NEUROPATHOLOGY OF HIV AND OPPORTUNISTIC INFECTIONS

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Late stages of HIV infection; NeuroAIDS:

1. subcortical dementia – HIV-associated dementia (HAD)

2. vacuolar myelopathy

3. sensory neuropathy

Despite highly active antiretroviral therapy (HAART), HAD is a major cause of disability and:

4. minor cognitive motor disorder (MCMD) becomes more common or more obvious
Clinical signs of HAD:

1. impaired memory and concentration;
2. psychomotor slowing;
3. apathy and social withdrawal;
4. motor deficits – ataxia, tremor, weakness.

Terminal stages: severe dementia, autism, incontinence and paraplegia
Neuropathology:

1. diffuse myelin pallor
2. multinucleated giant cells
3. increased macrophage/microglia activation
4. loss of neurons in deeper lamina of cerebral cortex and simplification of dendritic arborisation
Post-mortem brain sectioning
Brain slice from an HIV-infected patient
HIV encephalitis

White matter (myelin, stained blue) degeneration

Multinucleated giant cell (MNGC)
Imaging appearance of HIV encephalitis

Offiah & Turnbull, 2006
Functional magnetic resonance imaging (fMRI)

Perfusion MRI

Tucker et al. 2004
How does HIV cause the functional disturbances and white matter degeneration in the brain?

*Which cells in the brain are attacked by the virus?*
Cell types in the central nervous system

- Neuron
- Astrocyte
- Oligodendrocyte
- Capillary
- Microglia
1. impulse conduction through the axon and its terminals

2. neurotransmitter release at the synapse

3. excitation or inhibition of postsynaptic neuron

4. action potential
• **Glutamate** – excitatory neurotransmitter
• GABA-inhibitory neurotransmitter
The location of different cell types in the brain

Gonzalez-Scarano & Garcia, 2005
HIV binds to CD4 and a chemokine receptor

Chemokines attract white blood cells during inflammation
HIV neuroinvasion and MNGC formation

Gonzalez-Scarano & Garcia, 2005
Target cells for HIV in the brain:

*Binding of HIV surface envelope protein gp120 to CD4 and a chemokine receptor.*

Most CNS isolates are Macrophage-tropic HIV and use **CCR5** as a receptor (expressed on macrophages/microglial cells, astrocytes and subsets of neurons).

T cell-tropic HIV use **CXCR4** (expressed on subpopulation of neurons and glial cells).

**CD4** expressed only on macrophages/microglia
### Susceptibility of cells in the central nervous system to HIV infection

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Susceptibility</th>
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<tbody>
<tr>
<td>Perivascular macrophages</td>
<td>Yes</td>
</tr>
<tr>
<td>Microglia</td>
<td>Yes</td>
</tr>
<tr>
<td>Astrocytes</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Oligodendrocytes</td>
<td>No</td>
</tr>
<tr>
<td>Neurons</td>
<td>No</td>
</tr>
<tr>
<td>Brain endothelial cells</td>
<td>No</td>
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</tbody>
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Proposed mechanism of HAD:

1. HIV infections spread to brain through infected macrophages (and/or T cell)

2. infected and activated macrophages and microglia release virus- and/or host cell-derived factors that may affect neuronal function and lead to a cellular milieu that is neurotoxic

3. non-productive infection of astrocytes may disrupt their function and lead to astrocytic apoptosis that increases the neurotoxicity
HIV-derived molecules that affect neuronal function:

1. **Gp120 envelope protein**, can affect neurons that express receptors for this molecule

2. **regulatory proteins** such as the **nef** and **tat** protein
   
   tat protein unique since it can pass plasma membranes and reach nuclei of uninfected cells

*HIV strains from HAD patients differ in the sequence of both gp120 and tat.*
Factors released by activated macrophages and microglia

1. Cytokines (TNF-α, IL-1β)
2. Excitotoxins (quinolinate, glutamate)
3. Lipid mediators (arachidonate, its metabolites and platelet-activating factor)
4. Free radicals (nitric oxide and superoxide)
5. Amines (Ntox)

Only 10-15% of macrophages/microglia in AIDS brains are infected, the remainder may be immune-activated.
Neuro-degeneration and protection in AIDS

Gonzalez-Scarano & Garcia, 2005
Questions:

Can the brain be a reservoir for HIV in patients undergoing HAART?

Will MCMD (minor cognitive motor disorder) progress despite effective systemic HAART?
Most individuals harbor subclinical or latent infections in their brains.
Opportunistic infections in the brain

- Toxoplasmic encephalitis
- Progressive multifocal leukoencephalopathy (PML; papovavirus)
- Cytomegalovirus (CMV) encephalitis
- Cryptococcosis
- Tuberculosis - meningitis and tuberculoma
Toxoplastic encephalitis

- 25-50% of *Toxoplasma* seropositives infected with HIV develop toxoplastic encephalitis
- Congenital or postnatal infections
- Slow replication of bradyzoites in neurons (pseudocysts) during latency
- Headache, fever, confusion
- Multifocal necrotic encephalitis
Toxoplasma (red), brain cell (green)

Lueder et al., 1999
Toxoplasmic encephalitis
Can *Toxoplasma* parasites, which establish long-term persistent infections in neurons of the brain, have any consequences for brain function?
Rats, cats, people and parasites.


Children with latent toxoplasmosis had on average a lower IQ (93) than controls (110). *Alford et al 1974*

Infected men: higher tendency to disregard rules of the society, more suspecting, jealous and dogmatic

Infected women: more warm-hearted, out- and easy-going, but also more conscientious, persistent, moralistic and staid. *Flegr et al 1994,2000*
CMV (cytomegalovirus) encephalitis
PML (progressive multifocal leukoencephalopathy)

Papovaviruses in oligodendrocytes cause myelin destruction
Aspergillosis

Cryptococcal meningitis
Neuro-tuberculosis

Tuberculoma

Tuberculous basilar meningitis
Neuro-HIV in the HAART era:

• Brain as a HIV reservoir?
• Minor cognitive motor disorder more common?
• Immune reconstitution syndrome – tbc, cryptococcus?
• Toxic peripheral neuropathies?
• Vacuolar myelopathy?
• Each Human brain is unique and has a capacity that goes far beyond the most sophisticated machines and computers.

• but- Limited repair capacity

• Keep it free from viruses and other parasites and microbes! **BRAIN AWARENESS**
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