Central Nervous System Involvement in Primary HIV-1 Infection

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Outline

- Overview of primary infection
- Neurological syndromes in primary infection
- Results from cross-sectional multicenter neurological primary infection study
- Preliminary results from longitudinal San Francisco neurological primary infection cohort
Primary HIV Infection

HIV Exposure

**Acute infection**
- 7 days
- 14 days
- 21 - 28 days

- Plasma HIV RNA detectable
- Peak plasma viral load
- HIV EIA Ab positive
- Rising antibody titer; ‘detuned’ antibody indicates days after exposure

- Systemic acute retroviral syndrome (90%)
- Neurological syndromes (10%)
- HIV RNA detectable in CSF
- Plasma viral ‘set point’ reached

**Early chronic infection**
- 5 months
- 6 months

Central Nervous System Disorders in Primary HIV Infection


• **Cerebellar ataxia** (Scarpini E, 1991)

• **Myelopathy/Cauda equina syndrome** (Berger J, 1986; Denning D, 1987; Zeman A, 1991)

• **Optic neuritis** (Larsen M, 1998)
Peripheral Nervous System Disorders in Primary HIV Infection

- Guillain-Barre syndrome/inflammatory polyneuropathy (Hagberg L, 1986; Patton P, 1990)


- Peripheral neuritis (Calabrese, 1987; Brew B 1989)


→ Timing of onset and clinical syndromes suggest immune-mediated disease
Clinical Studies of CNS in Primary HIV Infection

- CSF HIV RNA levels higher in neurologically symptomatic vs. asymptomatic (4.11 vs 2.58 log, n=22)
- Presence of any seroconversion illness $\rightarrow$ more rapid cognitive impairment
- Presence of neurological symptoms $\rightarrow$ more rapid systemic disease progression
- CSF HIV RNA and beta-2-microglobulin decline after 48 weeks of antiretroviral therapy (n=6)

Multicenter Primary HIV Infection Cross-Sectional Study

- **47 total subjects**, 4 sites: Goteborg (12), Milano (17), Sydney (6), San Francisco (12)

- Primary infection confirmed by:
  - Negative HIV enzyme immunoassay (EIA), or
  - Prior recent negative serology/viral load, or
  - Recent infection by ‘detuned’ antibody

- Estimated duration of infection at visit (median, IQ range): **69.5 days (37.5 - 92)**
Cerebrospinal Fluid Viral Burden in Plasma and CSF

Plasma (mean +/- SD): 4.85 log 10 c/mL (+/- 1.01)
CSF: 3.45 log 10 c/mL (+/-1.30)

In multivariable model, plasma viral load is main predictor of CSF viral load (p < .001, adj r² 0.82)
CNS Inflammation & Barrier Permeability in Primary HIV Infection

White blood count (mean +/- SD): 12.9 cells/mm$^3$ (+/- 26.7)
Protein: 56.6 mg/dL (+/- 39.5)
Intrathecal Macrophage Activation in Primary HIV Infection

CSF Neopterin - pteridine produced by activated macrophages
- mean (+/- SD): 36.5 nmol/L (+/- 25.8)
Neuronal Injury Markers in Primary HIV Infection

CSF Tau

- Mean (± SD): 343.6 ng/L (± 423.3)

CSF NFL

- NFL - neurofilament light chain: 251.0 (± 403.0)
Central Nervous System (CNS) Injury in Untreated HIV-1 Infection

- Plasma HIV RNA level
- CNS injury (delayed)
- CNS injury (early)

Study visits: neuropsychological testing, lumbar puncture, MRI/MRS
# Baseline Data in Primary & Chronic Infection - San Francisco Cohort

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<tr>
<th></th>
<th>PHI</th>
<th>Chronic Infection</th>
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<tbody>
<tr>
<td></td>
<td>$n = 9$</td>
<td>$n = 8$</td>
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<tr>
<td><strong>Sex (M:F)</strong></td>
<td>9:0</td>
<td>7:1</td>
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<tr>
<td><strong>Age (years)</strong></td>
<td>39.1 (+/- 7.59)</td>
<td>43.8 (+/- 9.1)</td>
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<td><strong>Days post infection</strong></td>
<td>126.4 (+/- 44.3)</td>
<td>n/a</td>
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<tr>
<td><strong>CD4+ (cells/µL)</strong></td>
<td>585.1 (+/- 184.9)</td>
<td>201.4 (+/- 147.8)</td>
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<tr>
<td><strong>CD8+ (cells/µL)</strong></td>
<td>1027.3 (+/- 297.8)</td>
<td>1112.7 (+/- 800.9)</td>
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<tr>
<td><strong>Plasma log_{10} HIV RNA (cps/ml)</strong></td>
<td><strong>4.2</strong> (+/- 1.0)</td>
<td><strong>4.5</strong> (+/- 0.8)</td>
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<tr>
<td><strong>CSF log_{10} HIV RNA (cps/ml)</strong></td>
<td><strong>2.3</strong> (+/- 1.17)</td>
<td><strong>3.1</strong> (+/- 1.4)</td>
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<tr>
<td><strong>CSF WBC (cells/mm3)</strong></td>
<td><strong>11.8</strong> (+/- 26.2)</td>
<td><strong>3.3</strong> (+/- 2.9)</td>
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<tr>
<td><strong>CSF Protein (mg/dL)</strong></td>
<td><strong>47.1</strong> (+/- 23.6)</td>
<td><strong>54.9</strong> (+/- 21.4)</td>
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Values shown are means (+/- SD)
Systemic and CNS T-cell Activation in Primary HIV Infection

- % activated (CD38+HLADR+) CD8+ T lymphocytes is as elevated in CSF during primary as during chronic infection.
4 Tesla MRI/MR Single Voxel Spectroscopy

Cerebral metabolite markers:

- N-acetylaspartate (NAA) – neuronal function
- Choline (Cho) – macrophage infiltration
- Myo-inositol (mI) – astrocyte integrity
- Glutamate (Glu) – mediator of CNS toxicity

- Basal ganglia
- Frontal white matter
- Anterior cingulate cortex
- Parietal grey matter
In primary infection as compared to HIV-uninfected subjects:

- Decreased NAA (neuronal integrity) markers ($p < 0.05$)
- Increased choline (inflammatory) markers
Compartmentalization of HIV in the CNS in Primary Infection

Heteroduplex tracking assay (HTA) targeting env in longitudinal samples:

Subject 9001
- Neuroasymptomatic
- DPI, days post infection
- HIV-1 populations in CSF and blood remain concordant over time

Subject 7146
- Clinical meningitis
- Discordance between CSF and blood at day 156, with one variant enriched in CSF
- Populations again discordant at day 203

-- G. Schnell, R. Swanstrom
Conclusions -
The CNS in Primary HIV-1 Infection

- A high viral burden is found in the nervous system
- CSF HIV RNA correlates with plasma HIV RNA level
- Inflammation, macrophage and T-cell activation, and in some subjects neuronal injury occurs
- Brain metabolite measurements may be informative in understanding CNS effects
- Enriched or unique HIV-1 species may exist in the CSF versus plasma

Understanding CNS involvement may have implications for treatment during early HIV infection
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