HIV-Associated Common Neurological Opportunistic Infections Case Study: Practical Diagnostic Tips and Management

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The neurologic effects of HIV infection

- **It causes significant morbidity and mortality.**

- **Effect**
  - *Direct effect: HIV itself*
    - HIV associated dementia
  - *Indirect effect: result from immunodysfunction*
    - *By opportunistic infection (OI)*
    - HIV has neurotrophic features
      - develop OI and unusual neoplasms
Neurologic effects of HIV infections

- Neurological disorders affecting CNS and PNS occur in 40 - 80% of HIV patients who have high viral load and CD4 < 200.
- 10-20% presented with neurological problems.
Scope

• Incidence of AIDS in Thailand
• Prevalence or incidence of cerebral OI in Thailand
• Common CNS opportunistic infections & tumor in HIV
  – Toxoplasmosis
  – Cryptococcosis
  – Tuberculosis
  – Primary CNS lymphoma
  – Progressive multifocal leukoencephalopathy (PML)
  – Cytomegalovirus (CMV) encephalitis

• Summary
  – Practical diagnostic tips & management
  – Problem of diagnosis CNS OI
Incidence of AIDS in Thailand
Incidence of HIV in Thailand

- Study among Thai people
- Age > 10 years
- In 1994-1998
- ~ 20 cases / 100,000
- HIV1:
  - subtype AE >> B

Suwat Chariyalertsak, et al.  
Clinical Infectious Diseases 2001.
HIV patient: 101,945 cases reported to Ministry of Public Health of Thailand

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Prevalence or incidence of cerebral OI in Thailand
Incidence of AIDS defining illnesses HIV patient in Thailand 101,945 cases in 1994-1998:

- Tuberculosis: 28.9
- Cryptococcosis meningitis: 18.5
- Cerebral toxoplasmosis: 3.1
- HIV encephalopathy: 1.9
- CMV retinitis: 0.6
- CMV infection: 0.2
- Lymphoma: 0.2
- Primary CNS lymphoma: 0.1
- PML: 0.1

Prevalence of OI in 286 HIV IPD cases at Siriraj Hospital (mean CD4 74.7)

Incidence of OI in HIV studied at Chiang Mai University; compare pre and post HAART era

Common CNS opportunistic infections & tumor in HIV
# Common neurologic OI & neoplasm in AIDS

<table>
<thead>
<tr>
<th>Location</th>
<th>Predominant non-focal</th>
<th>Predominant focal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td>CMV encephalitis</td>
<td>Cerebral toxoplasmosis</td>
</tr>
<tr>
<td></td>
<td>VZV encephalitis</td>
<td>Primary CNS lymphoma</td>
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<tr>
<td></td>
<td>HSV encephalitis</td>
<td>Progressive multifocal leukoencephalopathy (PML)</td>
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<td></td>
<td>Metabolic encephalopathies</td>
<td>Cryptococcoman</td>
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<tr>
<td></td>
<td></td>
<td>Tuberculoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurosyphilis (meningovascular)</td>
</tr>
<tr>
<td><strong>Spinal cord &amp; root</strong></td>
<td>HSV or Zoster myelitis</td>
<td>CMV lumbar polyradiculopathy</td>
</tr>
<tr>
<td><strong>Meninges</strong></td>
<td>Cryptococcal meningitis</td>
<td>TB meningitis</td>
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<td></td>
<td></td>
<td>Syphilitic meningitis</td>
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<td>Metastatic lymphoma meningitis</td>
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Cerebral Toxoplasmosmosis
Cerebral Toxoplasmosis

- Prevalence: 20-40% of AIDS patients
- *The most frequent and treatable of focal complications in HIV*
- Primary infection:
  - eating raw beef
  - contact cat feces (common)
- Disease in HIV represents reactivation of a prior infection
Cerebral Toxoplasmosis: Clinical

- Vary: depends on location of lesions
  - Seizures
  - Headache
  - Symptoms & signs of increased ICP
  - Meningeal irritation
  - Lethargy, mental confusion
  - Coma
  - Chorea: pathognomonic? but rare
Cerebral Toxoplasmosis: Diagnosis

- **CT or MRI with contrast**
  - Focal inflammatory necrosis
  - **Involves:**
    - basal ganglia (most common),
    - Deep white matter
    - Gray-white junction
  - **Multiple nodular or ring-enhancing lesions**
    - With brain edema and mass effect
  - 14-22% single lesions
Cerebral Toxoplasmosis: Diagnosis

- **Identify** *serum Toxoplasma*
  - Serologic test is positive in almost all patients;
  - Therefore *negative serology nearly excludes this Dx*
    - 20% of negative can be disease

- **LP**
  - *Should avoid:*
    - *Brain herniation & result non specific*
  - Increase CSF protein ~ 50-200 mg/dL
  - 1/3 have a CSF lymphocytic pleocytosis
Cerebral Toxoplasmosis: Diagnosis

• *Therapeutic diagnosis*
  – *Improve significantly within 2 weeks*

• *Lesional biopsy* (CNS, muscles, LN)
  – If condition progress after empiric treatment
  – Patho: multiple diffuse necrotizing
Randomized Controlled Trial of Pyrimethamine Plus Sulfadiazine Versus Trimethoprim Plus Sulfamethoxazole for Treatment of Toxoplasmic Encephalitis in AIDS Patients

Subsai Kongsaengdao, MD, Kanoksri Samintarapanya, MD, Kanokporn Oranratnachai, MD, Wantana Prapakarn, MD, and Chatchawann Apichartpiyakul, PhD
Figure 1. A box percentile plot of CD8+ T-cell lymphocyte (A) and CD4+ T-cell lymphocyte (B). As in the box plots, the median, 25th, and 75th percentiles are marked with line segments across the box (middle, lower, and upper, respectively) and .025 and .975 quartiles as the boundary for each box plot. (C) The mean death rates of toxoplasma encephalitis. The vertical bars correspond to the immediate form of confidence interval for means, ci (improved confidence interval [CI] in STATA) (Poisson variable), and 95% CI, which were calculated by STATA, version 6.0. The x-axis corresponds to total, P50-S (pyrimethamine 50 mg/day plus sulfa dazaine 4 g/day), P100-S (pyrimethamine 100 mg/day plus sulfadiazine 4 g/day), and TMP-SMX (trimethoprim 10 mg/kg/day plus sulfamethoxazole 50 mg/kg/day) groups. The y-axis of A and B corresponds to units per cubic millimeter, and C corresponds to the percentage. 

P v. (otic) were calculated by the Kruskal-Wallis test.
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Figure 2. A computerized tomography scan with contrast-enhancing technique showing the different severities of toxoplasmic encephalitis (clinical therapeutic and cerebrospinal fluid titer indicated cerebral toxoplasmosis) in 3 AIDS patients with CD4+ T-cell lymphocytes at 10 cells/mm$^3$ (A), CD4+ T-cell lymphocytes at 30 cells/mm$^3$ (B), and CD4+ T-cell lymphocytes at 100 cells/mm$^3$ (C).
Cryptococcosis
Cryptococcal infection

• The point of entry of cryptococcus is the lungs
• Estimate incidence ~ 2 – 11% of cases
• *The most frequent fungal complications of HIV infection*
• **Patients presented with**
  – 1) *Chronic meningitis*
  – 2) *Focal signs: Cryptococcoma*
    • *Gelatinous cystic lesion in perivenous space of Basal ganglia*
    • Less frequent
Cryptococcal meningitis: Investigation

- **CSF (main Dx tool)**
  - Little abnormality (cell, protein, glucose)
    - Due to systemic lymphopenia
  - Lymphocytic pleocytosis (L 100%)
  - 50% decrease sugar content
  - 90% elevate protein
  - 50% *Indian ink* preparation positive
  - 90% *Cryptococcal antigen* positive
  - 95% *Fungal culture*: definite Dx
Cryptococcoma: Imaging
Tuberculosis
TB of CNS

- Tubercle bacilli spread hematogenously (miliary TB) throughout meninges and brain parenchyma.
- Nodules are encapsulated by surrounding tissue; these break down and bacilli are discharged into subarachnoid space.
- 2 Forms
  - 1) TB meningitis
  - 2) Tuberculoma
TB meningitis

- Thick white exudate forms in basal cisterns
- Infiltrating cranial nerves → CN palsy
- Vasculitis with arterial wall inflammation
- Thrombosis resulting in cerebral ischemia
- Hydrocephalus caused by inflammatory exudate obstructing cisterns
TB meningitis: Clinical

- History contact TB +/-
- Develops insidiously
- Fever
- Headache, stiff neck
- Focal neurological deficit
- Behavioral changes

*Clinical almost does not differ from other chronic meningitides.*
TB meningitis: Investigation

- CT / MRI: late stage
  - Meningeal enhancement (basal arachnoiditis)
  - +/- Hydrocephalus or cerebral infarction
TB meningitis: Investigation

- **LP: CSF; an important procedure**
  - High CSF pressure
  - Lymphocytic pleocytosis, high protein, low sugar
  - 0 – 30% AFB positive
  - 90% CSF C/S positive (time consuming)

- Survey systemic TB (CXR, urine, LFT):
  - Non specific and low yield

- Purified protein derivative (PPD)
  - 50 – 75% positive
Tuberculoma

• Quite common in HIV
• Tumor-like masses of tuberculous granulating tissue
• Most often multiple (also occurring single)
• Form in the parenchyma of the brain and range from 2-12 mm in diameter.
Tuberculoma: Clinical & Investigation

• As space-occupying lesion
  – +/- target lesion

• Involves periventricular area
  – Obstructive hydrocephalus

• Investigation
  – Imaging: ring-enhancing lesions
  – LP (harmful & non specific)
    • CSF contains a small number of lymphocytes, slightly increases protein and normal glucose (serous meningitis).
      – Because lesions are far from meninges.
TB meningitis: treatment

- **Formula as non-AIDS patient**
  - Empiric if suspect as fast as possible
- **Timing** 18 – 24 months
- **Steroid**
  - Reduce cerebral edema, intracranial hypertension, inflammatory response
  - Prevent hydrocephalus, vasculitis
  - There is a landmark study from Vietnam; reduce mortality 41 → 32%.
  - Still controversial in HIV (debate on immune status)
- **Not response**
  - Drug resistance
  - MAC
  - Wrong diagnosis

Primary CNS lymphoma
Primary CNS lymphoma (PCNSL)

- Hematologic malignancy which derived from B lymphocytes
- As many as 0.6% of patients with PCNSL concurrent with the diagnosis of AIDS.
- 2-6% of AIDS develop PCNSL

* Important DDx with Toxoplasmosis
Primary CNS lymphoma (PCNSL): Clinical

• Location
  – *Periventricular lesion (common)*
  – Basal ganglia & Thalamus
  – cerebellum

• Dementia
• Seizure
• Motor disturbances
• Cranial nerve dysfunction
PCNSL: Investigation

- **Imaging**
  - Multifocal intra-axial *periventricular tumors*,
  - Typically hyperattenuated or isoattenuated round or oval masses
  - *Ring or homogenous contrast enhancement*
  - Surrounding brain edema
  - +/- Diffuse leptomeningeal enhancement
  - Lesion can cross midline
Primary CNS lymphoma (PCNSL): Investigation

- **LP** (avoid: herniation)
  - CSF: abnormal cell
  - *usually Positive EBV virus in CSF* as detected by PCR

- **Stereotactic brain biopsy**
  - Pathology
  - *EBV stain*
Progressive multifocal leukoencephalopathy (PML)
PML

• A demyelinating disease of CNS
• Causes by the reactivation of JC virus
• Previous rare disease occurring only in patients with underlying severe impaired immunity.
• Recently, the incidence of PML has significantly increased related to the AIDS pandemic

PML: Clinical

- Variable corresponding to affected areas
- Rapidly progressive dementia
- Aphasia & dysarthria
- Personality changes and intellectual impairment which evolves over a period of several days to weeks.
- Confusional states
- Hallucination
- Coma

PML: investigation

- CT / MRI
  - Multiple non-enhancing white matter lesions
  - No pressure effect
PML: investigation for supporting evidence

• **CSF:**
  - Normal CSF profiles
  - *Demonstration of JCV – DNA (supporting evidence)*

• **Brain biopsy or autopsy:**
  - *Pathology confirmation*
  - Multiple demyelinated areas, loss of oligodendrocyte and eosinophilic intranuclear inclusion bodies
Cytomegalovirus (CMV) encephalitis
CMV encephalitis

- 1/3 of autopsy are found to be infected with CMV; however, the contribution of this infection to the total clinical picture is often uncertain

- **Association**
  - Late in the course of AIDS
  - Usually concurrent with CMV retinitis
CMV encephalitis: Clinical

- The encephalopathy evolves over 3-4 weeks
  - Consciousness change
  - Cranial nerve signs
    - Ptosis
    - Ophthalmoplegic paresis +/- pupil dilatation
    - Nystagmus
    - Facial palsy
    - Deafness
  - Painful lumbosacral polyradiculitis (paraplegia)
    - Cauda-equina syndrome
CMV encephalitis: investigation

- Imaging: MRI- T2W signal hyperintensity
  - Shows the process to be concentrated in the ventricular boarders *(necrotizing ventriculoencephalitis)*
  - May extend more diffusely through the adjacent white matter
  - A few case: meningeal enhancement by Gd
  - Reported case: extensive destructive lesions
CMV encephalitis: investigation

**CSF:**
- Shows an inflammatory response
  - *Neutrophile pleocytosis*
- Culture CMV usually negative
- IgG Ab titer are non-specifically elevated
- *Newer PCR methods may prove useful*

**Biopsy:** inclusion body
Tips of Diagnosis and Management
Tips

• The risk of AIDS-related disorders, particularly opportunistic infections,
  • Depends on several factors, including
    – CD4 count*
      » Provides critical information to guide evaluation
    – Past and current exposure to infectious agents
    – Intercurrent management
      » Such as the use of antibacterial prophylaxis
      » HAART

• The first consideration must be the stage of systemic HIV infection
CD4 & Neurologic problem in HIV

- **In early infection (CD4 > 500/µl),**
  - An autoimmune demyelinating neuropathy may develop
- **During middle stages of infection (CD4 200 µl to 500 µl),**
  - There is a greater risk of opportunistic infections such as
    - *Tuberculous meningitis*
    - Primary HIV-induced cognitive impairment
    - A minor cognitive and motor disorder
- **In advanced HIV infection (CD4 < 200 µl),**
  - The risk of several disorders increases, including
    - HIV-associated dementia
    - Vacuolar myelopathy
    - Distal sensory polyneuropathy
    - *Opportunistic infections* such as
      - Primary central nervous system lymphoma
      - Toxoplasmosis encephalitis
      - Progressive multifocal leukoencephalopathy (PML)
      - Cryptococcal meningitis
Tips

Only clinical cannot DDx
Recommend perform imaging

- Lesions + Mass Effect
  - Toxoplasmosis
  - PCNSL
  - Other Abscesses
- Lesions + No Mass effect
  - PML
  - HIV-E
Tips

- Ring enhancing lesions
  - The triad: general
    - Tumor
    - Pus
    - Subacute hematoma

- In HIV brain lesions
  - Toxoplasmosis
  - PCNSL
  - Tuberculoma
  - Cryptococcoma**
    (difference)

- There is no clear cut criteria to diagnose from this characters.
Tips: Modern technologies

- $^{201}$Thalium SPECT and PET can help to distinguish between PCNSL and abscesses.
- **Uptake in lymphoma >> abscesses**
  - SPECT: blood supply
  - PET: glucose metabolism
Tips

• Distribution and appearance of lesions
  – Deep white matter or periventricular lesions
    • Masses: PCNSL
    • Necrosis or enhancement: CMV (ventriculitis)
  – No enhancement
    • Cystic lesions at Virchow Robin space: Cryptococcoma
    • White matter lesion: PML
  – Density or intensity (compare to gray matter)
    • Iso-hyper ~ : PCNSL (high N/C ratio)
    • Hypo ~ : other abscesses
Tips

• The “target sign”
  – This sign has been defined as a central nidus of calcification or central enhancement surrounded by a ring of enhancement.
  – It has been considered a pathognomonic finding of CNS tuberculoma.
  – Some experts argue that the target appearance can find in toxoplasmosis, lymphoma and GAE.
  – Therefore, it’s now no longer used to suggest tuberculoma.
Tips

• LP
  – *CSF should be done in all HIV pts with new headache, fevers, cognition changes.*
  – *If no contraindication!!!*
  – Be careful in case with potential to herniation
    • Mass lesion in posterior fossa or midline shift
  – *Nearly normal CSF → still suspected cryptococcosis*
  – *PMN predominate: CMV radiculitis or early TB meningitis* (if not bacteria)
PCR, Ag, Ab tests

One of the most important supporting evidences

- **EBV DNA PCR**:
  - Very high association with PCNSL
    - 83-100% sensitivity
    - 95-100% specificity

- **Toxoplasma PCR**:
  - Sensitivity only 44-65%
  - Specificity 100%

- **JC PCR (for PML)**:
  - Sensitivity -93%
  - Specificity-92-100%

- **TB PCR in CSF**:
  - 48-100% sensitivity

- **Cryptococcal Ag**:
  - 91% sensitive
  - 100% specific
Tips

• **Therapeutic diagnosis in suspected case of cerebral toxoplasmosis (~ 2 weeks).**

• **Steroids should be added if**
  – Impending brain herniation
  – Clinical deterioration within 48 hrs of Rx
  – **still debate in HIV**

• **Stereotactic brain biopsy for definite diagnosis**
  – *Invasive tool → last investigation*
  – 88-98% of contrast enhancing lesions
  – 67% of non-enhancing lesions
Summary
Problem of diagnosis CNS OI in AIDS

- Multiple CNS OIs can be found (> 1 Dx).
- Multiple regions involvement
- Late diagnosis
  - Lesions can occupy in silent brain areas
  - Patients & physician lack of unawareness subtle S & S
- Clinical
  - No clinical pathognomonic
  - Clinical and severity variable between cases
  - Atypical presentations
    - Antibiotic prophylaxis
    - HAART
- Lack of specific investigation esp. imaging appearances
- Still Like
  - “a guessing game or Jigsaw puzzle”
Thank You

NINDS, NIMH, AusAID

Our colleagues

All audiences
Cerebral Toxoplasmosis: Treatment

• **Start Rx**
  – *When multiple ring enhancing brain lesions can be identified on imagings*

• If no improvement within 2 weeks \(\rightarrow\) works up for CNS lymphoma

• **Initial Rx ~ 4-6 months**
  – Pyrimethamine + sulfonamide + leucovorin
  – Dexamethasone indicates only edema and mass effect occurred.

• Lifelong for prevent relapse
Cryptococcal meningitis: Clinical

- Insidious onset
- Prolong fever
- Headache for several weeks to months
- Cognitive change, dementia
- Irritability, personality changes
- Focal neurological deficits
- Papilledema +/- visual loss
- 40% cranial nerve palsy
Cryptococcal meningitis: Treatment

• Systemic (iv) amphotericin B and flucytosine for synergistic effect
• Intrathecal Ampho B in the case showing poor response to systemic drug or impaired renal function
• Then oral fluconazole 200 mg/d for lifelong suppressive treatment
CNS Mycobacterium infection

- **2 particular types** of mycobacterium infection tend to complicated AIDS ~ 2 – 18%
  - *Mycobacterium tuberculosis* (*TB*)
    * Predominates among drug abusers and AIDS patients in developing countries
  - *Mycobacterium avium complex* (*MAC*) and atypical mycobacterium
Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

- A randomized, double-blinded, placebo-controlled study conducted in Vietnam, including patients with and without AIDS.

- Intravenous dexamethasone (0.4 mg/kg daily a week and then tapering doses for 3 weeks)
  - reduced mortality from 41% → 32%
  - but no effect on residual disability

Tuberculoma: Treatment

• Tuberculoma
  – *A similar course of ATB*
  – Decreased size of large abscess or disappearance of small abscesses
  – Calcified
Primary CNS lymphoma (PCNSL): Treatment & Prognosis

• Treatment
  – *PCNSL is highly radiosensitive and also response to steroids.*
    • +/- Surgery, chemotherapy
  – However, they frequently recur.

• Prognosis
  – A *poor prognosis* regardless of Rx
PML: disease characteristics

- It is characterized by wide spread demyelinating lesions, mainly of the cerebral hemispheres but sometimes of the brainstem and cerebellum and rarely of the spinal cord.
- The lesions vary greatly in size and severity from microscopic foci to massive multifocal zones of destruction of both myelin and axis cylinders involving the major part of hemisphere.
- Vascular changes are lacking, and inflammatory changes are present but usually insignificant.
- Initially occipito-parietal regions spread anteriorly
PML: Clinical

- Hemiparesis, quadriparesis & rigidity
- Ataxia and cerebellar syndrome
- Cranial nerve dysfunctions
- VF defects, visual impairment
- *Cortical blindness*
- 11% seizure (uncommon)
- Prognosis
  - Poor
  - Death in 3 – 6 months from symptom onset

PML: treatment

- *The disease is generally believed to be untreatable.*
- Aggressive Rx using antiretroviral drugs (esp. protease inhibitor) greatly slows the progression of PML and has been led to apparent remission.
- Antiviral agents (cytosine arabinoside, interferon, acyclovir has not been successful)
CMV encephalitis: Treatment

- *Gancyclovir and foscarnet if strongly suspected*
- However, CMV disease may develop and progress during treatment or maintenance therapy.