NERVOUS SYSTEM COMPLICATIONS OF HIV

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Disclosure

I HAVE NOTHING TO DISCLOSE
Outline

- Neurological Manifestations of HIV
- CNS Opportunistic Infections
- Clinical Scenarios
- HIV & Cognitive Impairment
- Peripheral & Toxic Neuropathy
Neurological manifestations of HIV/AIDS

Primary HIV neurologic disease (HIV is necessary and sufficient to cause the illness)
- HIV dementia
- HIV vacuolar myelopathy
- HIV neuropathy
- Autoimmune

Secondary or opportunistic neurologic disease
- PML
- Toxoplasmosis
- TB meningitis
- Cryptococcus meningitis

Treatment-related neurologic disease
- IRIS
- NRTI-induced neuropathy
## Common CNS Opportunistic Infections Incidence

<table>
<thead>
<tr>
<th>Region</th>
<th>Common CNS opportunistic infections</th>
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<tbody>
<tr>
<td>Asian and Pacific regions³</td>
<td>Cryptococcal meningitis, cerebral toxoplasmosis, tuberculous meningitis,</td>
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<tr>
<td></td>
<td>Japanese encephalitis B</td>
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<tr>
<td>Sub-Saharan Africa⁴</td>
<td>Tuberculous meningitis, cryptococcal meningitis, cytomegalovirus, malaria</td>
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<tr>
<td>Europe and North America²</td>
<td>PML, toxoplastic encephalitis, cryptococcal meningitis</td>
</tr>
<tr>
<td>South America³</td>
<td>Cerebral toxoplasmosis, tuberculous meningitis, cryptococcal meningitis;</td>
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<tr>
<td></td>
<td>Chagas disease is reported in southern US states and South America⁶</td>
</tr>
</tbody>
</table>

PML = progressive multifocal leukoencephalopathy.

Tan et al. Lancet Neurol 2012
Clinical Case

- A 37 years old man with new diagnosis of HIV (CD4 90, viral load 35K)
- Presented with 1-month worsening of right sided weakness
- No fever, headache or neck stiffness
- Unable to work due to weakness
Physical Examination

- Thin, chronically-ill appearing man
- Appropriately interactive, language fluent
- Moderately spastic right sided weakness involving arm and leg
- Reflexes +3 at Biceps, Triceps, Knee
- Upgoing toe on right
MRI Brain
<table>
<thead>
<tr>
<th>Focal Lesions</th>
<th>Diffuse Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
<td>PML</td>
</tr>
<tr>
<td>CNS lymphoma</td>
<td>Cryptococcal meningitis</td>
</tr>
<tr>
<td>Tuberculoma</td>
<td>TB meningitis</td>
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<tr>
<td>Cryptococcma</td>
<td>Acute HIV</td>
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<tr>
<td>Pyogenic abscess</td>
<td>CMV encephalitis</td>
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<tr>
<td></td>
<td>Neurosyphilis</td>
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<tr>
<td></td>
<td>HIV Dementia</td>
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</tbody>
</table>
Investigations

- Blood: RPR, CrAg, Toxo IgM antibody negative
- CSF: WBC 14, RBC 27, glucose 47, protein 55, VDRL, CrAg negative
- Micro: Blood cultures negative, CSF: Cultures negative
Toxoplasmosis

- Most common focal lesion in HIV patients in West
- Clinical presentation is variable
- Treat empirically and monitor for improvement
- Toxoplasmosis in HIV is reactivation of prior infection, e.g. IgM not helpful
- Serum IgG is positive in around 95% of patients
- Toxoplasma CSF PCR 35% sensitive, 100% specific
Initiation of ART in Toxoplasmosis

When do we initiate the treatment?
A. Immediately
B. After two weeks with close observation
C. Wait for 4-6 weeks before initiating ART given the risk of IRIS
D. Preferable to wait until the lesions resolve radiologically
IRIS

- **Immune Reconstitution Inflammatory Syndrome**
- Paradoxical clinical worsening, in 4-8 weeks after starting HAART
  - Worsening of a known infection
  - Unmasking of subclinical infection
- Neuroimaging: contrast enhancing lesions
- Steroids may be needed for ↑ICP, although therapeutic benefit controversial
- Most patients survive
Clinical Case

- A 42 years old man with HIV diagnosed in 2001 not on any treatment
- Severe headache and altered mental status
- CD4 29, viral load 150K
- LP with opening pressure of 28 cm H2O, CSF WBC 16, RBC 0, Protein 60, Glucose 27
- Serum CrAg 1:4096, CSF CrAg > 1:1024
- Started on Amphotericin & Flucytosine
- Ongoing headache with double vision
- Right CN VI palsy
CM and Intracranial Pressure

- Raised ICP is a common complication (75% > 20 and 25% > 35 mm H2O)
- Larger capsule size is associated with worse ICP and less inflammation

Robertson et al. J Infect Dis 2014
Adjunctive Dexamethasone Therapy for CM in HIV

Trial stopped for safety reasons. At 10 weeks, mortality was 47% in dexamethasone vs 41% in placebo. Disability was 25% vs 13%.

Beardsley et al. NEJM 2016
Cryptococcal Optimal ART Timing (COAT) Trial

Boulware et al. NEJM 2014
Mechanisms of HIV-related CNS Injury

Sutherland et al. Neurol Clin 2018
Age & HIV+ Cognitive Impairment

Cognitive impairment at follow-up among the HIV+ increased by 20% for each decade of advancing age.

Coban et al. AIDS 2017
HIV & Stroke

Gutierrez et al. PLoS One 2017
Range of HIV Neurocognitive Disorders

- **NP**: Abnormality in one cognitive domain
- **ANI**: Abnormality in two cognitive domains
- **MND**: Cognitive impairment with mild functional impairment
- **HAD**: Marked cognitive and functional impairment
HAND in Pre & Post CART

Saylor et al. Continuum 2018
HIV, HCV & Psychostimulants

Letendre et al. AIDS 2005
Meade et al. Drug Alcohol Depend 2015
## Treatment - CNS Penetration-Effectiveness Score

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
<th>Fusion Inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Delavirdine</td>
<td>Indinavir</td>
<td>Enfuvirtide</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Nevirapine</td>
<td>Indinavir-r</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td>Lopinavir-r</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td>Amprenavir-r</td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td></td>
<td>Atazanavir</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
<td>Amprenavir-r</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>Atazanavir-r</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine</td>
<td></td>
<td>Darunavir-r</td>
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Letendre et al. Arch Neurol 2008
Exercise & Neurocognitive Impairment in HIV+

Dufour et al. J Neurovirol 2013
Peripheral Neuropathy in HIV

HIV with peripheral neuropathy

NCV/EMG

DSP

Secondary causes?
(eg, toxic, metabolic, nutritional)

Yes

No

Attempt correction

Attempt correction

Yes

No

Symptomatic treatment
(eg, analgesic, tricyclic antidepressant, anticonvulsant) clinical trials

Extensive

Evidence of CMV?

Yes

No

Evidence of CMV?

Yes

No

Consider empiric ganciclovir

Nerve biopsy

Polyradiculopathy

LP

Extent of involvement?

Limited

Advanced immunosuppression

Yes

No

Immuno therapy
(eg, plasmapheresis, steroids, IVig)

CMV polyradiculopathy

PMNs

Monos

Cytology: lymphoma?

Yes

No

Follow

Bone marrow biopsy

Positive for lymphoma

RT/chemotherapy

Ganciclovir, foscarinet, cidofovir

CMV polyradiculopathy

LP
ART Toxic Neuropathy

- Mostly related to exposure to specific dideoxynucleosides (stavudine, didanosine)
- Prominent mitochondrial abnormalities, inhibit gamma DNA polymerase
- NRTIs not associated with toxic neuropathy: zidovudine, lamivudine, abacavir, tenofovir
- Risk factors include lower CD4 count, body mass index <18, age <35 years, genetic factors
Vacuolar Myelopathy

- “Holes” in spinal cord seen in advanced cases
- Clinical Features – onset over weeks-months
  - Painless spastic paraparesis, sensory ataxia, neurogenic bladder, paresthesia
  - Affects the thoracic cord & cervical cord
HIV causes neurological impairment either directly or by promoting opportunistic infections

Significant improvement has occurred since the HAART introduction

HAART can lead to CNS and PNS neuropathy

HAND remains a significant problem

Presence of other factors increase the burden on cognition
References


Thank You

I AM CURED
I AM HIV EQUAL