Neurological Complications of HIV
Kenya, June 13, 2012

Zelalem Temesgen MD, FIDSA, AAHIVS
Mayo Clinic
HIV-related CNS Disease

• CNS Mass Lesions
  • Toxoplasma
  • Primary CNS lymphoma
  • PML
  • Tuberculoma
  • Cryptococcoma
  • Neurocysticercosis
  • Primary brain tumor
  • Metastatic brain tumor
  • Bacterial abscess

• Non-Mass Diseases
  • Cryptococcal meningitis
  • TB meningitis
  • Bacterial meningitis
  • CMV meningoencephalitis
  • HIV encephalitis
  • HIV dementia
  • HSV, VZV, HHV6
Discussion Topics

• Cryptococcal Meningitis

• Tuberculous Meningitis

• Toxoplasma Encephalitis
Cryptococcal Meningitis
Cryptococcal Meningitis: Epidemiology

- Common cause of meningitis in Africa
- Rwanda, Pre-ARV era 1983-1992, HIV status unknown
  - 3476 CSF specimens from 2824 adults
  - 549 positive (19%) for Cryptococcal meningitis
    - *Cryptococcus*: 549
    - *N. meningitidis*: 115
    - *S. pneumoniae*: 68
    - *M. tuberculosis*: 26
    - Others: 19

Cryptococcal Meningitis: Epidemiology

• Most common meningitis in HIV/AIDS
  • Pre-ARV: 15-25% of HIV at presentation had crypto (Uganda, S.Africa, Ethiopia, Thailand)

• The most common AIDS-defining illness in 78-91% of patients presenting late

• CD4 < 100

• 13-44% of HIV deaths in Africa
Etiology of Meningitis in HIV

- Malawi\(^1\)
  - 573 patients suspected meningitis: 264 confirmed
    - 112 Crypto (43%)
    - 46 TB (18%)

- South Africa\(^2\)
  - 5578 LPs on 4549 patients
    - 820 (47%) etiology
      - 514 (63%) Crypto
      - 227 (28%) TB
      - 68 (8%) bacterial

- Others have also found a high proportion of meningitis in HIV is caused by crypto:
  - Zimbabwe\(^3\): 45%
  - CAR\(^4\) 31%

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3. Hakim. AIDS 2000;
RESULTS

A total of 708 HIV positive patients were admitted to the hospital under the Division of Medicine during the study period of January 2000 and June 2005. One hundred and fifty patients had neurological manifestations.

The various neurological manifestations observed

<table>
<thead>
<tr>
<th>Neurological manifestation</th>
<th>Frequency</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcal meningitis</td>
<td>33</td>
<td>22.0</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>28</td>
<td>18.7</td>
</tr>
<tr>
<td>Cerebral toxoplasmosis</td>
<td>19</td>
<td>12.7</td>
</tr>
<tr>
<td>Stroke syndrome</td>
<td>19</td>
<td>12.7</td>
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<tr>
<td>Tuberculous meningitis</td>
<td>16</td>
<td>10.7</td>
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<tr>
<td>HAD.PN/Myelopathy/Myopathy</td>
<td>21</td>
<td>14.0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>14</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>150</strong></td>
<td><strong>100.1</strong></td>
</tr>
</tbody>
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HAD = HIV Associated Dementia
PN = Peripheral Neuropathy

Cryptococcal meningitis was the commonest neurological complication in hospitalised HIV infected patients with neurological manifestations.
Cryptococcosis in Africa

Number of adult patients on anti-retroviral therapy (ART) in the hospital referral area, and the number of patients with India Ink positive cryptococcal meningitis presenting to the hospital by year, 2003-2008.

AIDS 2009 June 1;23(9):1182-1183

NO representative reduction in number of new India ink + cases even with ART
Cryptococcus Neoformans

- Encapsulated yeast, 4-6 μm
- Found naturally worldwide
  - Soil/debris contaminated with chicken/pigeon/bird droppings
  - Eucalyptus trees
Cryptococcal Disease: Pathophysiology

- Spores 
  - Eucalyptus tree 
  - Bird excreta

- Inhalation into lungs

- Lodging in alveoli

- Dissemination to central nervous system

- Positive culture
Cryptococcal Clinical Disease

1. **Pneumonia**

2. **Skin** (15%)
   - Papules, pustules, purpura, ulcers, cellulitis, plaques, abscess, sinus tracts.

3. **Bone** (<10%)
   - Vertebrae are most common site

4. **Urogenital tract**
   - Kidneys, prostate
   - Prostate known to serve as sanctuary/reservoir for persistent infection

5. **Other sites**
   - Liver, LNs, peritoneum, adrenals, eyes.

6. **Meningitis**

7. **Intraparenchymal CNS cryptococcomas**
   - Less common
Cryptococcal Meningitis: Presentation

- Subacute
  - Symptoms worsen over days to weeks.
  - May be asymptomatic initially

- Headache

- Fever

- Altered mental status (confusion)
  - Seizures ~10%
  - Focal neurologic findings less often
  - Meningismus - occasional
Cryptococcal Meningitis: Diagnosis

- Key to diagnosis:
  - Organism in the CSF
  - Cryptococcal antigen (Sensitivity: 93-100%)
  - India ink smears (sensitivity 25-50%)
  - Culture

- Other findings:
  - Opening pressure markedly elevated.
  - CSF

- Variable
  - Normal
  - Elevated protein
  - Low glucose
  - Mononuclear pleocytosis.
Diagnosis

- **CrAg**
  - **Serum:**
    - In patients with AIDS, the sensitivity of serum antigen testing is comparable to CSF testing.
    - Useful as a **screening test** or in patients who **cannot undergo LP**.
    - + serum CrAg => LP should be pursued.
    - Antigen titers generally correlate with organism burden.
  - **Issues**
    - Not accurate for making treatment decisions.
    - Serial CrAg titers are imprecise.
    - Does give general prognostic information.
      - Initial high titers (≥1 : 1024) correlate with high burden of yeasts, poor host immunity, and greater chance of therapeutic failure.
    - Encouraging when Ag titer is stable or dropping
      - especially with IRIS.
CRAG Studies in Resource-Limited Settings

- **Uganda**: 3 prevalence studies in pre-ARV CD4 ≤ 100
  - 5.8% (Lietchy¹); 8.9% (Meya²); 10.4% (Tassie³)
  - Meya: 26+/259 CD4 ≤ 100 (8.9%)
    - 21 treated: 71% survival 30 month
    - 5 not treated: all dead at 2 months
    - NNTest for 1 positive CRAG: 6.5 (95% CI: 5.0-8.6)
    - NNTest + treat to prevent 1 Crypto meningitis: 11.3; cost 190$
    - NNTest + treat to prevent 1 death: 15.9; cost 266$

- **South Africa** (Jarvis⁴): Mean CD4 97
  - 7% CRAG + (sens 100%; spec 96%)

- **Thailand** (Pongsai⁵) and Cambodia⁶
  - 12.9 % in CD4 ≤ 100 and 21%

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² Meya DB, Manabe YC, Castelnuovo B. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. CID 2010 15;51(4):448-55
³ Tassie JM Systematic Screening of Cryptococcal Antigenemia in HIV-Positive Adults in Uganda. JAIDS 2003; 33:3
⁴ Jarvis J. Screening for Cryptococcal Antigenemia in Patients Accessing an Antiretroviral Treatment Program in South Africa. CID 2009; 48:856-62
⁵ Pongsai. The role of serum cryptococcal antigen screening for the early diagnosis of cryptococcosis in HIV-infected patients with different ranges of CD4 cell count. Journal of infection 60(6) 2010
Diagnosis – other tests

- Blood, urine, sputum cultures
  - BCx + in up to two-thirds of AIDS-associated CM.

- Brain imaging
  - CT and MRI are usually normal.
  - Can have hydrocephalus, cerebral edema, or mass lesion (cryptococcoma).

![Multiple cryptococcomas (white lesions) in the brain](https://www.mycology.adelaide.edu.au)
Cryptococcal Meningitis: Treatment

- **Induction – 2 weeks**
  - Amphotericin B 0.7-1.0 mg/kg/day IV + flucytosine

- **Consolidation – 10 weeks**
  - Fluconazole 400mg/daily

- **Maintenance**
  - Fluconazole 200 mg/day
High dose Fluconazole vs Amphotericin B

- **Positives**
  - More easily accessible
  - Oral form well absorbed
  - Better tolerated
  - Less toxicity
  - Less costly

- **Negatives**
  - Possible inferiority in clinical efficacy
    - Seems comparable in African studies, but no head-to-head; and amphotericin B studies are with flucytosine
  - Slower sterilization of CSF
  - Interactions rifampin/NVP?
  - Some toxicity
Cryptococcal Meningitis: Mortality

• If not diagnosed and treated
  • almost 100% at 6 months

• If diagnosed and treated:
  • 10-25% mortality in developed countries
  • African studies: 30-70% 10-wk mortality even with Amphotericin B
In Sub-Saharan Africa, deaths due to Cryptococcal meningitis (530,000), may be more frequent than tuberculosis (350,000).

HIV: deaths from crypto 13-44%; deaths from TB 5-13%²,³,⁴

Comparison of deaths in sub-Saharan Africa due to HIV-related cryptococcosis

Figure modified from Park et al., AIDS 2009, 23: 525-530
Cryptococcal Meningitis: Intracranial Hypertension

• Common Cause of death
  • « Failure to manage elevated intracranial pressure is the most common and most dangerous mistake in management. » *Clinical Infectious Diseases* 2005;40:477
  You repeat the LP and remove 30mL

• Hydrocephaly is characteristic and dangerous
  • Symptoms of ICH: ↓ LOC, vomiting, severe headaches, papilloedema, cranial nerve palsies, vision disturbance

• Repeat LP is mandatory for therapeutic purpose:
  • Daily, based on clinical evolution and indication (20-30 mL)
  • Sometimes ventricular drain is necessary

• Neither steroids or diuretics are effective in managing crypto-associated ICH
Discontinuation of Secondary Prophylaxis

• Successful completion of initial phase

• Remain asymptomatic with regard to signs and symptoms of cryptococcosis,

• Have a sustained increase (i.e., >6 months) in CD4 counts to 200 cells/μL after ART
Cryptococcal Meningitis: IRIS

• 30% of patients with cryptococcal meningitis and HIV infection experience IRIS after initiation or reinitiation of ART

• Manifestations
  • lymphadenitis
  • meningitis
  • mass lesions (cryptococcomas)
  • pulmonary cavities
Management of CM IRIS

• **No need to alter** direct antifungal therapy (B-III).

• No definitive specific treatment for minor IRIS is necessary, because they resolve spontaneously in days to weeks (B-III).

• For major complications, such as CNS inflammation with increased ICP, consider **corticosteroids** (0.5–1.0 mg/kg per day of prednisone) or dexamethasone. Length and dose of the corticosteroid taper are empirically chosen and require careful following of the patient, and should be given with a concomitant antifungal regimen (B-III).

• NSAIDs and thalidomide have been used but with too little experience to make a recommendation (C-III).

• Continue ART

Perfect et al. CID 2010: *February*
Cryptococcal Optimal ART Timing (COAT) study

- ART-naïve, HIV-infected participants hospitalized with cryptococcal meningitis (CM)
  - Two sites in Uganda and one in South Africa

- Early ART while receiving CM treatment as inpatients vs. delayed (approximately 5 weeks after receiving CM treatment)
  - 14 days of amphotericin B followed by fluconazole

- Higher mortality rates among the 87 participants who received early ART compared with the 87 participants who received delayed HIV treatment

- Study terminated
Toxoplasma Encephalitis
Toxoplasmosis Epidemiology

• Antibodies increase with increasing age

• Seroprevalence rates vary by country
  • 15% in US
  • 50% in some European countries
  • Likely higher in developing countries
  • Kenya: 35% in pre-school to 60% in the early school age group

• No difference in seroprevalence by HIV status.

Bowry TR et al. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1986;80(3):439-441
Toxoplasma gondii

• A protozoan parasite that infects most species of warm blooded animals, including humans

• The only known definitive hosts for Toxoplasma gondii are domestic cats and their relatives
Toxoplasma Encephalitis

• Reactivation disease

• Most common cause of mass brain lesion in HIV

• The greatest risk occurs among patients with a CD4 count <50 cells/μL

• Usually subacute onset
  • 15-25% presentation may be more abrupt, especially with seizures

• Clinical presentation
  • Headache, confusion, and fever
  • Focal neurologic changes
  • New seizure
Toxoplasma Encephalitis: Diagnosis

- Serology (serum IgG)
  - If negative, TE unlikely

- Identification of organism
  - Biopsy
  - PCR on CSF
  - Sensitivity varies 11-77%.
  - Specificity is close to 100%.

- Imaging
  - MRI shows multiple ring-enhancing lesions
  - Location:
    - parietal or frontal lobes
    - thalamus or basal ganglia
Toxoplasma Encephalitis: Presumptive Diagnosis

- Compatible clinical picture
- Positive IgG
- Multiple mass lesions by CT, MRI
- Confirm presumptive diagnosis by monitoring for response to treatment (2 weeks) to specific anti-\textit{T. gondii} therapy
  - clinical and radiographic improvement
- Biopsy if response is not demonstrated
Toxoplasma Encephalitis: Treatment

- **Acute treatment:**
  - Pyrimethamine/sulfadiazine (+ folinic acid)
  - Alternate
    - Pyrimethamine/clindamycin
    - Trimethoprim/Sulfamethoxazole

- If there is clinical and radiologic improvement, acute therapy for TE should be continued for at least 6 weeks

- **Chronic maintenance therapy**
  - Same drugs but reduced dose

- **Discontinuation chronic maintenance therapy**
  - remain asymptomatic
  - have a >6 months sustained increase in their CD4 counts of >200 cells/μL after ART
Tuberculous Meningitis
Central Nervous System Tuberculosis

- Meningitis

- Intracranial tuberculoma

- Spinal tuberculosis
TB Meningitis

• Epidemiologic association with HIV not as pronounced.
  • Reports of increase in incidence in Africa, but still less frequent than cryptococcal meningitis

• HIV does not alter clinical manifestations, CSF findings, or response to therapy
  • Cerebral tuberculomas slightly more common in HIV-infected
TB Meningitis: Pathogenesis

- *Mycobacterium tuberculosis* bacilli enter the host by droplet inhalation
  - dissemination to the regional lymph nodes
  - bacilli seed to other parts of the body, including the meninges or brain parenchyma
    - small subpial or subependymal foci of metastatic caseous lesions
- TBM occurs when these foci increase in size and ruptures into the subarachnoid space
- Post-primary infection in infants and young children
- Chronic reactivation in older adults
TB Meningitis: Diagnosis (Imaging)

- CT normal in 30% of Stage I meningitis
- Hydrocephalus
- Basilar meningeal enhancement
- Cerebral infarcts
- Tuberculomas
- Hydrocephalus + Basilar meningeal enhancement = TB meningitis
Contrast-enhanced cranial CT of a patient with tuberculous meningitis.
(A) Contrast-enhanced CT of brain showing multiple tuberculomas in a patient with tuberculous meningitis; (B) chest X-ray showing miliary shadows.

TB Meningitis: Treatment

• Treatment principle similar as pulmonary TB
  • Initial phase
  • Continuation phase

• Drugs used – same

• Steroids for stage 2 and 3

• Duration of therapy — 9 to 12 months
  • Continuation phase 7-10 months

• Treatment of tuberculoma
  • Same drugs
  • Duration 18 months
TB meningitis: Sequencing of ART and Anti TB Rx

All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately.

All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART).

In patients with CD4 counts <50 cells/mm³, ART should be initiated within 2 weeks of starting TB treatment.

In patients with CD4 counts ≥50 cells/mm³ who present with clinical disease of major severity ART should be initiated within 2 to 4 weeks.

In patients with CD4 counts ≥50 cells/mm³ without severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 wks.
TB Meningitis: IRIS

• Usually occurs within the first 60 days of starting HAART therapy

• Reappearance of fever

• Expansion of preexisting intracranial tuberculomas

• If other sites involved
  • New infiltrates
  • New pleural effusions
  • Worsening lymphadenitis
  • Cutaneous lesions
  • Peritonitis
  • Epididymitis
  • Bowel perforation
  • Granulomatous nephritis
Summary

• Difficult to distinguish disease entities based on clinical grounds alone

• Reliable diagnostic capacity critical
  • CD4
  • CSF
  • CRAG
  • CT

• Aggressive treatment
  • Do not delay for confirmation of diagnosis

• Manage drug toxicities

• Manage drug interactions

• Manage IRIS