HIV brain infection and Alzheimer’s disease: what is common, what is different?

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ARROW meeting, Bucharest, October 2015
Clinical diagnosis – easy to distinguish

- **AD (there is no cause)**
  - Late, aged people
  - Progressive, strictly cortical deficits (etiologically untreatable)
  - No motor signs but only very late in evolution
  - Behavioral changes rarely in the onset of the symptomatology (except depression, except atypical forms), etc
  - Evolving brain atrophy at repeated imagery examinations

- **HAND (there is a cause: HIV)**
  - Generally young or middle aged
  - Subacute usually, afterwards progressive, alleviated with ART (etiologically treatable)
  - Motor signs
  - Behavioral changes, etc
  - Different MRI-evident brain lesions
  - Signs of immunodeficiency
Role of neuroimaging in multidisciplinary approach towards Non-Alzheimer’s dementia

Satya Narayana Patro¹ - Rafael Glikstein¹ - Prasad Hanagandi¹ - Santanu Chakraborty¹

Fig. 9 HIV-Associated Dementia (HAD). A 56-year-old female with a several-month history of generalized weakness, confusion and memory loss. a & b axial T2W and FLAIR images of the brain at the level of ventricles show diffuse symmetrical white matter hyperintensity and mild generalized atrophy. c & d axial T2W and FLAIR images at the level of centrum semiovale reveal similar diffuse symmetrical hyperintensity in the white matter.
Dementia

- A syndrome
- More than 50 etiologies
- Few treatable (HAND – treatable)
- Most of dementia – neurodegenerative disease, mostly AD
- At least 2 cognitive fields affected progressively
- AD – most common cause of dementia over all
We will probably always have to ask

What is Alzheimer’s disease?

http://www.efesalud.com/noticias/los-retos-de-la-enfermedad-de-alzheimer/
A.D. Auguste Deter

• 1901 – 51 y.o. – aphasia, aggressive behavior, paranoia, auditory hallucinations, delusions
• 1906 – death – pathological examination – A. Alzheimer (Kraepelin) – report in 1907:

‘Ich hab mich verloren’
(I have lost myself)
A presenilin 1 mutation in the first case of Alzheimer’s disease

Auguste Deter is undoubtedly one of the most famous patients in medical history. She was the middle-aged woman in whom Alois Alzheimer first reported on “eine eigenartige Erkrankung der Hirnrinde” (a peculiar disorder of the cerebral cortex) more than a century ago.¹

Figure: Sequence chromatograms of 28 bp of exon 6 of PSEN1 in DNA extracted from brain samples of Auguste Deter

Sequencing detected a c.526T→C substitution. Both the sequence of the forward DNA strand (A) and the sequence of the reverse strand (B) are shown. The resulting aminoacid change, Phe176Leu, is indicated (F/L). The slight compressions at positions c.533 and c.537 were resolved on the reverse strand.

**Fig. 4:** Plaque with a large zonal layer constituted by an aggregation of filamentous material. A macrophage (m) lies in the center of the plaque and near the colorless and amorphous region.

**Fig. 5** shows a plaque with a bulky central nucleus and typical phenomena of neurotisation. The fibers coming from the new formation penetrate into the plaque. They arrive at the vicinity of the nucleus, they surround it and give off collaterals that end each with a button and form a rosette.

**Fig. 6.** Fiber with a terminal ball. The black precipitate could be evidenced near it. The ball is degenerating.

**Fig. 7.** Plaque with a central nucleus constituted by an argyrophilic central zone and a radial peripheral zone. The zonal layer is made up by fibers that are short, thick, sometimes thin at their extremity, undulated; by other thinner fibers (f, f) that creep into the first ones (f, e) forming argentophilic corpuscles (ca, ca’) around the central nucleus.
Cells, tissues, and organisms have an intrinsic property of fighting off the effects of various stressors, defined as the homeostatic reserve. In young/adult organisms, the homeostatic reserve is well in excess of the levels of maximal metabolic stressors still compatible with life. With the passage of time and increasing age, the combined effects of a decrease in the efficiency of the repair mechanisms, changes in mitochondrial status, and an increased accumulation of the ROS-induced damage drastically reduce the level of homeostatic reserve to levels that are still compatible with normal levels of activity. On this background, the neurodegenerative processes act either through an increase in the levels of metabolic stress or through a further decrease in the homeostatic reserve, such that in various regions of the brain where these changes take place, the homeostatic reserve becomes insufficient and neuronal loss ensues. (Toescu EC et al., 1999)
Basic things - AD

- Age increase – more dementia
- Familial cases (defined inheritance pattern) – only 5-10% - earlier age of onset ( - 65 yo.)
- Genetic defects – chr. 21, 19, 14, 12, 1
- More than half of FAD – due to presenilin 1 mutations, few to APP and few to presenilin 2 mutations
- Sporadic – late onset – cholesterol transporter ApoE
- Also α-2-macroglobulin genetic locus in 30% of AD cases
Processes influencing clinical expression of dementia

Additional opportunities for interventions

- Aging related decline
- Genetically determined disease process
- Environmental risk factors
- Comorbidity
- Neuronal repair and compensation mechanisms

DEMENTIA
Alzheimer’s disease

- Cell signaling dysfunction (early)
  - Oxidative stress
  - Calcium dysbalance
  - Energy depletion
  - Neurotransmission deficit

- Synapse loss

- Cell loss (late)
  - Apoptosis
  - Necrosis
The Amyloid Cascade Hypothesis

Ghandi S., J. Clinical Investigation, 2005
Tau Pathology in AD

- Tau protein Hyperphosphorylation
  - Increased Kinase: GSK-3β, Cdk-5, MAPK
  - Decreased Phosphatase: PP2-A, PP2-B

- Tau stabilisation of microtubules
- Dissociation of p-Tau from microtubules
- Microtubule instability
- PHF AND NFT formation
- Cell Death

After B. Winblad, 2004
Does tangles/plaques correlate with the cognitive function?


- Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease.
  - Department of Psychiatry, HUG Belle-Idée, University of Geneva School of Medicine, Switzerland.
  Panteleimon.Giannakopoulos@medecine.unige.ch
**Tau versus Aβ**

- Aβ plaques or Aβ load – probably not the sole cause of AD
  - People without dementia have some Aβ load (*but might be in early AD stages!*)
  - Clearance of Aβ by active immunization did not produce clinical benefit (*but it might have been too late!*)
  - NFT correlate with cognition during evolution of AD (Braak stages)

- Soluble aggregates of Aβ peptides (oligomers) have been proposed as pathogenic agent
Hypothetical depiction of biomarker changes during the progression of Alzheimer disease (AD) from onset of pathology through dementia prepared by Alzheimer’s Disease Neuroimaging Initiative investigators.
Aβ and BBB

LRP-1 = low density lipoprotein receptor-related protein
RAGE = receptor for advanced glycation end-products

Aβ in:
- blood
- vessels (CAA)
- brain tissue

Drawing following the concept of Deane et al., Nature Med, 2003
Or should we understand tau and Abeta in completely different ways?

- **Tau** molecular behavior – functions in DNA protection and RNA integrity in physiological conditions/under oxidative stress (Violet et al., 2014)

- **β-amyloid** – imported in mitochondria, localized to mitochondrial cristae – toxicity, decreased energy levels (Ankarcrorna M. group, 2008-2015)
THE CHOLINERGIC HYPOTHESIS
(2003)

Normal

Early AD

Ch Transporter
VAChT
NGF
M₂AChR
M₁AChR
ACh
TrkA NGFR
nAChR
Microtubule
ChAT
AChE

Glial Cell
Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS–ADRDA criteria


The NINCDS–ADRDA and the DSM-IV-TR criteria for Alzheimer’s disease (AD) are the prevailing diagnostic standards in research; however, they have now fallen behind the unprecedented growth of scientific knowledge. Distinctive and reliable biomarkers of AD are now available through structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analyses. This progress provides the impetus for our proposal of revised diagnostic criteria for AD. Our framework was developed to capture both the earliest stages, before full-blown dementia, as well as the full spectrum of the illness. These new criteria are centred on a clinical core of early and significant episodic memory impairment. They stipulate that there must also be at least one or more abnormal biomarkers among structural neuroimaging with MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis of amyloid β or tau proteins. The timeliness of these criteria is highlighted by the many drugs in development that are directed at changing pathogenesis, particularly at the production and clearance of amyloid β as well as at the hyperphosphorylation state of tau. Validation studies in existing and prospective cohorts are needed to advance these criteria and optimise their sensitivity, specificity, and accuracy.
Still debating a cause and diagnostic criteria for Alzheimer’s disease

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Received: October 30, 2007; Accepted: October 30, 2007

We have all heard of Alzheimer’s disease (AD) and of suffering from the burden of dementia, although the main cause of this illness described over a century ago remains hotly debated. There is no doubt that in the last decades a lot of progress has been achieved in understanding the pathogenic mechanisms of AD but no unifying theory was able to entirely explain the occurrence of neuropathological lesions and the progression of the disease yet [1]. Even though the AD classical hallmarks are the senile plaques and the neurofibrillary tangles, the amyloid cascade and the discovery of presenilins, genetics has made a big promise to AD research. Characterization of the \( \gamma \)-secretase complex, which executes the final proteolytic cut of the precursor to yield the amyloid, is probably one important pay-off. Clinical trials using \( \gamma \)-secretase inhibitors will probably give answers to two questions. The amyloid cascade theory ultimate question comes first: is it enough to inhibit \( \beta \)-amyloid production to stop AD? The second question is linked to the physiological \( \gamma \)-secretase function [15]: will the inhibitors be safe enough?
Panel 1: Glossary of terms

Mild cognitive impairment
Variously defined but includes subjective memory or cognitive symptoms or both, objective memory or cognitive impairment or both, and generally unaffected activities of daily living; affected people do not meet currently accepted dementia or AD diagnostic criteria

Amnestic mild cognitive impairment
A more specified term describing a subtype of mild cognitive impairment, in which there are subjective memory symptoms and objective memory impairment; other cognitive domains and activities of daily living are generally unaffected; affected people do not meet currently accepted dementia or AD diagnostic criteria

Preclinical AD
The long asymptomatic period between the first brain lesions and the first appearance of symptoms and which concerns normal individuals that later fulfil AD diagnostic criteria

Prodromal AD
The symptomatic predementia phase of AD, generally included in the mild cognitive impairment category; this phase is characterised by symptoms not severe enough to meet currently accepted diagnostic criteria for AD

AD dementia
The phase of AD where symptoms are sufficiently severe to meet currently accepted dementia and AD diagnostic criteria

Dubois et al., 2007
Figure: Alzheimer’s disease starts and should be identified before the occurrence of full-blown dementia (as for other dementing conditions)

AD = Alzheimer’s disease; VD = vascular dementia; FTD = frontotemporal dementia; PPA = primary progressive aphasia; DLB = dementia with Lewy bodies.
Hypothesized Natural Course of Sporadic AD

Onset of MCI*  Clinical diagnosis of AD

Estimated start of amyloid deposition

Degree of cognitive impairment

* MCI - mild cognitive impairment

Modified from PJ Visser, 2000
Pathophysiological Processes Leading to AD

Possible Targets for Therapy

Aging

Disbalance: calcium, energy, antioxidant triangle

Beta- and gamma-secretases

Increased Aβ production

Oxidative stress

Synaptic damage

Neurodegeneration

Neuronal death

Cognitive dysfunction

Genetic factors: APP & presenilin Mutations, ApoE

Environmental risk factors

Vascular factors

Beta- and gamma-secretases

Protein aggregation

BBB

Micro RNAs

Micro- & astroglia activation

Inflammation

Neurotransmitters Deficits (Ach, etc.)

Adapted from Bengt Winblad
Mild Cognitive Impairment (MCI) % transition per year to AD

MCI $\rightarrow$ AD 12%/yr

Control $\rightarrow$ AD 1-2%/yr

Treatment outcomes

<table>
<thead>
<tr>
<th>Treatment outcomes</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease arrest</td>
<td></td>
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<tr>
<td>Slowed progression</td>
<td></td>
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<tr>
<td>Symptomatic benefit</td>
<td></td>
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<tr>
<td>No effect</td>
<td></td>
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<tr>
<td>Cure</td>
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</table>
AD treatment (cognitive)

- Limited effect
  - ChE inhibitors
  - Memantine

Winblad et al. 1999
WHAT ABOUT HIV AND BRAIN?
HIV-1 neuroinvasion. 1) "Trojan Horse hypothesis" for entry of HIV-1 into the brain via migration of infected monocytes which differentiate into perivascular macrophage. 2) The passage of infected CD4+ T cells into the brain. Other probable causes of CNS infection might be: 3) the direct entrance of the virus via tight junctions across the membrane and 4) entrance of HIV-1 by transcytosis phenomenon.
HIV neurologic complications

• HIV infection of the CNS begins early in systemic infection
• Might be asymptomatic for long time
• Neurologic signs/symptoms (a multitude) – a result of HIV infection itself but also of opportunistic infections – sometimes difficult to distinguish
• Widespread ART diminished HIV invasion of CNS and neurologic complications (however, still 25% in most developed countries) – but increase of lifespan/aging increases risk of neurodegeneration/dementia
• Dementia burden in all HIV-infected adults population: up to 40%1
• Dementia – a syndrome/might have more than one cause

1 – Sacktor et al, 2007
HAND (HIV-associated neurocognitive disorder)

- HIV infection frequently results in cognitive disturbance
- Historically, first entity described: AIDS related dementia (AIDS dementia complex, HIV dementia)

Abstract

Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome.

Ho DD, Rota TR, Schooley RT, Kaplan JC, Allan JD, Groopman JE, Resnick L, Felsenstein D, Andrews CA, Hirsch MS.

Abstract

We conducted virus-isolation studies on 56 specimens from the nervous system of 45 patients in order to determine whether human T-cell lymphotropic virus Type III (HTLV-III) is directly involved in the pathogenesis of the neurologic disorders frequently encountered in the acquired immunodeficiency syndrome (AIDS) and the AIDS-related complex. We recovered HTLV-III from at least one specimen from 24 of 33 patients with AIDS-related neurologic syndromes. In one patient, HTLV-III was isolated from the cerebrospinal fluid during acute aseptic meningitis associated with HTLV-III seroconversion. HTLV-III was also isolated from cerebrospinal fluid from six of seven patients with AIDS or its related complex and unexplained chronic meningitis. In addition, of 16 patients with AIDS-related dementia, 10 had positive cultures for HTLV-III in cerebrospinal fluid, brain tissue, or both. Furthermore, we cultured HTLV-III from the spinal cord of a patient with myelopathy and from the sural nerve of a patient with peripheral neuropathy. These findings suggest that HTLV-III is neurotropic, is capable of causing acute meningitis, is responsible for AIDS-related chronic meningitis and dementia, and may be the cause of the spinal-cord degeneration and peripheral neuropathy in AIDS and AIDS-related complex.
Stages in the evolution of untreated CNS HIV infection

• Primary (early) HIV infection (PHI) ~ 1 year after exposure

• Chronic neuro-asymptomatic infection (NA) – evolving – changes as the immune system is altered

• HIV-associated neurocognitive disorder (HAND) – subacute onset and progression
Why HAND?

• Neurocognitive disorder – the new entity stated by DSM 5
• DSM 5 categorizes minor and major neurocognitive disorders based on presumed etiology and degree of severity\textsuperscript{1}
• Together with HIV, in current practice a variety of clinical (comorbidities), social and psychological factors might contribute to HAND – there are no definite biomarkers to establish/distinguish etiology\textsuperscript{2}

HIV-associated neurocognitive disorders

Five New Things

1) HAND includes: HIV-associated dementia, asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND)
2) Mild HAND forms – highly prevalent, diagnosed through neuropsychological testing
3) Unknown whether using a cART regimen with superior CNS penetration improves the prognosis
4) HIV clades and subtypes might matter for prognosis
5) Comorbidities (vascular, other infections, drug abuse) – should be identified and treated
What about HAND?

Levine et al. BMC Medical Genomics 2013, 6:4
http://www.biomedcentral.com/1755-8794/6/4

**RESEARCH ARTICLE**  Open Access


Andrew J Levine\(^1\)\(^*,\) Jeremy A Miller\(^2\)\(^*,\) Paul Shapshak\(^3\), Benjamin Gelman\(^4\), Elyse J Singer\(^1\), Charles H Hinkin\(^5\)\(^,\)\(^6\), Deborah Commins\(^7\), Susan Morgello\(^8\), Igor Grant\(^9\) and Steve Horvath\(^2\)\(^,\)\(^10\)
Common gene expression changes in AD and HAND (Levine AJ et al., 2013)

<table>
<thead>
<tr>
<th>Gene probe</th>
<th>Function</th>
<th>Scaled intramodule connectivity kIN/max (kIN)</th>
<th>AD hippocampus</th>
<th>HIV frontal cortex</th>
<th>HIV basal ganglia</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Up with impairment</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CTDSP2</td>
<td>Cancer</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>SASH1</td>
<td>Cancer</td>
<td>0.84</td>
<td>0.95</td>
<td>–</td>
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<tr>
<td>FBXW12</td>
<td>Cancer</td>
<td>0.86</td>
<td>0.79</td>
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<tr>
<td>HIPK2</td>
<td>Cancer</td>
<td>0.77</td>
<td>0.74</td>
<td>0.72</td>
<td></td>
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<tr>
<td>CASC3</td>
<td>Cancer</td>
<td>0.74</td>
<td>–</td>
<td>0.74</td>
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<tr>
<td>CEP350</td>
<td>Cancer</td>
<td>0.72</td>
<td>0.90</td>
<td>–</td>
<td></td>
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<tr>
<td>PGF</td>
<td>Cancer</td>
<td>0.71</td>
<td>–</td>
<td>0.73</td>
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<tr>
<td>HS1BP3</td>
<td>Neurologic</td>
<td>0.71</td>
<td>–</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Down with Impairment</td>
<td></td>
<td>AD hippocampus</td>
<td>HIV frontal cortex</td>
<td>HIV basal ganglia</td>
<td></td>
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<tr>
<td>SCG5</td>
<td>Neurologic</td>
<td>0.96</td>
<td>–</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>VDAC1</td>
<td>Mitochondria</td>
<td>0.95</td>
<td>0.99</td>
<td>0.92</td>
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<tr>
<td>KIAA1279</td>
<td>Neurologic</td>
<td>0.93</td>
<td>–</td>
<td>0.70</td>
<td></td>
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<tr>
<td>PFDN4</td>
<td>Mitochondria</td>
<td>0.92</td>
<td>0.84</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>MDH1</td>
<td>Mitochondria</td>
<td>0.90</td>
<td>0.84</td>
<td>1.0</td>
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<tr>
<td>ATP5G3</td>
<td>Mitochondria</td>
<td>0.90</td>
<td>0.95</td>
<td>0.99</td>
<td></td>
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<tr>
<td>DYN111</td>
<td>Neurologic</td>
<td>0.89</td>
<td>0.83</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>PCMT1</td>
<td>Neurologic</td>
<td>0.86</td>
<td>0.98</td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>

| TOMM20       | Mitochondria | 0.86                                    | –              | 0.92               |                 |
| KLC1         | Microtubule  | 0.86                                        | 0.96           | 0.84               |                 |
| NDFIP1       | Neurologic   | 0.86                                        | 0.73           | 0.84               |                 |
| KIFAP3       | Neurologic   | 0.85                                        | 0.87           | –                  |                 |
| THYN1        | Mitochondria | 0.85                                        | 0.74           | 0.78               |                 |
| GOT1         | Mitochondria | 0.84                                        | 0.83           | 0.84               |                 |
| TBC1D9       | Neurologic   | 0.84                                        | 0.75           | 0.90               |                 |
| UCHL1        | Neurologic   | 0.84                                        | 0.84           | 0.92               |                 |
| ACTR10       | Neurologic   | 0.84                                        | 0.88           | 0.85               |                 |
| C5SD1        | Mitochondria | 0.83                                        | 0.83           | 0.75               |                 |
| SMAP1        | Mitochondria | 0.82                                        | 0.76           | –                  |                 |
| C14orf2      | Mitochondria | 0.82                                        | 0.77           | 0.76               |                 |
| PEX11B       | Mitochondria | 0.81                                        | 0.93           | –                  |                 |
| SLC4A1AP     | Mitochondria | 0.81                                        | 0.71           | –                  |                 |
| COPS4        | Mitochondria | 0.81                                        | 0.87           | 0.79               |                 |
| ITFG1        | Mitochondria | 0.80                                        | 0.84           | 0.76               |                 |
| GLOD4        | Mitochondria | 0.79                                        | –              | 0.83               |                 |
| DNAJA2       | Mitochondria | 0.78                                        | 0.74           | 0.73               |                 |
| SUCLA2       | Mitochondria | 0.76                                        | 0.87           | 0.84               |                 |
| NDUFB6       | Mitochondria | 0.76                                        | –              | 0.78               |                 |
| EBNA1BP2     | Mitochondria | 0.76                                        | –              | 0.72               |                 |
| TUBA4A       | Mitochondria | 0.75                                        | –              | –                  |                 |
| HINT1        | Cancer       | 0.75                                        | 0.86           | 0.80               |                 |
Mechanisms of HIV-related neuronal injury

- The pathogenic mechanisms of HIV-brain infection are not fully elucidated
- HIV enters the CNS through infected cells (is BBB intact or not? Probably it enters easier or massively if BBB is altered)
- Macrophages/microglia toxic release
- Apoptosis is triggered probably by different HIV proteins
- Excitotoxicity is responsible for part of cell death/calcium dysbalance
- Aggregation of abnormal proteins
- Trans-synaptic spread –similar to prions, similar to neurodegeneration?
Cerebral β-amyloid deposition predicts HIV-associated neurocognitive disorders in APOE ε4 carriers


A-HIV Neurobehavioral Research Program and California NeuroAIDS Tissue Network, San Diego, La Jolla, California, USA

Fig. 1. β-Amyloid (Aβ) and phospho-Tau (p-Tau) pathology in the middle frontal cortex of HIV-infected adults

Immunohistochemical staining with anti-Aβ antibody (clone 4G8) shows diffuse plaques of focal (a, arrows) or widespread (b) density in the cortex; scale bars 500 μm.

Immunohistochemical staining with anti-p-Tau antibody (clone AT8) shows scattered neurites (c, arrows), an intraneuronal neurofibrillary tangle (d, arrow), and a cluster of dystrophic neurites, consistent with a neuritic plaque, (e, arrow); scale bars 30 μm.
## HAND treatment trials

**Table 2. Review of studies that have assessed the efficacy of neuroprotective drugs.**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Sample</th>
<th>Design</th>
<th>Main findings</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antioxidants</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OPC-14117 (240 mg/day)</td>
<td>30 patients with cognitive impairment</td>
<td>12-week double-blind, placebo-controlled, randomized study; follow-up with neuropsychological tests</td>
<td>Only a trend towards improvement in cognitive scores</td>
<td>[74]</td>
</tr>
<tr>
<td>Selegiline (2.5 mg 3-times/week per os)</td>
<td>36 patients with cognitive impairment on stable antiretroviral regimen</td>
<td>10-week randomized, double-blind, placebo-controlled trial; follow-up with neuropsychological tests</td>
<td>Cognitive improvement on verbal memory ($p = 0.002$); only a trend towards improvement of psychomotor speed</td>
<td>[75]</td>
</tr>
<tr>
<td>Transdermal selegiline (1.0 mg/cm x 15 cm² patch)</td>
<td>14 patients with cognitive impairment on stable antiretroviral regimen</td>
<td>10-week placebo-controlled study; follow-up with neuropsychological tests</td>
<td>Improvement in verbal learning ($p = 0.03$) and motor/psychomotor function ($p = 0.03$)</td>
<td>[76]</td>
</tr>
<tr>
<td>Transdermal selegiline (6 mg/24 h or 3 mg/24 h)</td>
<td>128 patients with cognitive impairment</td>
<td>24-week placebo-controlled study; follow-up with neuropsychological tests and proton MRS</td>
<td>No cognitive or functional benefit; no MRS change</td>
<td>[77,79]</td>
</tr>
<tr>
<td>Transdermal selegiline (6 mg/24 h or 3 mg/24 h)</td>
<td>86 patients with cognitive impairment</td>
<td>24-week open-label treatment phase offered to patients having completed the 24-week placebo-controlled study above; follow-up with neuropsychological tests</td>
<td>Improvement in a cognitive global score (NPZ-B: $p = 0.03$) and in psychomotor ($p &lt; 0.01$), fine motor/nonverbal ($p = 0.02$) and frontal system ($p &lt; 0.01$) function domains</td>
<td>[77,78]</td>
</tr>
</tbody>
</table>
# HAND treatment trials

<table>
<thead>
<tr>
<th><strong>Antiapoptotic drugs</strong></th>
<th>8 patients with cognitive impairment</th>
<th>Single-arm, open-label 12-week pilot study; follow-up with neuropsychological tests</th>
<th>Improvement in a clinical global deficit score (p = 0.008) [80]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium (300 mg 2-times/day)</td>
<td>13 patients with cognitive impairment</td>
<td>10-week open-label study; follow-up with neuropsychological tests and MRI (MRS, diffusion tensor imaging and functional MRI)</td>
<td>No change in cognitive performance; changes in MRS metabolite ratios in the frontal gray matter, suggestive of improvement (p &lt; 0.03) [81]</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>41 patients with mild-to-severe AIDS dementia complex or HIV-associated neuropathy</td>
<td>Phase I and Phase II trial, 16-week placebo-controlled study; follow-up with neuropsychological tests</td>
<td>No significant cognitive change; only a trend for an improvement on the higher dose [82]</td>
</tr>
<tr>
<td><strong>CCR5 antagonists</strong></td>
<td>215 patients with cognitive impairment</td>
<td>6-month double-blind, placebo-controlled trial; follow-up with neuropsychological tests</td>
<td>No cognitive benefit [83]</td>
</tr>
<tr>
<td><strong>PAF antagonists</strong></td>
<td>30 patients with cognitive impairment</td>
<td>10-week randomized, placebo-controlled trial; follow-up with neuropsychological tests</td>
<td>Only a trend toward cognitive improvement, especially for verbal memory [84]</td>
</tr>
<tr>
<td><strong>TNF antagonists</strong></td>
<td>64 patients with cognitive impairment</td>
<td>10-week randomized, double blind, placebo-controlled trial; follow-up with neuropsychological tests</td>
<td>No cognitive benefit, except for a slight improvement in motor function on higher doses (p = 0.01) [85]</td>
</tr>
</tbody>
</table>

cART: Combination antiretroviral therapy; MRS: Magnetic resonance spectroscopy; NMDA: N-methyl-d-aspartate; NPZ-8: Neuropsychological composite z-score of eight cognitive subtests.
Table 2. Review of studies that have assessed the efficacy of neuroprotective drugs (cont.).

<table>
<thead>
<tr>
<th>Agents</th>
<th>Sample</th>
<th>Design</th>
<th>Main findings</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NMDA antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine (40 mg/day)</td>
<td>140 patients with mild-to-severe AIDS dementia complex on stable cART</td>
<td>16-week Phase II randomized, double-blind, placebo-controlled trial; follow-up with neuropsychological tests and MRS</td>
<td>No cognitive benefit; increase in the NMDA:creatinine ratio in the frontal white matter (p = 0.04) and parietal cortex (p = 0.02) on MRS</td>
<td>[86]</td>
</tr>
<tr>
<td>Memantine (40 mg/day)</td>
<td>99 patients with mild-to-severe AIDS dementia complex on stable cART</td>
<td>Up to 60-week open-label treatment phase offered to patients having completed the 16-week placebo-controlled study above [86]; follow-up with neuropsychological tests</td>
<td>Cognitive improvement at week 12 for patients randomized to memantine in previous study as compared with those randomized to placebo. No benefit during the 48-week extension</td>
<td>[86,87]</td>
</tr>
</tbody>
</table>
Review Article

HIV-Associated Neurocognitive Disorders: The Relationship of HIV Infection with Physical and Social Comorbidities

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**FIGURE 1:** Neurocognitive disorders: role of HIV infection, comorbidities, and assessments.
## AD & HAND similarities

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evolution</td>
<td>Chronic, progressive, incurable</td>
</tr>
<tr>
<td>Coexistence of other causes/morbid factors</td>
<td>Vascular disease, aging, psychological and social factors</td>
</tr>
<tr>
<td>Brain volume</td>
<td>Progressive brain atrophy</td>
</tr>
<tr>
<td>Pathogenic mechanisms</td>
<td>Neuronal apoptosis, involvement of microglia, neuroexcitotoxicity</td>
</tr>
<tr>
<td>Pathology</td>
<td>A-beta deposition and tau hyperphosphorylation (in HAND mainly in ApoE4 positive)</td>
</tr>
</tbody>
</table>
## AD & HAND differences

<table>
<thead>
<tr>
<th>Criterion</th>
<th>AD</th>
<th>HAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious etiology</td>
<td>Some data – however improbable</td>
<td>Certain</td>
</tr>
<tr>
<td>BBB alteration</td>
<td>Certain</td>
<td>Unclear</td>
</tr>
<tr>
<td>Associated brain vascular disease</td>
<td>The rule (amyloid angiopathy but atheromatosis as well)</td>
<td>Might be, but not a rule</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Subacute</td>
</tr>
<tr>
<td>Neuropsychological testing</td>
<td>Many tests</td>
<td>Not enough tested</td>
</tr>
<tr>
<td>Type of cognitive deficit</td>
<td>Amnestic type</td>
<td>Different type, executive, attention deficit, including behavior</td>
</tr>
<tr>
<td>Imagery</td>
<td>More evident atrophy (enthorinal cortex, hippocampus, temporal lobe)</td>
<td>Different imagery changes (atrophy of anterior cingulate, primary motor and sensory cortex)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Symptomatic</td>
<td>Etiologic (Anti-retroviral)</td>
</tr>
<tr>
<td></td>
<td>Cholinesterase inhibitors efficacious</td>
<td>Rivastigmine might have an effect</td>
</tr>
</tbody>
</table>
Conclusions

• At a clinical level, differentials is relatively easy
• Whenever it might be HAND we should test
• Imagery is different (no evident atrophy in HAND)
• Comorbidities are a rule in both AD and HAND
• Pathogenic mechanisms are in part similar, interestingly
• ART is essential for limiting HAND
• Symptomatic treatment works in AD, might work in HAND
Thank you!

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