryptococcal disease is one of the most important opportunistic infections and a significant contributor to early mortality in HIV infected subjects. Cryptococcal antigenemia occurs in Nigeria, but the magnitude of this disease remains unclear. This study was carried out to determine the prevalence of CrAg among HIV infected and HIV seronegative subjects and to assess the relationship between CD4 count and CrAg in HIV-positive subjects attending Adeoyo Maternity Teaching Hospital, Yemetu, Ibadan.

In a hospital-based case-control study using simple random sampling, 114 HIV-seropositive individuals (cases) and 228 HIV-seronegative individuals (controls) were recruited. A semi-structured interviewer-administered questionnaire was used to collect data from subjects and retrospective review of CD4 count records in HIV infected subjects. Five millilitres of venous blood were collected from each participant. Serum Cryptococcal antigen testing was done using CrAg Lateral Flow Assay. Data was analyzed using descriptive statistics and bivariate analysis at 5% level of significance.

Mean age of cases was 41.2 ± 10.0 years and 85 (74.6%) were females while mean age of controls was 38.9 ± 13.7 years and 156 (68.4%) were females. The prevalence of CrAg among cases was 11.4% and 7.0% among controls. Cases were about two times more likely to test positive for CrAg. However, the association was not statistically significant (OR: 1.71, 95%CI: 0.79 - 3.68). Individuals with CD4 counts of ≤100 cells/µl were 20 times more likely to have positive serum cryptococcal antigen than individuals with CD4 counts >100 cells/µl (OR: 20.3, 95%CI: 5.23-78.9).

This study has demonstrated significant prevalence of Cryptococcal antigenemia among the study population; however, prevalence was significantly higher among cases. Screening for CrAg should therefore be part of routine tests amongst all confirmed HIV seropositive cases, since asymptomatic cryptococcal antigenemia predicts impending cryptococcal infection with probable mortality.

Keywords: Cryptococcal antigen, opportunistic infections, HIV, fungal infections

Introduction

Cryptococcosis is an infection with the fungus *Cryptococcus*. It is a serious opportunistic infection among people with compromised immune systems, such as those with advanced HIV/AIDS. *Cryptococcus* species are found in the soil and in avian feaces throughout the world (1). Most people probably breathe in small amounts of microscopic, airborne spores every day because *Cryptococcus* is common in the environment. Sometimes, these spores cause mild symptoms of respiratory infection, but at other times there are no symptoms at all (2). In healthy people, the fungus usually does not cause serious illness because the immune system can fight off the fungus, therefore they remain asymptomatic. However, in immunocompromised individuals, the fungus can stay hidden in the body and later re-activate, spreading to other parts of the body and causing serious disease (3).

Human immunodeficiency virus (HIV) belongs to the genus *Lentivirus* of the *Retroviridae* family, which is responsible for HIV infection (4). The HIV destroys the human immune system thereby producing a group of symptoms and signs called Acquired Immune Deficiency Syndrome (AIDS)(5). In a healthy host, opportunistic organisms (OIs) rarely cause diseases. However, they cause diseases in individuals with weak immune system such as those with HIV/AIDS. The opportunistic disease infections can be caused by many different organisms, including bacteria, viruses, parasites, or fungi. In HIV/AIDS patients, they include Tuberculosis, Cryptococcal meningitis, *Pneumocystis* pneumonia and *Candida* infection (4).

Cryptococcal disease is a major contributor to early mortality in HIV infected subjects(6). Cryptococcal infections in humans are caused exclusively by two *Cryptococcus* species namely *Cryptococcus neoformans* and *Cryptococcus gattii*. However,

Cryptococcus neoformans is the most common biological agent implicated in Cryptococcal disease in patients with AIDS (7). Cryptococcosis is not contagious and as such cannot spread from person-to-person. Cryptococcal meningitis (CM) occurs after *Cryptococcus* has spread from the lungs to the central nervous system causing inflammation of the meninges. Meningitis can also be caused by a variety of other organisms, including bacteria, viruses, and other fungi (8). Cryptococcal meningitis is the second most common life-threatening HIV-associated opportunistic infection after tuberculosis and may be responsible for up to 20% of deaths in resource limited settings. In sub-Saharan Africa alone, there are more than 700,000 new cases and about 500,000 deaths each year due to CM, which may exceed those attributed to tuberculosis meningitis (9).

In low-resource settings, about half of all patients with CM usually die from it. There are various reasons why the death rate is so high in these parts of the world: first, patients often present with the disease at an advanced stage thus making treatment to be less effective. Second, there are no clinical criteria that reliably predict the diagnosis of Cryptococcosis, and routine diagnostic laboratories often lack the ability to perform fungal cultures or CrAg testing (8). Third, Amphotericin-B, the required medication to treat CM is very expensive or not readily available in these areas of the world. Hence, many patients with CM are treated sub-optimally (10).

The estimated overall number of People Living with HIV (PLWHIV) by the end of 2014 was approximately 36.9 million. Sub-Saharan Africa was the most affected region, having an average of 25.8 million PLWHIV and 66% of all people with HIV infection living in the region (11). About nine percent of all people living with HIV globally reside in Nigeria. Available data shows that the prevalence of *Cryptococcus neoformans* infection among HIV-infected patients is up to 40% in most parts of the world particularly in sub-Saharan Africa and Southeast Asia which are considered the epicenters of the HIV/AIDS pandemic (10).

Cryptococcal antigen (CrAg) is a marker for cryptococcal infection. The antigen is produced by the fungus *Cryptococcus* spp. Cryptococcal screening is a key strategy to prevent development of cryptococcal meningitis and ultimately death in infected subjects. Detection of CrAg in blood and cerebrospinal fluid weeks to months before the patient develops symptoms of cryptococcosis is now possible (13). Patients who are found to have cryptococcal antigen in their body are much more likely to develop meningitis than those who do not have antigen. The presence of CrAg in body fluids predicts development of cryptococcosis (14). Therefore, early CrAg screening in HIV subjects may be helpful in minimizing HIV-associated mortalities.

Nigeria is the second largest HIV epidemic country in the world after South Africa(11). Diagnosis of HIV occurs at a late stage and treatment coverage in the country is relatively low. With these challenges, patients continue to die of HIV-related opportunistic infections (OIs) in the weeks prior to and months following initiation of anti-retroviral therapy (ART) (9). Management of CM requires complex treatments and usually prolonged hospitalizations, representing a significant increase in health costs. Treatment of asymptomatic or latent cryptococcal infection with oral fluconazole is a much less expensive and highly available option compared to standard-of-care for meningitis (13,15). This study was therefore conducted to determine the prevalence of CrAg and to compare the CD4 count and the presence of CrAg among individuals attending Adeoyo Maternity Teaching Hospital, Yemetu, Ibadan, Oyo State.

Methods

Study Area

Adeoyo Maternity Teaching Hospital is a government owned specialized service hospital in Yemetu, Ibadan, Oyo State, Southwestern Nigeria. It was selected because it houses a PEPFAR clinic and serves as a major maternity hospital and general hospital for children and adult patients.

Study Design and Population

A hospital-based case-control study design was employed in this study. The study populations were Nigerian adults (age range 18-65 years), male and female. Cases were HIV seropositive subjects while controls were HIV seronegative subjects attending Adeoyo Maternity Teaching Hospital, Yemetu Ibadan. Patients with recent diagnosis of any other form of meningitis and patients on antifungal treatment for any other fungal disease were excluded from this study. Patients with chronic infections such as diabetes mellitus, chronic obstruction pulmonary disease and chronic granulomatous infections were also excluded from the study.

Ethical Approval

Ethical approval for this study was obtained from Oyo State Ministry of Health Ethical Review Committee. Administrative approval was also obtained from the management of Adeoyo Maternity Teaching Hospital, Yemetu before starting the study. Ethical principles were maintained during the study. These included;

a. A written informed consent was attached to the questionnaire for the subjects to obtain individual consent to participate in the study.
b. Confidentiality of data: the content will not be disclosed to anybody except co-investigators.
c. Beneficence: results of Cryptococcal antigen screening was given to the managing clinical team free of charge
d. Voluntariness: every target participant had the right not to participate in the study when approached.

Sample size determination

The minimum number of participants required for the study was calculated to be 114. Therefore, 114 cases and 228 controls were recruited for this study. Hence 342 subjects were recruited for this study at a ratio of a case to two controls.

Sampling Technique

Simple random sampling technique was employed to recruit study participants. This involved sampling participants that meet the inclusion criteria within the recruiting period (January and March 2018) until the calculated sample size was obtained.

Data Collection

A well-structured, pre-tested, interviewer-administered questionnaire was used to obtain information from selected study participants (HIV-positive and HIV seronegative adults) who consent to participate in the study. The questionnaire consists of four sections,

a. Socio-demographic characteristics (Sex, Age in years, Level of Education, Occupation and Marital Status)
b. Risk factors for acquiring Cryptococcal infection
c. Clinical features suggestive of Cryptococcal infection
d. Retrospective review of CD4 count records in HIV infected subjects (among cases)

Sample Collection

Five milliliter (5ml) whole blood was aseptically collected by venipuncture and dispensed into a plain specimen bottle using sterile disposable syringe and needles from both HIV-seropositive and HIV-seronegative subjects. Blood samples were placed erect in the tube rack for 30 minutes to allow for clot retraction. Clotted blood samples were centrifuged in a bench centrifuge at 4,000 revolutions per minute for 3-5 minutes to obtain serum after clot retraction. Separated serum samples were stored at -20^{o}C pending laboratory analysis.

Sample analysis

Serum CrAg was determined using Cryptococcal Antigen Lateral Flow Assay (CrAg LFA) (Dynamiker Biotechnology, China). This detection kit is a simple, sensitive and qualitative latex test. It uses sandwich immuno-chromatographic assay for the detection of capsular polysaccharide antigens of *Cryptococcus* species complex (*Cryptococcus neoformans* and *Cryptococcus gatti*) in human serum and cerebrospinal fluid (CSF).

Quality Control

Research assistants were trained on how to administer questionnaires on respondents. Questionnaires were pre-tested before field work at another hospital in Ibadan, Oyo State. Quality control was ensured on latex kits for determining CrAg. A coloured band appearing in the control region was considered as an internal positive procedural control. This confirmed sufficient specimen volume and correct procedural technique. External positive and negative controls provided by the manufacturers were assayed along with each batch of serum samples analyzed. This was done to ensure that the tests are functioning properly. Data obtained was be cleaned before analysis.

Data Analysis

Data was entered and analyzed using Epi info software version 7.2. Quantitative variables were summarized using mean and standard deviation while qualitative variables were summarized using frequencies and proportions. Bivariate analysis was used to test the association between variables and the level of significance was set at $p \leq 0.05$. The dependent variable in this study was the presence or absence of Cryptococcal antigen. Independent variables include age, gender, marital status, religion, level of education, HIV status, socio-economic status, ethnicity, smoking status, neck pain, fatigue, fever, cough, headache, sensitivity to light, neurologic deficit, history of exposure to pigeons/excreta and history of organ transplant.

Results

A total of 342 subjects participated in this study which was conducted between January and March, 2018. One hundred and fourteen of the subjects were HIV seropositive while 228 were HIV seronegative. Blood sample was collected from all the participants while some sections of the questionnaire were not answered by all.

Prevalence of Cryptococcal Antigen among HIV Seropositive and Seronegative Subjects

Table I shows that the mean age of HIV seropositive subjects was 41.2 ± 10.0 years while that of HIV seronegative subjects was 38.9±13.7 years. Amongst cases, female participants constitute 85 (74.6%) while 104 (91.2%) of the study participants are married while among controls, female participants constitute 156 (68.4%) and 176 (61.8%) of the study participants are married.

Thirteen (11.4%) participants tested positive for serum cryptococcal antigen among cases while sixteen (7.0%) participants tested positive for serum cryptococcal antigen among controls. Among cases, the most affected age group was 41-50 years with seven (6.1%) positive subjects and 11(9.6%) of the CrAg positive participants were females while 12 (10.5%) were married. The most affected age group among controls was 21-30 years with six (2.6%) CrAg positive subjects in age group less than 20 years had no positive cases. Nine (3.9%) of the CrAg positive participants were females while 11 (4.8%) were married.

Table I. Demographic Characteristics of HIV Seropositive and Seronegative Subjects Screened for Cryptococcal Antigen

Variables	Cases				Controls			
	Freq (n=114)	(%)	CrAg Freq (n=13)	(%)	Freq (n=228)	(%)	CrAg Freq (n = 16)	(%)
Age Group (years)								
<20	-	-	-	-	15	6.6	-	-
21-30	18	15.8	2	-	57	25	6	2.6
31-40	44	38.6	7	1.75	70	30.7	5	2.2
41-50	32	28.1	1	6.1	36	15.8	1	0.4
51-60	15	13.2	3	0.9	26	11.4	3	1.3
>60	5	4.4		2.6	24	10.5	1	0.4
Mean ± SD	41.2±10.0				38.9 ± 13.7			
Total				11.4				7.0
Gender								
Male	29	25.4	2	1.8	72	31.6	7	3.1
Female	85	74.6	11	9.6	156	68.4	9	3.9
Marital Status								
Single	10	8.8	1	0.9	51	22.4	5	2.2
Married	104	91.2	12	10.5	142	62.3	11	4.8
Co-habiting	-	-	-	-	9	3.9	-	-
Widowed	-	-	-	-	18	7.9	-	-
Divorced/Separated	-	-	-	1	7	3.1	-	-
Type of family								
Monogamy	70	61.4	10		182	79.8	11	4.8
Polygamy	35	30.7	2		46	20.2	5	2.2
Missing	9	7.9	1		-	-	-	-
Religion								
Christianity	61	53.5	10	8.8	127	55.7	11	4.8
Islam	50	43.9	-	-	100	43.9	5	2.2
Traditional	3	2.6	3	2.6	1	0.4	-	-
Educational Level								
None	6	5.3	-	-	6	2.6	-	-
Primary	40	35.1	2	1.8	26	11.4	1	0.4
Secondary	47	41.2	8	7	72	31.6	3	1.3
Tertiary	20	17.5	3	2.6	96	42.1	5	2.2
Postgraduate	1	0.9	-	-	27	11.8	7	3.1
Occupation								
Student	2	1.8	2	1.8	56	24.6	6	2.6
Civil servant	13	11.4	1	0.9	56	24.6	1	0.4
Farmer	3	2.6	9	7.9	10	4.4	2	0.9
Business/Trader	89	78.1	-	-	49	21.5	3	1.3
Unemployed	2	1.8	1	0.9	32	14	3	1.4
Retired	5	4.4	-	-	23	10.1	1	0.4

Table II. Comparison between the prevalence of Cryptococcal Antigen among HIV Seropositive and Seronegative Subjects

		Result of CrAg Screening		Odds Ratio	95% CI	Chi-square	P-value
		Positive	Negative				
HIV Status	Positive	13	101				
	Negative	16	212	1.71	(0.79 - 3.68)	1.8839	0.1699
	Total	29	313				

Figure I. Bar Chart showing the proportion of Cryptococcal Antigen among cases and controls

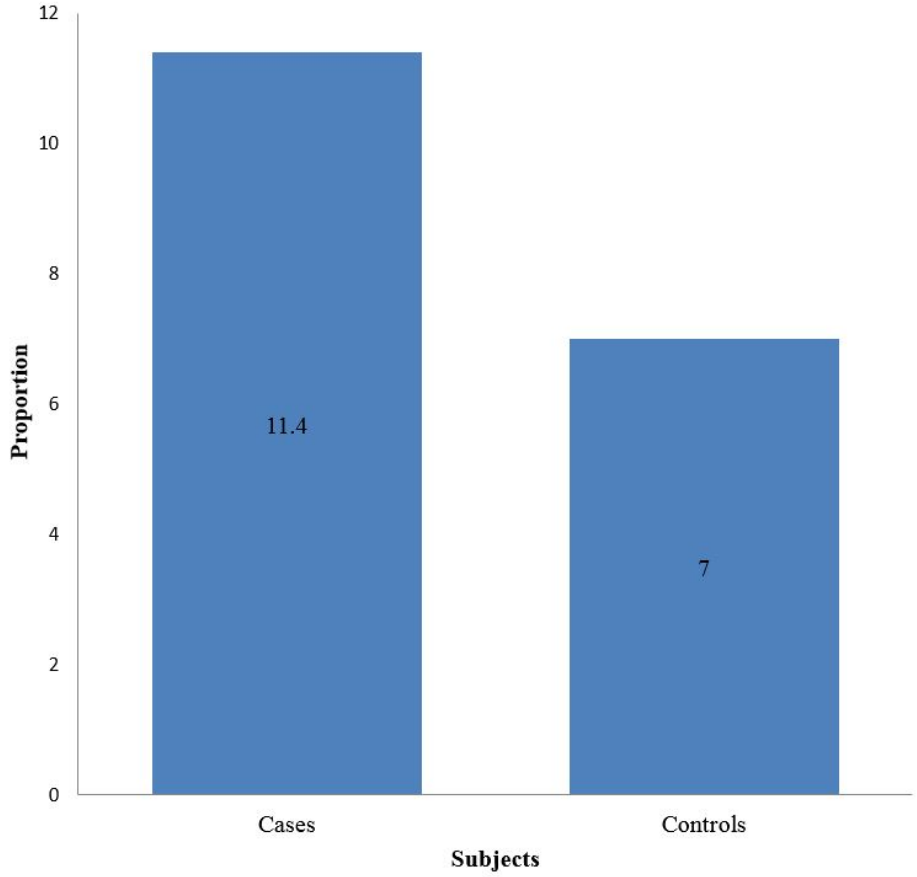

Table III. Distribution of CD4 counts among HIV Seropositive Subjects Screened for Cryptococcal Antigen at Adeoyo Maternity Teaching Hospital Yemetu Ibadan

	CrAg Positive, n=13 (%)	CrAg Negative, n=109 (%)
CD4 Counts (cells/µl)		
≤100	8 (61.5)	7 (6.4)
101 - 200	1 (7.7)	15 (13.8)
>200	4 (30.8)	74 (67.9)
Missing	0	5* (6.8)
Mean ± SD	188.7 ± 201.2	445.3 ± 302.1

* = CD4 counts not included

Figure II. Distribution of CD4 counts among HIV infected subjects with Cryptococcal Antigen

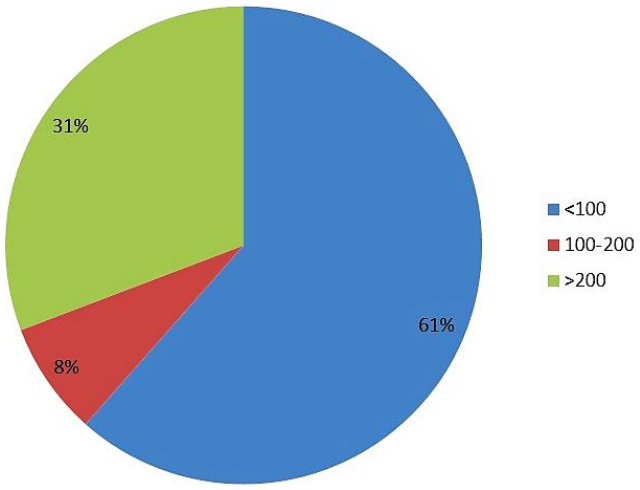

Table IV. Relationship between CD4 counts and results of Cryptococcal Antigen screening among HIV Seropositive Subjects

	Result of CrAg Screening					
	Positive	Negative	Odds Ratio	95% CI	Chi-square	P-value
CD4 Count						
≤100	8	7				
>100	5	89	20.3	5.23 - 78.99	28.3903	<0.00000*
Total	13	101				

* = statistical significance

Comparison between prevalence of Cryptococcal Antigen among Cases and Controls

Figure I show the proportion of Cryptococcal Antigen among cases and controls. Table II shows comparison between the prevalence of CrAg among cases and controls. Thirteen participants out of 114 HIV seropositive subjects tested positive for CrAg thereby giving a prevalence of 11.4%. Sixteen participants out of 228 HIV seronegative subjects tested positive for CrAg thereby giving a prevalence of 7.0%. There was a cumulative prevalence of 8.5% among all the study participants. HIV positive subjects were about two times more likely to test positive for CrAg. However, the association was not statistically significant (OR: 1.71, 95%CI: 0.79 - 3.68).

Distribution of CD4 counts among HIV Seropositive Subjects Screened for Cryptococcal Antigen

Table III shows distribution of CD4 counts among cases. The mean ± standard deviation of CD4 counts (cells/µl) in CrAg positive subjects were significantly lower when compared with CrAg negative subjects. The CD4 count results for five of the CrAg negative subjects were not found during retrospective review of laboratory records.

Relationship between CD4 counts and results of Cryptococcal Antigen screening among HIV Seropositive Subjects

Figure III shows the distribution of CD4 counts (cells/l) among HIV infected subjects who tested positive for cryptococcal antigen. Most of the HIV infected subjects (eight out of 13) had CD4 counts of <100 cells/l, only one had CD4 count of between100-200cells/l while four subjects who tested positive for cryptococcal antigen had higher counts. Table IV shows association between CD4 counts and results of cryptococcal antigen screening among HIV seropositive subjects. Individuals with CD4 counts of ≤100cells/µl were 20 times more likely to have positive serum cryptococcal antigen than individuals with CD4 counts >100 cells/µl and this association was found to be statistically significant (OR: 20.3, 95%CI: 5.23-78.9).

Discussion

Cryptococcal antigen was present among both cases and controls. However, the prevalence of serum CrAg was higher among HIV seropositive subjects. There was a statistically significant inverse association between subjects' immune status and the risk of having serum CrAg. Individuals with diminished CD4 counts (<100 cells/µl) were more likely to have positive serum CrAg than individuals with higher counts.

The observed prevalence (11.4%) of CrAg among HIV seropositive subjects in this study is similar to the findings of those in Ethiopia and in southeast Nigeria who reported a prevalence of 12.7%, 10.2% and 13.1% respectively (14, 15). Despite several interventions and investments to fight the scourge of HIV/AIDS, cryptococcosis continues to be a major public health challenge especially as patients continue to die of HIV-related OIs (16). Our observed prevalence is higher than the 5.0%, 5.7%, 2.1%, 3.3% and 1.2% prevalence rates reported in United Kingdom, Uganda, South Africa, Namibia and (17)(16) northwest Nigeria, respectively (13, 17 - 20). Also, our observed prevalence is lower than the 16.7% prevalence rate observed in Maiduguri, northeastern, Nigeria (18). The discordance in the observations may be due to environmental conditions and differences in sample size as well as presence and rate of use of HIV intervention services. Also, study location and HIV prevalence appear to influence the incidence of cryptococcosis in HIV/AIDS. The higher prevalence of CrAg among HIV seropositive subjects in Borno State as observed previously (18) may be because pigeon raring is more common in the North than in the Southern part of Nigeria where our study was conducted.

Findings from the current study lend further credence to the opinion that Cryptococcus is present in the environment, but the infection manifests and thrive mostly among individuals with altered immune response system. Our finding is discordant to the 0% reported among HIV seronegative pregnant women in southeastern Nigeria (19). Although pregnant women are considered immunosuppressed, the stage of their pregnancy was not reported in the study. However, this finding might be due to absence of Cryptococcus species in their environment, as the level of contamination of their environment cannot be ascertained. Most of the studies available on prevalence of cryptococcosis in HIV-seronegative subjects are retrospective usually among patients with cryptococcal meningitis (18, 19). Although, cryptococcal infection is widely known to affect both HIV-seropositive and seronegative individuals, the severity is more among immunosuppressed persons especially when their CD4 count drops below 100 cells/µl. Studies in Vietnam and China (21, 22) showed that cryptococcosis is becoming common in patients

with apparently normal immune systems and HIV seronegative subjects. The discordance recorded further confirms that the level of exposure to Cryptococcus varies according to the level of environmental contamination by the fungus from the primary source.

Our finding of a higher prevalence of serum CrAg among HIV seropositive subjects when compared with HIV seronegative subjects corroborates findings from other studies (19,21). This further suggests that cryptococcal infection is a common opportunistic infection among HIV seropositive individuals (23). From our study, HIV positive subjects were about two times more likely to test positive for CrAg. Though, the association was not statistically significant, this further indicates that the organism is present in the environment and that exposure to the antigen is similar among both HIV seropositive and seronegative individuals. However, the response in terms of containment of infection is responsible for the severity of the clinical manifestations of the infection among immunocompromised individuals (24, 25). Cryptococcosis remains a disease with significant morbidity and mortality in the developed and developing worlds and the relative burden among persons without HIV infection is increasing (26). It is therefore very important to control environmental contamination through proper environmental sanitation to prevent undue exposure most importantly those that are immunosuppressed. This will also help to reduce OIs among HIV infected subjects.

Several studies have reported immunosuppression and autoimmune disorders as the number one risk factor for Cryptococcal antigen infection and Cryptococcus meningitis (13, 29-30). Our study shows that individuals with low CD4 counts (<100 cells/µl) were much more likely to test positive for cryptococcal antigen than individuals with higher CD4 counts. This association was found to be statistically significant, which further justifies the importance of helper T cells in the protection against opportunistic infections in the body and justifies the monitoring of CD4 counts in HIV seropositive subjects (21, 25). HIV seropositive patients, in addition to monitoring their CD4 count, should also be screened regularly for presence of opportunistic organisms (infections) to ensure that they could receive early treatment and improve their survival.

Conclusions

The presence of cryptococcal antigen among HIV seropositive and seronegative populations confirms the availability of Cryptococcus in the environment. The prevalence of serum cryptococcal antigen was however higher among HIV seropositive subjects with low CD4 counts and may predict impending cryptococcal infection. Therefore, regular CrAg screening should be part of the routine tests amongst all confirmed HIV seropositive cases and particularly those with CD4 counts <100cells/mm^3.

Limitations

Serum CrAg testing, which is the method employed in this study, does not usually detect antibodies in the early stage of infection or in chronic immunosuppressive subjects. Also, antigens may not be detectable in blood if infection is localized in the lungs. Kits for cryptococcal screening are expensive and not readily available; hence, continuous monitoring is and testing higher ratios of controls to cases was difficult. These may limit the generalization of our findings.

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