

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

HIV and the Nervous System

- 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

HIV and the Nervous System

- 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

HIV and the Nervous System

- 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

HIV and the Nervous System

- 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

HIV and the Nervous System

- 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

HIV and the Nervous System

- 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 (HADDC), HIV dementia (HIV-D), AIDS dementia complex (ADC)
 - Mild or minor cognitive/motor disorder
 - Severe manifestations: dementia complex or myelopathy

HIV 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

HIV and the Nervous System

■ 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

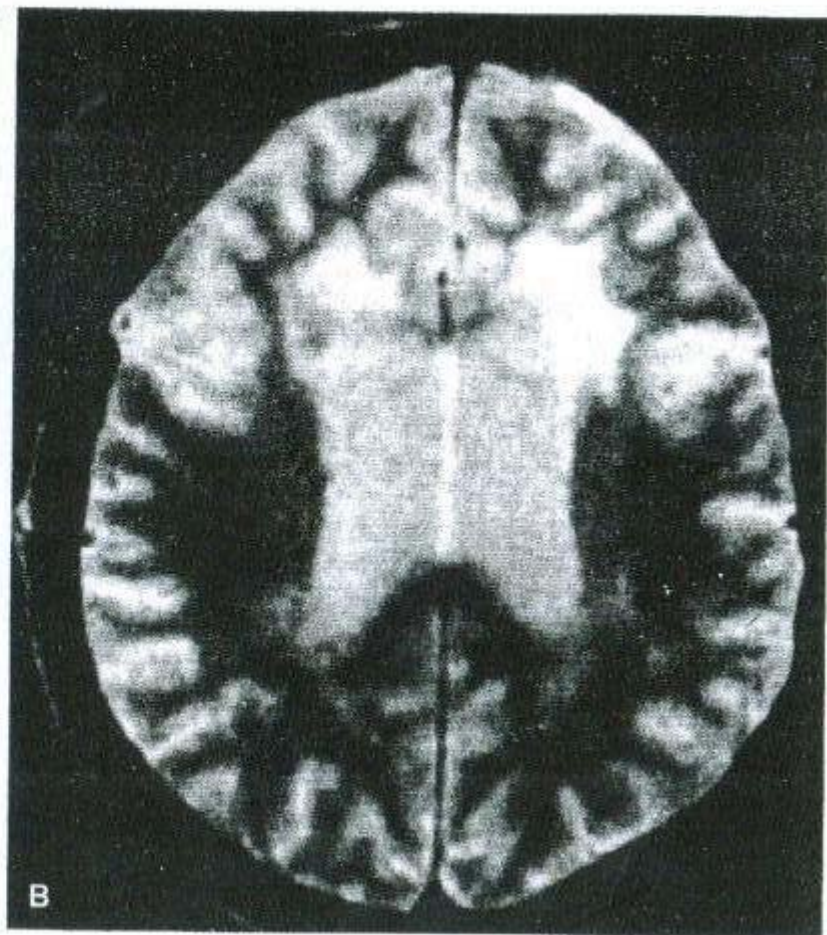
HIV and the Nervous System

- 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

HIV and the Nervous System

■ 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)



HIV and the Nervous System

- 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

HIV and the Nervous System

- 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

HIV and the Nervous System

- 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

HIV and the Nervous System

- Neuropathies and myopathy
 - Distal sensorimotor neuropathy, most common
 - Chronic inflammatory demyelinating polyneuropathy
 - Mononeuritis multiplex
 - Autonomic neuropathy
 - Myopathy
 - Due to HIV or medication, metabolic factors

HIV and the Nervous System

- 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

HIV and the Nervous System

■ 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

HIV and the Nervous System

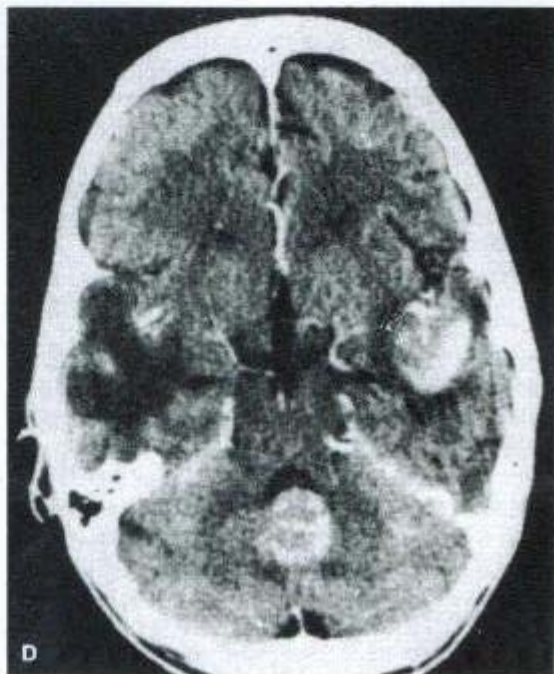
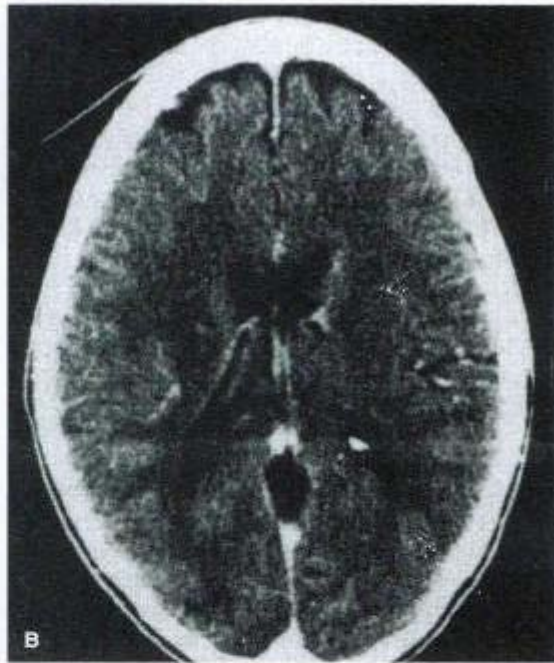
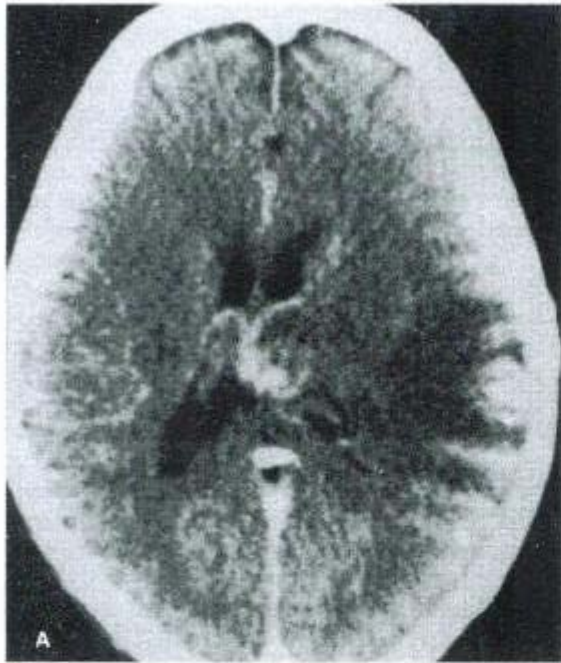
■ Toxoplasmosis

- 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

HIV and the Nervous System

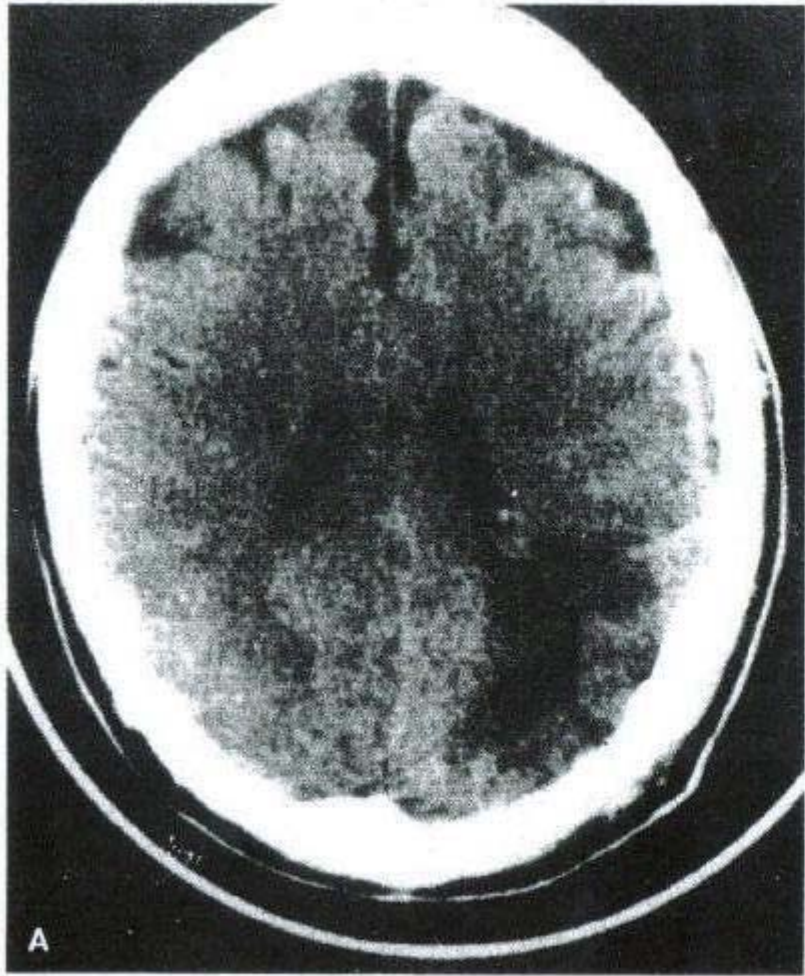
■ Toxoplasmosis

- 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

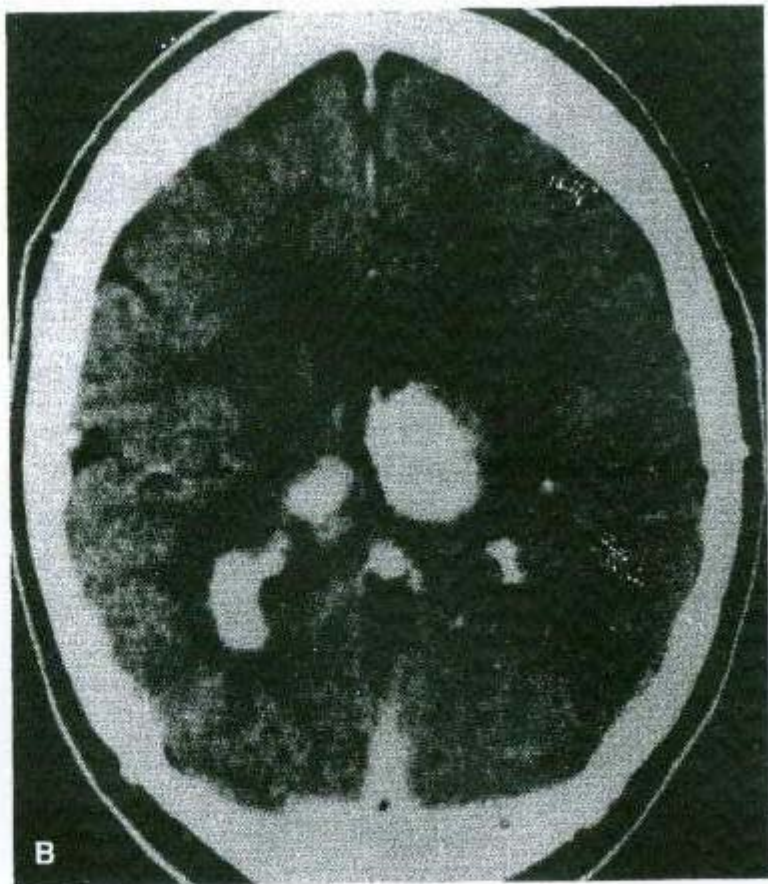
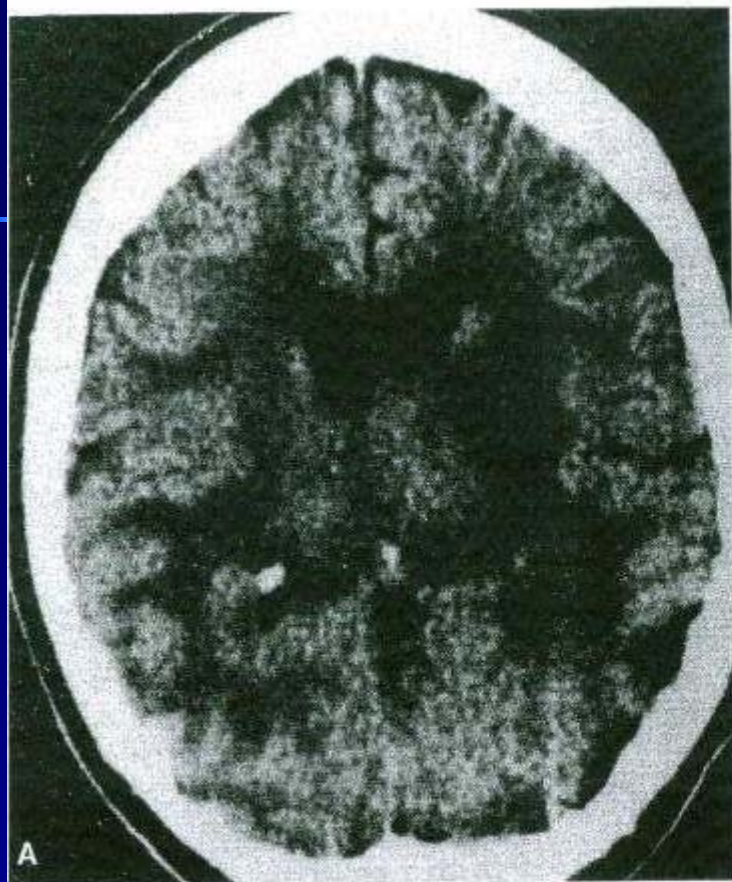
- Progressive Multifocal Leukoencephalopathy
 - Rare before AIDS; incidence 1 to 5.3% AIDS cases, before HAART
 - Progressive focal signs; may be AIDS defining
 - JC virus infection of oligodendrocytes
 - Diagnosis: MRI, brain biopsy, PCR of CSF



HIV and the Nervous System

■ 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



HIV and the Nervous System

- 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

HIV and the Nervous System

- 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

HIV and the Nervous System

- 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

HIV and the Nervous System

- 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