

# **HIV AND THE BRAIN**

## **Introduction:**

(1) The cognitive, neurological (motor) and, secondarily, the behavioral changes seen in patients with HIV infection were described early in the epidemic in 1983 and called AIDS Dementia Complex (ADC) by Navia and Price in 1986.

(2) It was noted to have mild to severe symptoms, most often related to the degree of immune compromise.

(3) In the pre-HAART era:

90% of patients found to have HIV in CNS within weeks of seroconversion.

90% of patients found to have neuropathology at autopsy.

20-30% of patients showing signs of cognitive decline or neurological disturbance at the time of AIDS diagnosis (noticeable on bedside examination or Mini-Mental State examination).

20-30% showing very mild symptoms (patient reports or Neuropsychological Testing).

20-25% overall prevalence of significant cognitive deficits.

Because moderate to severe dementia occurred in the absence of opportunistic infections, ADC eventually added as an AIDS-defining condition (at the same time as CD4 counts less than 200).

ADC was noted to be a significant independent risk factor for death due to AIDS (up to a 50% increase in mortality).

## **I. Competing Nomenclature:**

(1) AIDS Dementia Complex (1986-1997) with Memorial Sloan Kettering Staging:

0 – Normal

0.5 – Equivocal or Subclinical signs (no impairment of work or ADLs)

1 – Unequivocal evidence (impairment of only the most demanding aspects of work and ADLs)

2 – Moderate (cannot work but still able to perform basic ADLs)

3 – Severe (major intellectual incapacity and motor disability)

4 – End Stage (vegetative, mute, paraparesis, incontinence)

(2) WHO/American Academy of Neurology Staging: (1998—2008):  
HIV-1-associated Cognitive/Motor Complex

0 – Normal

0.5 – Omitted

1 – HIV-1-associated "Minor" Cognitive/Motor Complex

2 – 4 Unchanged

- (3) **Antinori/Arendt/Becker et al Staging (2007):**
  - HIV-associated Neurocognitive Disorder (HAND)**
  - (a) **Asymptomatic**
  - (b) **Mild Neurocognitive Disorder (MND)**
  - (c) **HIV-associated Dementia (HAD)**

## **II. Scope of the Problem (post-HAART—1996):**

- (1) **Most opportunistic infections and constitutional symptoms have decreased in the HAART era, except the incidence of CNS lymphoma, PML and HAND has actually increased.**
- (2) **Results of the AIDS Longitudinal Linked Randomized Trials (ALLRT—ACTG—1160 patients all taking 3-drug regimens) showed ongoing 21% with clinically significant cognitive decline, thought to be due to:**
  - (a) **Prolonged exposure to HIV itself and to Inflammatory Cytokines and Chemokines.**
  - (b) **Resistant and possibly Neurovirulent Strains of HIV in CNS.**
  - (c) **Potential for virological escape from HAART.**
  - (d) **Suboptimal penetration of HAART medications into CNS.**

**26% of patients demonstrated mild to moderate impairment at initial visit. Of these, 56% had sustained mild impairment even after 20 additional weeks of HAART (but 44% improved). Factors associated with ongoing impairment:**

- (a) **History of CD4 count less than 200.**
- (b) **Age of patient.**
- (c) **Immunologic status (but no clear relationship to plasma or CSF VLs—possibly due to the restricted range of VLs with HAART).**

**There was no evidence of virologic factors associated with decline  
Shortcoming of study was use of only 3 Neuropsychological Tests.  
In other studies non-verbal memory and psychomotor tasks were impaired with normal concentration and attention.**

## **III. Establishment of Infection:**

**Usually within weeks of seroconversion, HIV has crossed the Blood Brain Barrier (BBB) via infected Macrophages.**

**These infect Microglia and Endothelial Cells.**

**There is also non-productive infection of Astrocytes leading to proliferation of these cells.**

**Infected Endothelial Cells lead to a leaky BBB and enhanced entry of virus  
Macrophages and Microglia represent a Reservoir of HIV, like CD4 cells.**

#### **IV. Pathology and Biochemistry:**

**Three common pathologies noted at autopsy:**

- (1) White matter pallor and gliosis.**
- (2) Multinucleated Giant Cells (primarily Microglia and Macrophages).**
- (3) Vacuolar Myelopathy (primarily in Cervical and Thoracic Cord (but also in Subcortical areas).**

**However, these are NOT markers of Dementia—Pallor and gliosis are not specific, Multinucleated Giant Cells in only about 50% of patients with Dementia (but do represent active HIV replication), Vacuolar Myelopathy can occur without evidence of cognitive decline.**

**Secondary pathologies at autopsy:**

- (1) Atrophy and loss of volume in Neocortex.**
- (2) Volume loss in Basal Ganglia (oddly, less in the HAART-era with increasing loss in Hippocampus and Temporal Cortex).**
- (3) Axonal damage associated with increasing Apoptosis (also seen in Endothelial Cells, leading to even leakier BBB).**

**Neuroinflammation—noted early in the pre-HAART era, may be one of the only consistent markers (along with Microgliosis and Macrophage Invasion) predicting and leading to reduced synaptic and dendritic density. Thus inflammation itself can be considered a pathological mechanism. Inflammation should decrease with treatment, but this is not seen in recent autopsies in spite of decreased CNS VL and decreased cellular infiltration.**

**UNDETECTABLE VL DOES NOT EXCLUDE COGNITIVE DECLINE**

**Aging and Other Neurodegenerative Diseases:**

**In-vivo imaging studies show similarities with HAD and Parkinsons, Alzheimers and Lewy Body Dementias (amyloid and Lewy Bodies). It appears that a lasting, even well-controlled, HIV infection may hasten the aging process and thus facilitate the development of these other neurodegenerative diseases.**

**Direct HIV Neurotoxicity:**

**gp120 (a coat protein) opens Calcium Channels in Neurons and Stimulates Macrophages to increase Quinolinic Acid production.**

**Tat (Transactivator of transcription) compromises synaptic function via protein folding and mitochondrial malfunction.**

**Neurotoxicity from Neurotoxins Released by Infected or Stimulated Macrophages and Microglia (a very partial list):**

- (1) **Interferon alpha (IFN- $\alpha$ ) overproduction leads to an erroneous and exhaustive immune activation leading to immune suppression and progression to AIDS. In the brain, excessive and ongoing IFN- $\alpha$  production can correlate with neurocognitive impairment.**
- (2) **Decrease in Leptin (hormonal regulation of energy homeostasis) leads to impaired learning and memory.**
- (3) **Increase in plasma Osteopontin precedes systemic and CNS symptoms**
- (4) **Interleukin-1 leads to Astrocyte proliferation and disruption.**
- (5) **Interleukin-1 stimulates production of Quinolinic Acid which leads to stimulation of NMDA (glutamic-N-methyl-D-aspartate) which opens Calcium channels and impairs neurons.**
- (6) **Tumor Necrotic Factor-alpha (TNF- $\alpha$ ) and Beta-2-microglobulin impair oligodendrocytes which are essential for myelin maintenance, leading to vacuolar myelopathy.**

**Intestinal Involvement:**

**HIV infection affects the intestinal tract with leakage of bacteria into the bloodstream, which leads to an increase in Lipopolysaccharide levels which leads to monocyte activation and transmigration of peripheral monocytes into the CNS.**

**Possible Toxicity of HAART Itself**

- V. Neuroimaging:**
- CT—Cortical atrophy only.**
  - MRI—Pallor of white matter, especially subcortical/subfrontal Vacuolization, mostly in cord, but also subcortical.**
  - PET—Early increase in metabolism in thalamus and basal Ganglia, later decreased metabolism in frontal cortex.**
  - MRS—(Magnetic Resonance Spectroscopy) shows decrease in Glutamate in frontal lobe (activating neurotransmitter). Also shows certain metabolites associated with SIV severity.**
  - Blood-Oxygen Level-Dependent Functional MRI shows that patients with low CNS-penetration HAART showed global signs of oxidative stress.**
  - Further MRS and fMRI studies may yet discover an accurate marker for the dementia.**

## **VI. Clinical Features:**

- (1) Cognitive—Decreased concentration and attention which lead to perceived or real decline in S-T memory, impaired problem-solving (frontal lobe executive function), difficulty shifting tasks, psychomotor slowing (of thought and speech). These symptoms can gradually progress to catatonia and mutism.**
- (2) Neurological (Motor)---Impaired balance, ataxia (impaired gait), lower extremity weakness, tremors, decreased fine motor control (e.g. small handwriting), dysdiadochokinesia (impairment of central visual and peripheral rapidly alternating movements), increased lower extremity reflexes and pathological release signs, myoclonus, chorea, asterixis, incontinence. These symptoms can progress to paraparesis/paraplegia.**
- (3) Behavioral---The most variable symptoms, thus less reliable. Apathy, social withdrawal (often without the dysphoria associated with depression), decreased emotional spontaneity (often described as loss of personality).**
- (4) Atypical Presentations---Anxiety, agitation, hyperactivity, mania, regression and psychosis (this may represent the shift of infection away from the Basal Ganglia to the Hippocampus and Limbic Areas).**

## **VII. Treatment:**

**There have been over 20 major clinical trials, some still recruiting, but none has shown a treatment option which consistently prevents or reverses impairment. HAART was most helpful in the vast majority of cases.**

- (1) The effectiveness of HAART is dependent on each individual drug's penetration into the CNS. The most important study in this regard:**

**CNS HIV Anti-Retroviral Therapy Effectiveness Research (CHAMBER), a multi-center study with 467 participants, all of whom were taking a 3-drug regimen at the outset and remained on 3 drugs for the following 20 weeks. Drugs were assigned values of 0, 0.5 and 1 on the basis of their levels in CSF and biochemical properties, used to approximate their levels in the CNS.**

**CPE (CNS Penetration-Effectiveness) was defined as the sum of the values of the individual drugs. An increase of one CPE unit corresponded to a 2.5 increase in the odds of undetectable VL in CSF.**

- 1 = High Penetration (Zidovudine, Abacavir, Delavirdine, Nevirapine, (Amprenavir/Ritonavir, Fosamprenavir/Ritonavir, Atazanavir/Ritonavir, Indinavir/Ritonavir, Lopinavir/Ritonavir).**
- 2 = Intermediate Penetration (Stavudine, Lamivudine, Emtricitabine, Efavirenz, Amprenavir, Fosamprenavir, Atazanavir, Indinavir)**
- 3 = Low Penetration (Tenofovir, Didanosine, Zalcitabine, Nelfinavir, Saquinavir, Saquinavir/Ritonavir, Ritonavir, Tipranivir/Ritonavir, Enfuvirtide).**

**(2) Other Treatments (minimally effective if at all):**

**Steroids—may temporarily decrease inflammation and block certain Interleukins.**

**Interferons—may block Interleukins.**

**Thalidomide—blocks some Tumor Necrotic Factor (TNF-a) effects.**

**Ca<sup>++</sup> Channel Blockers could decrease damage to neurons but none yet crosses BBB effectively.**

**Memantine (and Dextromethorphan) are NMDA antagonists.**

**Anti-Parkinson Agents may also block NMDA-induced degeneration of Substantia Nigra ( overlap with Parkinsons Disease).**

**Selegiline (reversible MAOI)—No benefit.**

**Lithium and Valproic Acid—glucagon synthetase inhibitors but of little benefit.**

**Miraviroc (CCR5**

**inhibitor)—poor entry into CNS but excellent suppression in gut lymphocytic tissues.**

**Minocycline—suppresses SIVE (SIV-encephalitis) via inhibition of Apoptosis-Signal-Regulating Kinase.**

**VIII. Conclusions:**

- (1) HAD prevalence has not decreased significantly since start of HAART, but is delayed and mostly less severe.**
- (2) Long-term HIV infection may hasten aging and development of other Neurodegenerative Diseases.**
- (3) The best predictive marker for HAD is the overall condition of the immune system.**
- (4) Infected and activated Macrophages and Microglia are a major Factor in the development of HAD.**
- (5) HAART is not sufficient to treat HAD, so the search for improved anti-retrovirals and adjunctive treatments goes on.**

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