HIV and the Central Nervous System: neurocognitive aspects

VIH y Sistema Nervioso Central: aspectos neurocognitivos

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HIV - Myelopathy
HIV-ass. Dementia
ANCE + MNCD
Pathophysiology of CNS infection by HIV (Kaul et al., 2001)
HIV-1-associated dementia

**symptoms:**
- motor impairment
- cognitive deficits
- personality changes
- depression
HIV-Dementia-Scale (Power et al., 1995)

- Memory:
  Try to remember four words (cat, trousers, yellow, banana).
- Attention:
  antisaccadic eye movements (20 commands)
- Psychomotor velocity (measurement):
  Write down the alphabet in capital letters!
- Memory:
  Which are the four words you were asked to remember?
- Construction:
  Copy the cube as fast as you can!
For isometric force measurement the patient’s index finger is fixed with its middle and endphalange in a plastic ring of variable diameter, which is connected to a force transducer (KD-45-20 with double bars and resistive DMS, ME-technical systems, Hennigsdorf / Berlin). The patient is asked to respond as fast as possible with an index finger extension to an acoustical signal of 50 ms duration. In an off-line analysis reaction time = RT (time span between the beginning of the acoustical signal and the contraction) and contraction time = CT (time span between the beginning of the contraction and its maximum), as well as force amplitude (AM) and the rate of rise of tension (RRT=AM/RT) are calculated.
Fine Motor Testing

- Most Rapid Index Finger Extensions (MRC):
  - Reaction time (RT)
  - Contraction time (CT)
Stroop Colour Test

rot = red
grün = green
gelb = yellow
blau = blue
Pattern of HIV-associated neuropsychological Deficits

HIV Neurobehavioral research center (HNRC), San Diego, USA
Impairment of all day’s living by HIV

HIV Neurobehavioral research center (HNRC), San Diego, USA
MRT-Study

n = 743/2346  Age: 39.39 ± 10.34 a  Sex: ♂=677  ♀=66  Duration of infection: 3.76 ± 3.62

Symptoms:
- Focal neurol. deficits n=206  ⇒ Opp. infection
- cognitive/motor deficits n=160  ⇒ HAD
- Headach, unspecific complaints n=422  ⇒ unsuspicious

Viral load (plasma):
- <1.000 n=644
- 1.000 - >10.000 n=36
- >10.000 n=63

Drugs:
- w/o therapy n=304
- monotherapy n=240
- Dual combination n=65
- HAART n=134
**PET-Study**

<table>
<thead>
<tr>
<th>n = 15</th>
<th>Age: 42 ± 11 a</th>
<th>Sex: ♂</th>
<th>Duration of infection: 4.8 ± 4.3 a</th>
</tr>
</thead>
</table>

**Symptoms:** minor motor deficits (MMD)

**Viral load:**
- < LOD  n=5
- <1.000  n=1
- 1.000-10.000  n=1
- 10.000-30.000  n=4

**Drugs:**
- wW/o drugs  n=3
- NRTIs  n=7
- HAART  n=9
Possible time-line of motor defects in HIV-patients

Phase 1: Normal, metabolic and electrophysiological function
Phase 2: Elevated viral load. Penetration of HIV in basal ganglia; elevated blood flow and hypermetabolism, compensation of electrophysiological deficits
Phase 3: Secondary hypometabolism and beginning of clinical deficits; beginning glial proliferation
Phase 4: Progression of phase-3 modifications and beginning neuronal death
# MRS-Study

**n = 32**

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex: ♂</th>
<th>Duration of infection:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>43.1 ± 11.1 a</td>
<td></td>
<td>a) 7.8 ± 5.6 a</td>
</tr>
<tr>
<td>b)</td>
<td>38.2 ± 5.4 a</td>
<td></td>
<td>b) 8.3 ± 6.1 a</td>
</tr>
<tr>
<td>c)</td>
<td>43.4 ± 10.4 a</td>
<td></td>
<td>c) 5.5 ± 4.5 a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms:</th>
<th>n=10</th>
<th>n=8</th>
<th>n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) asymptomatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) ANI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) MMD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Viral load:</th>
<th>n=5</th>
<th>n=1</th>
<th>n=1</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) 1.000 - &gt;30.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) 1.000 - &gt;30.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) 1.000 - 10.000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs:</th>
<th>N=6</th>
<th>n=2</th>
<th>n=13</th>
<th>n=1</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) HAART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) HAART w/o</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) NRTIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) No thearpy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Kernspinspectroscopy (MRS)
## Pathological results (percent of the study population) detected in the first ever recorded contraction-test

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal population</td>
<td>0.0%</td>
</tr>
<tr>
<td>Manifest</td>
<td>77.9%</td>
</tr>
<tr>
<td>No test</td>
<td>41.2%</td>
</tr>
<tr>
<td>Gene detected</td>
<td>16.7%</td>
</tr>
<tr>
<td>Gene not detected</td>
<td>30.8%</td>
</tr>
<tr>
<td>HAART</td>
<td>35.7%</td>
</tr>
<tr>
<td>No HAART</td>
<td>31.2%</td>
</tr>
<tr>
<td>HIV</td>
<td>91.0%</td>
</tr>
<tr>
<td>Chorea Huntington</td>
<td></td>
</tr>
</tbody>
</table>

### Contraction analysis in Chorea-Huntington and HIV-1-positive male adults against the healthy population
In 2004 American and Australian studies described changes in the clinical presentation of HIV-1-associated dementia.

As possible causes have been discussed:

- Hormonal deficits
- Mitochondrial toxicity of highly active antiretroviral medication (HAART)
- Neprilysin-inhibition by „tat“
New Aspects of HIV-associated CNS Disease in the HAART-Era

- changed phenotype: less severe dementia cases, more mild cognitive deficits
- neuropathology: neuronal cell death, gliosis, microglia-activation, persistent synapo-dendritic damage (proteosomics)
- in long-term survivors chronic immune activation (CCL3L1; MIP1alpha), during physiological aging, deposition of abnormal proteins in the brain
- rising importance of co-factors and co-morbidities, e.g., metabolic disturbances (insulin resistance), hypertension, alcohol and drug abuse, viral co-infections (HCV), mitochondrial toxicity of HAART
ANI = asymptomatic HIV-1-associated, neurocognitive impairment

1. **Acquired deficits in cognitive performance** (verbal fluency, executive functions, speed of information processing, attention, working memory, verbal and visual learning, visual information processing); results of at least 2 **standardised tests range outside one standard deviation**.

2. Deficits do **not** affect all days’ living.

3. Deficits persist more than one month.

4. Other reasons for ANI have been excluded, i.e., there should be no severe depression, psychosis and no active drug and alcohol abuse.
MNCD = HIV-1-associated, mild neurocognitive deficits

1. Results of at least two standardised tests range outside one standard deviation.

2. The cognitive deficits affect all days’ living.
   i. Patients complain of reduced intellectual capacity, inefficiency in their profession + at home as well as of difficulties in social interaction
   ii. Confirmation or primary report of the above mentioned deficits by the patients’ family and/or partner

3. The deficits persist more than one month.

4. Other causes for the symptoms have been excluded (psychiatric diseases, drug and/or alcohol abuse).
ANI and MNCD

Should clinical and/or neuropsychological improvement occur, the term „in remission“ is added to ANI/MNCD.
HAD = HIV-associated dementia

1. Marked cognitive impairment in at least two neuropsychological tests in different cognitive functions; test results have to range outside two standard deviations.

2. All days’ living can not be managed without support.

3. The deficits persist more than one month.

4. Other causes have been excluded.
In diagnosing ANI, MNCD and HAD the following interfering variables have to be taken into account:

**Primary variables:**
- age
- hepatitis C-co-infection
- vascular or Alzheimer’s dementia
- psychiatric co-morbidity
- severe head trauma

**Secondary variables:**
- drug and/or alcohol abuse
- opportunistic cerebral infections
Arendt et al., JNV, 2007
### Correlations with CSF-VL (log)

<table>
<thead>
<tr>
<th></th>
<th>Log_{10} VL blood</th>
<th>CSF: cells</th>
<th>CSF: protein</th>
<th>CSF: lactate</th>
<th>IgG-Index</th>
<th>CD4 count</th>
<th>HIV-duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL CSF &gt; VL Plasma</td>
<td>Log_{10} VL CSF</td>
<td>0.890</td>
<td>0.618</td>
<td>0.643</td>
<td>0.416</td>
<td>0.629</td>
<td>-0.459</td>
</tr>
<tr>
<td>VL Plasma &gt; VL CSF</td>
<td>Log_{10} VL CSF</td>
<td>0.789</td>
<td>0.476</td>
<td>0.289</td>
<td>0.160</td>
<td>0.381</td>
<td>-0.197</td>
</tr>
</tbody>
</table>

### Correlations with CSF-VL (log)

<table>
<thead>
<tr>
<th></th>
<th>CSF: MCP1</th>
<th>CSF: Gal3</th>
<th>CT right hand</th>
<th>CT left hand</th>
<th>HIV-demen. scale</th>
<th>GPT: domin. hand</th>
<th>GPT: non-domin. hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL CSF &gt; VL Plasma</td>
<td>Log_{10} VL CSF</td>
<td>0.791</td>
<td>0.503</td>
<td>-0.111</td>
<td>0.047</td>
<td>0.049</td>
<td>-0.191</td>
</tr>
<tr>
<td>VL Plasma &gt; VL CSF</td>
<td>Log_{10} VL CSF</td>
<td>0.270</td>
<td>0.287</td>
<td>-0.229</td>
<td>-0.273</td>
<td>-0.245</td>
<td>0.551</td>
</tr>
</tbody>
</table>
Cytokine-Array

Here’s how it works:

Array support
Cocktail of Biotin-Ab
Labeled streptavidin

Sample
Incubation of Sample With arrayed antibody Supports
Incubation with Biotinylated Ab
Incubation with Labeled streptavidin

1-2 hrs
1-2 hrs
2 hrs

Detection of signals
Data analysis and graph

Positive Control
CXCL16
MCP-1
TIMP-1
TIMP-2
MMP-3
Biomarkers with relevance for HIV-associated CNS-disease

- Viral load in cerebrospinal fluid (CSF)
- Markers for oxidative stress (ceramide + DNA-metabolites)
- CXCL12 (SDF1) as protective marker
- Neurofilament light-chain-protein – marker for axonal degeneration
- Sialoadhesin as a marker for HIV-CNS-penetration
- Genotyp of the host: CCL3L1
- Mitochondrial haplotypes T42/6
HAART 2008

NRTIs (*Nukleoside-/Nukleotide-Reverse-Transcriptase-Inhibitors*)
- Zidovudine AZT (Retrovir®)
- Lamivudine 3TC (Epivir®)
- AZT + 3TC (Combivir®)
- Abacavir ABC (Ziagen®)
- AZT + 3TC + ABC (Trizivir®)
- 3TC + ABC (Kivexa®)
- Didanosine ddI (Videx®)
- Zalcitabine ddC (Hivid®)
- Stavudine d4T (Zerit®)
- Tenofovir TDF (Viread®)
- Emtricitabine FTC (Emtriva®)
- FTC + TDF (Truvada®)
- FTC + TDF + EFV (Atripla ®)

NNRTIs (*Non-Nukleoside-Reverse-Transcriptase-Inhibitors*)
- Nevirapine NVP (Viramune®)
- Efavirenz EFV (Sustiva®)
- Delavirdine DLV (Rescriptor®)
- Etravirine (Intensce ®)

PIs (*Protease-Inhibitors*)
- Saquinavir SQV (Invirase500®)
- Indinavir IDV (Crixivan®)
- Nelfinavir NLV (Viracept®)
- Ritonavir RTV (Norvir®)
- Fosamprenavir APV (Telzir®)
- Lopinavir/Ritonavir LPV/r (Kaletra®)
- Atazanavir ATV (Reyataz®)
- Tipranavir TPV (Aptivus®)
- Darunavir (Prezista ®)

Fusion-Inhibitors
- Enfurvirtide T20 (Fuzeon ®)

Integrase-Inhibitors
- Raltegravir (Isentress)
- GS-9137 (Phase I)

Maturation-inhibitors

CCR5-Antagonists
- Maraviroc (Celsentri)
CSF penetration

CHARTER study

- 347 patients on ART; plasma and CSF probes
- Antiretrovirals will be assigned to penetration rates (0; 0.5, 1) based on literature research
- High penetration scores are positively correlated to low viral load in CSF
- The correlation does not depend on plasma-VL, duration of therapy and kind of drugs

Letendre et al., CROI 2006
New therapies with potential CNS-effectivity

- erythropoetine
- MCP-1-activating substances
- MDR-modulators
- lithium (to date proven effectivity in animal studies + *in-vitro*)
- minocycline
- cytokine-antagonists
Cofactors and Comorbidities

- Age
- Vascular disease
- Mitochondrial toxicity of HAART
- Psychiatric disease (esp. depression and drug abuse)
- Hepatitis virus C Coinfection
- Neurosyphilis
Depression negatively influences therapy adherence!
Drugs frequently used by HIV-positive patients worldwide

- Alcohol
- Cannabis (-derivatives)
- Amphetamine (-derivatives)
- Heroine
Alcohol effect in HIV-infection

**Alcohol**
- stimulates HIV-replication in infected cells
- influences cytokin-synthesis
- decreases CD8+-cell count
- decreases immune function (f.ex. macrophage function)
- increases permeability of the blood brain barrier
- has synergistic effects with neurotoxic HIV-proteins (inhibits N-methyl-D-aspartate-NMDA-receptor function as well as Na+/Ca++-exchange among others)
Mechanism of cannabis action in CNS

nerve terminal

Na\(^+\) channel

MAP kinase

krox 24

nucleus

tetrahydrocannabinol (\(\Delta^2\)-THC)

the active ingredient of cannabis

Cannabinoid CBL receptor

N and P/Q type voltage dependent Ca\(^{2+}\) channel

inwardly rectifying K\(^+\) channel

A-type K\(^+\) channel

phosphorylation

ATP

adenylate cyclase

cAMP

synaptic cleft
Cannabis and derivatives

- Negative influence on cognition
- Negative influence on the immune system
- Important in AIDS-defined patients
Action of amphetamines within CNS
Methamphetamine

- Increases neuronal damage
- Elevates the risk of developing neuropsychological deficits in HIV(+) patients
- Proven, selective damage of dopaminergic neurons esp. of the basal ganglia in animal studies
- Seems to be especially dangerous for HIV/HCV-co-infected patients
- Mitochondrial toxicity in combination with HIV-tat
Methamphetamine

- provokes neuronal damage
- increases the risk of neuropsychological deficits in HIV-patients
- leads in animal studies to selective damage of dopaminergic neurons in the basal ganglia
- is especially dangerous in HIV-HCV-co-infected patients
- acts synergistically with HIV-tat with respect to mitochondrial toxicity
Action of heroine within the CNS
Methadone substituted HIV(+) patients showed extremely bad results in neuropsychological test batteries!

Rodriuez Salgado D, Rodriuez Alvarez M, Seoane Pesqueira G.
Pain: Tractus spinothalamicus

(c) Lateral Spinothalamic tracts

Sensory homunculus of left cerebral hemisphere

Axon of first-order neuron

Second-order neuron

MESENCEPHALON

Lateral spinothalamic tract

MEDULLA OBLONGATA

SPINAL CORD

Pain and temperature sensations from right side of body
Pain sensations in HIV-positive individuals

- Headache
- Neuropathic pain
- Pain in muscles
- Skeletal pain
- Ubiquous pain
- Postherpetic neuralgia
Diffuse nociception

**Poteaseinhibitors**

- Saquinavir SQV (Invirase® 500®)
- Indinavir IDV (Crixivan®)
- Nelfinavir NLV (Viracept®)
- Ritonavir RTV (Norvir®)
- Fosamprenavir APV (Telzir®)
- Lopinavir/Ritonavir LPV/r (Kaletra®)
- Atazanavir ATV (Reyataz®)
- Tipranavir TPV (Aptivus®)
- Darunavir DRV (Prezista®)