High Prevalence of Cryptococcal Antigenemia among HIV-infected Patients Receiving Antiretroviral Therapy in Addis Ababa, Ethiopia

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OUTLINE

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Introduction

- Cryptococcosis is caused by an encapsulated yeast
  - Cryptococcus neoformans

- The portal of entry is the respiratory tract
  - Resulting in a pulmonary cryptococcosis - inapparent clinical course
Introduction cont’d

• Preconditions for haematogenously dissemination to other organs, especially to CNS
  – Primary diseases that weaken the immune defenses

• Despite limited data, it is estimated there are > 700,000 cases of Cryptococcal Meningitis (CM) in SSA annually resulting in > 500,000 deaths with ~70% case fatality rate

(F. H. Kayser, 2005; Park BJ et al, 2009)
Cryptococcal antigenemia preceded symptoms by a median of 22 days add to the scientific rationale of a screen and treat strategy (French, N., et al., 2002)

- WHO guideline recommend screening in high prevalence RLS among those with CD4<100 cells/ul (WHO, 2011)

ART alone is insufficient treatment for CRAG-positive persons (Meya, D.B., et al., 2010)

Immune-mediated clearance, becomes less likely as antigen titer increases (Jarvis N, et al., 2009)
Despite these facts **CRAG screening is not routine** in Ethiopia.

There is lack of published data on the rate of cryptococcal antigenemia in HIV-infected patients in Ethiopia.

Provide **baseline data** on the rate of cryptococcal antigenemia for further studies on the clinical impact of using cryptococcal antigenemia screening.
Objective

- To determine the prevalence of Cryptococcal antigenemia and to assess associated factors among HIV-Infected patients attending Black Lion and ALERT Hospital ART clinics in Addis Ababa, Ethiopia
Methods

• Study Design and Patients
  – A cross sectional study was conducted among adult HIV-infected patients with CD4 < 200/µl - irrespective of ART status
  – Consecutive patients were enrolled between May and August 2011 from the outpatient ART clinics of both Black Lion and ALERT hospital
Methods cont’d

• Inclusion Criteria
  – CD4 count $\leq 200/\mu l$

• Exclusion Criteria
  – Treated for Cryptococcal infection in last 3 months
  – Taking systemic antifungal agent at time of visit
Methods cont’d

• Ethical Considerations
  – Written informed consent was obtained from all study participants
  – Approved by
    • AHRI/ALERT IRB
    • Emory university IRB
    • AAU Medical Faculty research and ethics review board
  – Result was communicated to the treating physician
Methods cont’d

- **Data Collection**
  - Patient interview, physical examination and medical chart review
    - Demographics
    - Clinical signs and symptoms
    - Medical history (opportunistic infection, ART use, most recent CD₄ count)

- **Laboratory Testing**
  - A Cryptococcal Antigen Latex Agglutination Test (CALAS Meridian) was performed (according to the Insert)
Methods cont’d

• Data Analysis
  – Data was entered into an online REDCap database and analyzed using SAS version 9.3
  – Univariate & multivariate logistic regression analyses were performed to assess risk factors for a positive cryptococcal Ag test result
  – Risk factors with possible significance or those with biologic plausibility and known to be associated with cryptococcal disease were included in the model
• **Patients and antigen screening**
  
  – A total of 369 HIV-infected patients were enrolled
  
  – The mean age was 36 years and 56% were female
  
  – Majority of patients were on ART (74%) and had been receiving for a mean duration of 34 months
  
  – The mean CD4 count was 123 cells/μl and 31% had a CD4 count less than 100 cells/μl
  
  – 25% of them had history of prior pulmonary and extra pulmonary tuberculosis (9%)
Patients and Ag screening...

- Of the 369 patients, 31 (8.4%) were positive for cryptococcal antigen test (CrAg)

  - The overall prevalence of 8.4% is in line with results from Uganda (5-9%), South Africa (13%), and Kenya (6%)

  - Limited data despite its similar mortality rate with TB in SSA HIV patients (Park BJ et al., 2009)
Patients and Ag screening...

All antigen titers were $\geq 1:8$
- May indicate the possibility for the development of symptomatic cryptococcal disease
- Higher Ag titers were predictor for the development of CM & IRIS after commencement of ART (Jarvis N, et al., 2009; Jarvis N, Harrison TS, 2007; Pongsai P, et al., 2010)
Patients and Ag screening...

- 26 (84%) of 31 patients with a positive CrAg test were receiving ART for a mean duration of 37 months
  - Lack of HIV viral load data on these patients may limit to base screening recommendations on ART response
Result & Discussion cont’d

• In contrast to prior studies done in SSA (Jarvis JN et al, 2009; Liechty CA et al, 2007), high prevalence 18(7.1%) was found among patients with CD4 counts 100-200 cells/μl

  – Which calls into question whether screening recommendations should be expanded to include patients with CD4 counts <200 cells/μl

  – But inclusion of patients already on ART in our study might be a factor
Figure 1. Percentage of HIV Infected Patients with Cryptococcal Antigenemia by CD4 count and Antiretroviral Use

- CD4<100 - 11%
- CD4 100 to 150 - 8.9%
- CD4 >150 - 5.7%
Table 1. Univariate and Multivariate Analysis of Risk Factors for Cryptococcal Antigenemia among HIV infected patients in Addis Ababa, Ethiopia (n=369)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate Analysis</th>
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<th>Multivariate Analysis</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.05 (1.01-1.09)</td>
<td>0.02</td>
<td>1.05 (1.002-1.09)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.12 (1.00-4.51)</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Site 1 vs. 2</strong></td>
<td>4.05 (1.20-13.63)</td>
<td>0.02</td>
<td>5.49 (1.57-19.16)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;18.5 kg/m²</td>
<td>0.39 (0.13-1.13)</td>
<td>0.08</td>
<td>0.32 (0.10-0.98)</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>Currently employed</td>
<td>1.33 (0.62-2.87)</td>
<td>0.46</td>
<td></td>
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<tr>
<td>On ART</td>
<td>1.91 (0.71-5.10)</td>
<td>0.20</td>
<td>2.60 (0.91-7.45)</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

**CD4 count status**

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>&lt;100</strong></td>
<td></td>
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<tr>
<td>100-150</td>
<td>2.08 (0.83-5.21)</td>
<td>0.34</td>
<td>2.81 (1.06-7.47)</td>
<td>0.04</td>
</tr>
<tr>
<td>151-200</td>
<td>1.60 (0.61-4.20)</td>
<td>0.11</td>
<td>1.81 (0.65-5.04)</td>
<td>0.26</td>
</tr>
<tr>
<td>1.00</td>
<td></td>
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<td>1.00</td>
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**Symptoms**

<table>
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<tr>
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<th>OR (95% CI)</th>
<th>P</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>2.14 (0.98-4.67)</td>
<td>0.06</td>
<td>2.95 (1.26-6.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>Headache</td>
<td>1.04 (0.46-2.35)</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photophobia</td>
<td>1.46 (0.41-5.18)</td>
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</table>

**Signs**

<table>
<thead>
<tr>
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<th>OR (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Fever (≥ 38.3 °C)</td>
<td>1.22 (0.45-3.33)</td>
<td>0.70</td>
</tr>
<tr>
<td>Meningismus</td>
<td>3.71 (0.37-36.79)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

BMI, body mass index; ART, antiretroviral therapy; OI, opportunistic infection
Result & Discussion cont’d

• After controlling for ART use and CD4 count
  – Patients at site 1 as compared to site 2 were more likely to have cryptococcal antigenemia (aOR 5.49, 95% CI 1.57-19.16)

• Catchment area of site one- more verdant areas on the outskirts of Addis compared to site two
  – Favorable ecological habitat of C. neoformans- rotting wood and trees (including eucalyptus) and soil contaminated by bird guano (Chowdhary A et al., 2012; Ellis H et al., 1990)
Persons who reported a fever were more likely to have cryptococcal antigenemia (aOR 2.95, 95% CI 1.26-6.87).

But 64% of positive patients reported no fever and 48% reported a lack of any symptoms.

- Consistent with other SSA studies (Liechty et al., 2007, Jarvis et al., 2009) - indicated relatively high rates of asymptomatic cryptococcosis.
Table 2. Predicting Cryptococcal Antigenemia Based on the Presence of Individual or Combination of Clinical Symptoms (n=369)

<table>
<thead>
<tr>
<th>Symptom(s)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>36</td>
<td>80</td>
<td>14</td>
<td>93</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>72</td>
<td>9</td>
<td>92</td>
</tr>
<tr>
<td>Photophobia</td>
<td>10</td>
<td>93</td>
<td>12</td>
<td>92</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>23</td>
<td>81</td>
<td>10</td>
<td>92</td>
</tr>
<tr>
<td>Fever, Headache, or Photophobia</td>
<td>42</td>
<td>62</td>
<td>10</td>
<td>92</td>
</tr>
<tr>
<td>Fever, Headache, and Photophobia</td>
<td>9</td>
<td>97</td>
<td>3</td>
<td>92</td>
</tr>
</tbody>
</table>

- **Poor sensitivity:**
  - Individual symptom (10-36%), combination of symptoms (9-42%)

- **Less than optimal specificity:**
  - Individual (72-93%), combinations of symptoms (62-97%)

Our findings are similar to results from a prior study conducted in Uganda (French N et al., 2002)

- Adult HIV infected patients with low CD4 counts in high burdened settings should be screened for cryptococcal antigenemia regardless of symptoms

Meya et al. demonstrated pre-emptive therapy with fluconazole in asymptomatic CrAg positive patients as cost effective intervention (Meya DB, et al., 2010)
Limitations

- Viral load testing was not available
- There was absence of lumbar puncture for CrAg positive patients
- The study took place at only two hospital HIV clinics in Addis Ababa
Conclusion & Recommendations

• We found a previously unreported high prevalence of cryptococcal antigenemia with CD4 counts ≤ 200 cells/μl, including those on ART

• No utility of symptom screening in disease detection
Recommendations Cont’d

• It indicates **the need to scale up cryptococcal disease screening** among HIV-infected persons and suggest it may be beneficial to expand current cryptococcal screening recommendations

• Further large-scale studies of cryptococcal disease are currently underway in South Africa and are needed in Ethiopia to better understand the true extent of disease burden
Acknowledgement

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  – AHRI/ALERT
  – Emory University Global Health Institute
  – AAU-ALIPB

• INDEPTH Network

• ISC-2015 Scientific Programme Committee

• Haramaya University
Thank You!

- Semen Mountain
- Bule Nile Fall
- Awash National Park
- Dallo Depression

- Axum Obelisk
- Lalibella
- Fasil Castel: Gondar
- Lucy: Australopithecus afarensis

- Ephany
- Easter and Christ-Mas
- Finding of the True Cross

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