Clinical presentation and outcomes in hospitalized patients with Cryptococcal Meningitis and HIV coinfection in Zimbabwe

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Outline

• Introduction

• Overview of research projects
  – Early vs Delayed ART in Treatment of Cryptococcal Meningitis in Africa
  – Mortality and Cryptococcal Meningitis in Africa

• Research Questions

• Discussion
Cryptococcal Meningitis - Epidemiology

• Approximately One million people with AIDS develop Cryptococcal Meningitis (CM) annually
• Estimated 12 week mortality rates range from 9% in North America and Western Europe to 70% in sub-Saharan Africa
• 625,000 deaths annually are due to CM, 80% of them occur in sub-Saharan Africa
• Deaths associated with CM are higher than those associated with Tuberculosis
Estimated Cryptococcal Meningitis Annual Cases [with HIV prevalence rates]

Total: 957,900 (371,700 – 1.54 million)

North America
7,800
[760 000 – 2.0 million]

Caribbean
7,800
[210 000 – 270 000]

Latin America
54,400
[1.5 – 2.1 million]

Western & Central Europe
500
[580 000 – 1.0 million]

Middle East & North Africa
6,500
[280 000 – 510 000]

Sub-Saharan Africa
720,000
[20.5 – 23.6 million]

Eastern Europe & Central Asia
27,200
[1.1 – 1.9 million]

East Asia
13,600
[480 000 – 1.1 million]

South & South-East Asia
120,000
[3.5 – 5.3 million]

Oceania
100
[66 000 – 93 000]

Park, B et al. AIDS. 23(4):525-530, February 20, 2009
Deaths in sub-Saharan Africa related to CM as compared to other common infectious diseases

Park, B et al. AIDS. 23(4):525-530, February 20, 2009
Cryptococcal Meningitis

- Yeast
- It is ubiquitous in soil and typically found in soil with bird droppings
Global Phenotypic Distribution

- There are four different types of C. neoformans- A to D based on serotyping
  - Types B & C are called C neoformans var. gattii
  - Type A – C neoformans var. grubii
  - Type D – C. neoformans var. neoformans
- Type D is the most common cause of disease in sub-Saharan Africa
- Leading cause of meningitis in AIDS patients in Africa (Hakim, 2000)
- Responsible for 13-42% of deaths among patients with AIDS (Mwaba, Moosa/Coovadia CID 1997 24:131)
Diagnosis

- India Ink
  - Sensitivity is user dependent

- Cryptococcal Antigen Test
  - Sensitivity and Specificity >98%

(pathology.mc.duke.edu/.../CNSlecture2/tbafb.jpg)
Cryptococcal Meningitis is an AIDS defining opportunistic infection
Clinical Presentation

• Headache – acute vs. chronic
• Neck Stiffness
• Severe wasting
• Oral thrush
• Waning level of consciousness
• Fever
• Confusion
Treatment Options

Induction Therapy
• Amphotericin B (0.7-1mg/kg/d) plus flucytosine (100mg/kg/d (divided in 4 daily doses) x 2 weeks)) followed by

Consolidation therapy
• Fluconazole (400mg/d) for a minimum of 10 weeks.

Suppression therapy
• Fluconazole 200mg po for life or until CD>200 for more than 6 months
• Mortality on this regimen is significantly reduced to 9.4%
  – US study where severely ill patients in comas etc., were excluded, good clinical management of high pressure disease was available.
• Fluconazole monotherapy is suboptimal, however it is the most affordable option in Zimbabwe.
US Treatment Guidelines: Management of raised ICP

• Measure initial opening pressure
• Daily LPs
  – Removal of CSF that halves the opening pressure (typically 20-30mL)
• Corticosteroids, mannitol and Acetazolamide are not recommended
• LP should be repeated at 2 weeks
  – To determine if CSF has cleared
  – Determine appropriate subsequent management
Clinical Outcomes

• In the absence of treatment Mortality is 100%
  – Median survival from the time of diagnosis was 19 days in those treated with fluconazole and 10 days in the untreated group (Mwaba, P., Postgrad Med J (2001) 77:769)

• 64% in-hospital mortality in a South African study (Mossa, M.Y, Clin Infect Disease (1997) 24:131)

• Median survival in a SA study of patients treated with Fluconazole 400mg vs 200mg was 76 and 82 days respectively (p=0.27)
  – In hospital mortality was 25%
  – 10% of patients were known be alive at 6 months
  – 3% after one year (Schaars, C.F, BMC Infect Dis (2006) 6:118)
Cryptococcal Meningitis is characterized by a high mortality rate
Cryptococcal Meningitis Study
Objectives

• Determine rates of cryptococcal meningitis in a large public hospital
• Determine clinical presenting features of Cryptococcal meningitis
• Determine in-patient mortality rate in patients with CM
• Determine predictors of mortality
Cryptococcal Meningitis in Harare

- Retrospective cohort analysis
- Patients admitted to a large tertiary central hospital between Sept 2006-Sept 2007
- 123 patients identified with a discharge diagnosis of Cryptococcal meningitis
Diagnosis

- India Ink
  - Sensitivity is user dependent
- Cryptococcal Antigen Test
  - Sensitivity and Specificity >98%
- Clinical diagnosis
Patients diagnosed with Cryptococcal Meningitis (n=123):
India Ink Positive (n=77)
CSF CRAG Positive (n=23)
India Ink Negative (n=9)
CSF CRAG Negative (n=1)a
Previously CM diagnosis and treatment (n=7)
Clinical diagnosis CM (n=1)b
India Ink Data Unavailable (n=14)
Previous CM diagnosis and treatment (n=8)
Clinical diagnosis of CM (n=6)c
Clinical Diagnosis of CM

8 patients had a clinical diagnosis of CM
- CSF CRAG and India Ink negative, had a previous history of CM.
- India ink negative, CRAG not done presented with seizure, headache and CD4 of 25, and was treated with fluconazole as there was no other identified etiology for his presentation. He did well and was discharged on fluconazole.

6 patients with clinical diagnosis of CM.
1. 14 days of headache GCS of 14, clinical diagnosis of CM, placed on fluconazole, and survived to discharge.
2. Headache for 14 days, no focal neurological signs, a CD4 of 64 was treated presumptively for CM with fluconazole and survived through till discharge.
3. Presented with a headache, was on ART and TB therapy, no previous hx of CM and was started on fluconazole and survived through to discharge.
4. Presented with a HA for 3 days, had started ART 45 days earlier treated with fluconazole and survived through to discharge.
5. Presented with 7 days of headache, no other focal findings, and treated with fluconazole however deceased during course of admission.
6. Presented with 3 weeks of severe headache, no focal neurological signs, previously been on ART 2 years prior however defaulted for financial reasons. Was treated with fluconazole and survived through to discharge.
Patient demographics

- Mean Age 37.81 years (±8.59)
- Age range 20-72 years
- 44% of patients were female
Other OIs: TB and Cryptococcal Co-infection

• TB infection is very common – Is HIV associated tuberculosis a risk factor for development of cryptococcal disease?

• Recent study from Cape Town outpatient cohort
  – Previous history of TB associated with the development of CM (OR = 4.94, 95% CI = 1.1 -22.4, p=0.039)
  – Previous history of pulmonary TB associated with the development of CM (OR = 6.87, 95% CI = 1.5 -31.2, p=0.013)
  – Pulmonary TB within 2 years of clinic enrollment even more strongly associated with development of CM (OR = 8.7, 95% CI = 2.4 -32.0, p=0.039)

(Jarvis JN et. Al AIDS 2010 24: Epub)
TB and CM in hospitalized patients

• 16.26% had a previous history of TB and were treated for TB.
  – Four individuals (20%) with a previous history of TB were also on ART at the time of presentation.

• 22.76% of patients (n=28) were actively receiving TB treatment at the time of admission with a diagnosis of cryptococcal meningitis.
HIV immune reconstitution inflammatory syndrome (IRIS) is a clinical syndrome that typically occurs within 12 weeks of initiation of ART with clinical deterioration due to pathological inflammatory responses.

Typical organisms include Mycobacterium Tuberculosis, Cryptococcus neoformans, MAC, CMV, HSV.

There are two types of IRIS:
- Unmasking – unmasking of a previously unidentified infection with the onset of ART
- Paradoxical IRIS - development of the clinical syndrome from an infection that was previously appropriately treated prior to the initiation of ART
Paradoxical Cryptococcal IRIS Case Definition

(A) Antecedent requirements

* Taking antiretroviral therapy
* Cryptococcal disease diagnosed pre-ART by positive culture or typical clinical features plus positive India ink staining or antigen detection
* Initial clinical response to antifungal therapy with:

(1) partial or complete resolution of symptoms or signs, fever, or other lesions, or
(2) reduction in CSF cryptococcal antigen or quantitative culture

(B) Clinical criteria

* Event occurs within 12 months of ART initiation (unless culture positive, in which case event must occur within 3 months of initiation of antifungal therapy)
* Clinical deterioration with one of the following inflammatory manifestations of cryptococcosis (see text for possible rarer manifestations):

- Meningitis
- Lymphadenopathy
- Intracranial space-occupying lesion/s
- Multifocal disease
- Cutaneous / soft tissue lesions
- Pneumonitis or pulmonary nodules

(C) Other explanations for clinical deterioration to be excluded:

* Non-adherence or suboptimal antifungal therapy, indicated by an increase in quantitative culture or antigen titer, or any positive cryptococcal culture after 3 months.
* Alternative infection or malignancy in the affected site
* Failure of ART excluded if possible (e.g. failure to achieve ≥1 log10 copies/mL decrease in VL by 8 weeks of ART)
Unmasking IRIS Case Definition

ART-associated cryptococcosis
We propose that ART-associated cryptococcosis (all cases of cryptococcosis that are diagnosed during ART) should be defined as follows:

* Taking antiretroviral therapy (ART)
* No recognized cryptococcal disease at ART initiation
* Clinical deterioration caused by cryptococcosis (supported by microbiological, histological or serological evidence)

Unmasking cryptococcal IRIS (provisional)
We propose that the following could suggest a diagnosis of unmasking cryptococcal IRIS:

* Criteria for ART-associated cryptococcosis (above) are met
* Unusual, exaggerated or heightened inflammatory manifestations, for example:
  - Meningitis with markedly elevated leukocyte count or opening pressure
  - Painful or suppurating lymphadenopathy
  - Rapidly-expanding CNS lesions
  - Unusual focal site
  - Granulomatous inflammation on histology
  - Pneumonitis, particularly if cavitating or necrotic

* Event occurs early after ART initiation *
* Failure of ART excluded if possible (e.g. ≥1 log10 copies/mL decrease in VL by 8 weeks of ART)

* No specific time limit is proposed for unmasking cryptococcal IRIS, pending further research. Onset within 1 month of initiation of ART is supportive of IRIS, rather than immunodeficiency-related disease.
Previous ART exposure in cohort

• 26% (n=32) of patients admitted with cryptococcal meningitis had a previous history of ART use.
  – 12.5% (n=4) of these had discontinued ART prior to hospitalization reasons for default/discontinuation included:
    • Financial (n=2)
    • Psychosis and psychiatric admission (n=1)
    • Concurrent TB treatment discontinued 1 mo after starting TB treatment.
• 6 patients were on 2nd line therapy, and all had been switched to 2nd line therapy in the setting of clinical deterioration while on ART.
• Patients were on 2nd line therapy at least 3 years after initiation of ART (range 1194-1592 days), with the exception of two patients:
  – One who was on 2nd line therapy after 266 days of first line therapy and another after 351 days.
CM IRIS vs ART Treatment failure

• 13 (46.42%) patients developed CM within 12 weeks of initiation of ART.
• 9 patients developed CM between 12 weeks and 1 year after initiation of ART.
• 6 patients had developed CM more than 1 year after initiation of ART. 4/6 had developed CM in the setting of ART treatment failure.
  – 1 patient who developed CM after 796 days had defaulted ART due to financial reasons and was not on ART at the time of admission.
  – Another had initiated ART in 2003, four years prior to admission but had been switched to 2nd line regimen prior to presentation with CM.
  – A third who had started ART 1194 days prior to admission had been switched to 2nd line therapy 1 year prior to presenting with CM.
  – Another developed CM 730 days after initiation of ART had defaulted his ART and was not on ART at the time of admission, date of default was not available.
  – Another had been on ART for 1267 days prior to initiation of ART and was switched to 2nd line during this admission for presumed treatment failure.
  – Another had been on ART for 1592 days and subsequently switched to 2nd line therapy when they developed CM.
• All of these individuals had a previous history of CM
89% of patients presented with headache
Median duration of headache 14 days (IQR 6, 21)
Presenting focal neurological signs

<table>
<thead>
<tr>
<th>Focal Neurological Signs details</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd nerve palsy</td>
<td>2</td>
</tr>
<tr>
<td>6th nerve palsy</td>
<td>2</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>4</td>
</tr>
<tr>
<td>Blindness</td>
<td>4</td>
</tr>
<tr>
<td>Focal hemiparesis</td>
<td>4</td>
</tr>
<tr>
<td>Not communicating</td>
<td>9</td>
</tr>
<tr>
<td>Facial paralysis</td>
<td>1</td>
</tr>
</tbody>
</table>
Baseline Laboratory data

• CSF Parameters
• WBC parameters
• LFTs
• Electrolytes
CSF Parameters

- CSF cell counts were typically normal in 67.48% of patients
- Mild elevations in CSF proteins were noted in most patients
  - Median CSF protein 95 (IQR 56, 138)
- CSF glucose: serum glucose ratios were levels were low in three quarters of the patients (n=52)
  - Mean CSF Glucose 2.21 (±1.32) mmol/L (nl range 2.2-3.9) (n=81)
Peripheral cell counts

- Mean WBC 4.93 (±2.44) (n=86)
- Median TLC 690 (IQR 510, 1000) cells/mm³ (n=56)
- CD4 counts available for 22 patients
  - Median CD4 count 33.5 cells/mm³ (IQR 16, 88)
Anemia

- 81% of females were anemic with Hgb <12 g/dL
- 85.7% of males were anemic with Hgb <14
Primary Outcome measure: Mortality

• In hospital mortality was 33.33%
• Mortality rates were comparable between men and women
  – 37.03% mortality among the women,
  – 30.43% mortality among the men (p=0.44)
• Mortality rate was 34.38% among those who had exposure to ART
• Median time to death from admission was 4 days (IQR 2, 8)
CM Associated mortality
## Predictors of CM associated mortality

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Alive (n = 82) n (%)</th>
<th>Died (n = 41) n (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to start ART ≥ 85</td>
<td>11 (61.1) (n = 18)</td>
<td>4 (40) (n = 10)</td>
<td>0.42</td>
<td>0.082 – 2.2</td>
</tr>
<tr>
<td>Previous history of Fluconazole</td>
<td>20 (24.4) (n = 79)</td>
<td>13 (31.7) (n = 38)</td>
<td>1.44</td>
<td>0.62 – 3.32</td>
</tr>
<tr>
<td>Headache</td>
<td>76 (96.2) (n = 79)</td>
<td>34 (89.5) (n = 38)</td>
<td>0.34</td>
<td>0.07 – 1.61</td>
</tr>
<tr>
<td>Decreased LOC</td>
<td>2 (2.44) (n = 79)</td>
<td>7 (17.1) (n = 38)</td>
<td>8.24</td>
<td>1.52 – 44.58*</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (14.6) (n = 79)</td>
<td>7 (17.1) (n = 38)</td>
<td>1.2</td>
<td>0.43 – 3.34</td>
</tr>
<tr>
<td>Weight loss</td>
<td>14 (17.1) (n = 79)</td>
<td>8 (19.5) (n = 38)</td>
<td>1.18</td>
<td>0.45 – 3.1</td>
</tr>
<tr>
<td>Seizures</td>
<td>13 (15.9) (n = 79)</td>
<td>14 (34.2) (n = 38)</td>
<td>2.75</td>
<td>1.12 – 6.77*</td>
</tr>
<tr>
<td>Focal Neurological signs</td>
<td>8 (9.8) (n = 79)</td>
<td>17 (41.5) (n = 38)</td>
<td>6.55</td>
<td>2.32 – 18.47*</td>
</tr>
<tr>
<td>CSF_WBC ≥ 51</td>
<td>8 (14.6) (n = 55)</td>
<td>3 (10.3) (n = 29)</td>
<td>0.68</td>
<td>0.16 – 2.8</td>
</tr>
<tr>
<td>CSF_WBC ≥ 11</td>
<td>17 (30.9) (n = 55)</td>
<td>8 (27.6) (n = 29)</td>
<td>0.85</td>
<td>0.31 – 2.32</td>
</tr>
<tr>
<td>India Ink positive</td>
<td>46 (56.1) (n = 82)</td>
<td>30 (73.2) (n = 41)</td>
<td>2.31</td>
<td>0.93 – 4.9</td>
</tr>
</tbody>
</table>
Time to death is independent of previous ART exposure, or previous Fluconazole

\( P = 0.53 \)
Time to death is not associated with previous history of CM or seizures

P=0.69

P=0.79
In Summary

• CM mortality is strongly associated with clinical presentation particularly
  – Seizures
  – Focal Neurological signs
  – Decreased level of consciousness

• Effective algorithms are required to make significant differences in decreasing CM related mortality
Key clinical questions for improving outcomes

• Increasing access of Amphotericin Therapy
  – 15 patients (12.2%) were treated with amphotericin B
  – 6/15 (40%) died during the admission

• Improved CSF pressure management
  – Resource limitations

• Health care delivery systems and the process of care and identify points of intervention

• Pre-admission prevention
  – Serum CRAG screening
  – Fluconazole prophylaxis
  – Community education
Key Research Questions

• Steroids in the treatment of CM
  – New diagnosis CM
  – CM IRIS
• Defining CM IRIS in a sub-Saharan African population
• Immunological predictors of IRIS
• Targeted treatment for IRIS
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Didn’t just do research

• Clinical work
• A little bit of fun and hanging out
Common adolescent rash