The Neurology of HIV Infection

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HIV/AIDS Epidemiology

- World-wide pandemic, 40 million affected
- U.S.- Disproportionate seroconversion, prevalence and death rates among African-Americans
- Leading cause of death in African American men 25 to 44 and women 25-34
HIV and the Nervous System

- Neurologic disorders in 70% clinical series, 80% autopsy, 10-20% initial
- Virus enters nervous system at time of primary infection
  - Asymptomatic
  - Acute self-limited disorders
  - Chronic syndromes
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- Cerebrospinal fluid studies show early CNS invasion, intrathecal antibody synthesis
- *In situ* studies show only microglial cells and macrophages infected, not glial cells and neurons
- CD4 and chemokine receptors present but viral replication restricted
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- Is the virus neurotropic?
- Data inconclusive: neurologic disorders may occur early when immunosuppression is not severe and are not always correlated with increased viral burden in affected tissue.
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- Mechanism of neural injury is indirect
  - Cytokines
  - Excitotoxic amino acid injury
  - Voltage-mediated increase in intracellular calcium
  - Chemokines, lipid inflammatory mediators, HIV toxic proteins
  - Immune based injury
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- **Acute Syndromes:** HIV-related
  - Aseptic meningitis or encephalopathy
  - Leukoencephalitis
  - Seizures
  - Transverse myelitis
  - Cranial and peripheral neuropathy (Bell’s)
  - AIDP (Guillain Barre, Miller Fisher variant)
  - Polymyositis; myoglobinuria
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- Acute HIV-related syndromes indistinguishable from those caused by other viruses
- CSF pleocytosis, typically lymphocytic, may be present
- Initial HIV serology may be negative and should be repeated in 1-3 months; consider viral load assay
- Co-infections: hepatitis B and C
Chronic syndromes-HIV related

Brain:
- Chronic or recurrent CSF pleocytosis
- Dementia and mild cognitive impairment
- Psychiatric disorders
- Stroke
- Seizures
- Degenerative disorders: ataxia; multiple system atrophy; Parkinson
HIV and the Nervous System

- Chronic Syndromes: HIV-related
- Spinal cord, Peripheral Nerve, Muscle
  - Progressive myelopathy
  - Anterior horn cell disease
  - Cranial and peripheral neuropathy
  - Autonomic neuropathy
  - Myopathy
HIV and the Nervous System

- HIV/Cognitive Motor Complex
  - Confusion with terminology, current common usage: HIV-1-associated dementia complex (HADC), HIV dementia (HIV-D), AIDS dementia complex (ADC)
  - Mild or minor cognitive/motor disorder
  - Severe manifestations: dementia complex or myelopathy
HI V and the Nervous System

- HIV-1 Associated Cognitive/Motor complex
  - Mild: Abnormal neuropsychological studies; non-impairing; often non-progressive
  - Severe: progressive subcortical dementia presenting with apathy, withdrawal, psychiatric disorders, motor slowness, leg weakness and spasticity, peripheral neuropathy
    - Static or progressive
    - Hepatitis C co-infection in drug users worsens signs
    - Children: microcephaly, loss of milestones, dementia
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- AIDS Dementia
  - Pathologic changes in brain more common than clinical syndrome
  - Prevalence: CDC-7.3%, 1987-1991; MAC-4% prevalence, 7% annual rate, 15% probability before death
  - HAART: decreased incidence and mortality
  - Relationship to viral load suggested but not proven; drug resistance and protected reservoir
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- AIDS dementia is AIDS defining
- May be sole manifestation of advanced immunosuppression
- CSF: normal or minor abnormalities; markers of immune activation-HIV p24, B-microglobulin, tumor necrosis factor, neopterin, tryptophan, interleukins
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- AIDS Dementia
  - Pathology: microglial nodules; giant cells; focal perivascular demyelination, gliosis and frontal neuronal loss
  - CT/MRI: atrophy; ventricular dilatation; periventricular or subcortical white matter changes
  - Functional neuroimaging abnormal (PET, SPECT, MRS and fMRI)
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- Predictors of Dementia
  - CD 4+ lymphocytes < 100
  - Anemia
  - AIDS defining infection or neoplasm
  - Post-HAART, dementia independent of immunosuppression
  - Role of anti-retrovirals with good CNS penetration
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- **Evaluation of Dementia**
  - Exclude secondary OI or neoplasm
  - Nutritional deficiency or metabolic disorder
  - Degenerative disorder unrelated to HIV

- **Treatment**
  - HAART; studied without clear benefit-
    seligiline, nimodipine, anti-oxidants
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- Stroke-0.5-8% in retrospective studies
- Seizures-half due to secondary causes
- Leukoencephalopathy-MS like clinical picture
- Progressive Myelopathy-progressive spastic paraparesis
- Amyotrophic lateral sclerosis-better with HAART
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- Neuropathies and myopathy
  - Distal sensorimotor neuropathy, most common
  - Chronic inflammatory demyelinating polyneuropathy
  - Mononeuritis multiplex
  - Autonomic neuropathy
  - Myopathy
    - Due to HIV or medication, metabolic factors
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- Post-HAART: Marked decline in secondary OI and neoplasms; African Americans at risk due to delayed diagnosis or refusal of treatment

- Clinical syndromes: meningitis; encephalitis; focal cerebral syndromes; stroke; seizures; myelopathy; cranial and peripheral neuropathy and myositis
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- Meningitis
  - Cryptococcus most common cause; diagnosis by CSF; good response to treatment with anti-fungals and immune reconstitution
  - Other treatable entities: tuberculosis; neurosyphilis; MAI
  - Viral causes: CMV; HSV; VZV
Toxoplasmosis

- Most common cause of mass lesion
- Clinical: chronic progressive focal signs; seizures; involuntary movements
- CT or MRI: enhancing lesions with mass effect, involve basal ganglia
- CSF PCR-detection rates 40-80%; toxo antibodies-95%
- Differential: lymphoma, especially solitary lesion
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- Toxoplasmosis
  - Brain biopsy necessary if toxoplasmosis titer is negative and no response to anti-toxo therapy
  - Immune reconstitution with HAART eliminates the need for chronic suppressive therapy
**HIV and the Nervous System**

- **Progressive Multifocal Leukoencephalopathy**
  - Rare before AIDS; incidence 1 to 5.3% AIDS cases, before HAART
  - Progressive focal signs; may be AIDS defining
  - JC virus infection of oligodendrocytes
  - Diagnosis: MRI, brain biopsy, PCR of CSF
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- Lymphoma
  - Markedly reduced incidence post HAART
  - Clinical: encephalopathy; focal signs; seizures; cranial neuropathy
  - Laboratory: Abnormal MRI with single or multiple enhancing lesions; positive CSF cytology. Diagnosis: brain biopsy or CSF
  - Treatment: Chemotherapy and HAART
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- **Other syndromes:**
  - Movement disorders: usually due to OI, especially toxoplasmosis
  - Myelitis: herpes group viruses, tuberculosis, pyogenic bacteria, fungus and toxo
  - Infectious retinopathy: syphilis, toxo, CMV or Candida
  - Polyradiculopathy-CMV
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Other causes of CNS/PNS disorders
- Drug or medications: anti-retrovirals and neuropathy or myopathy
- Nutritional deficiencies: B12, thiamine, folic acid, glutathione
- Hormonal deficiency: testosterone
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- Risk of CNS/PNS involvement from initial exposure and seroconversion to end stage disease
- All levels of the neuraxis may be affected; multiple syndromes over time
- HAART or immune reconstitution is important for prevention and recovery
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- Special Issues in the African American population
  - High seroconversion rate
  - Large reservoir of undiagnosed and untreated
  - Popular belief systems about dangers of treatment leading to refusal of care
  - Need for better population based research to determine effective intervention models and education messages