Cerebrospinal Fluid HIV-RNA and Neurocognitive Deficits:
Are Lumbar Punctures Needed in Impaired Subjects with Undetectable Plasma Viral Load?


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Department of Medical Sciences,
University of Torino, Torino
No Conflicts of Interest to Declare
When is Lumbar Puncture indicated?

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Symptomatic neurocognitive disorders</td>
<td></td>
<td>Self/relatives complaining cognitive problems without obvious confounding conditions</td>
<td>Patients stable on ART with plasmatic Low-Level Viremia</td>
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<tr>
<td>On-cART patients with CVE and HAND or other neurological signs/symptoms</td>
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Table 1. Fourteen Key Clinical Questions That Were Identified and Addressed During the International Program

1. Which patients should be screened for HAND, and when? How often should patients be screened?
2. How can physicians identify patients at greater risk of HAND?
3. Which tools should be used to screen for HAND?
4. Which comorbidities should be considered in a patient with HAND?
5. How can HAND be differentiated from neurodegenerative diseases in older patients?
6. How should neuropsychological testing be approached in the diagnosis of HAND?
7. In addition to cognitive testing, which other assessments should be used in the diagnosis of HAND (e.g., psychiatric assessment, lumbar puncture/CSF analysis, imaging, exclusion of other pathologies)?
8. What is the role of lumbar puncture/CSF analysis in the management of HAND, and when should it be performed?
9. When, and how often, should neurocognitive performance be reviewed in patients who have been diagnosed with HAND?
10. What is the natural history of ANI and MND, and how should this impact patient management?
11. What interventions should be considered in treated patients with persistent or worsening NCI and CSF viral load <50 copies/mL (nondetectable)? Should the ARV be changed when the virus is not detectable in the CSF?
12. What is the risk of ARV-related neurotoxicity? What should be done if ARV neurotoxicity is suspected?
13. When/how should pharmacological agents other than ARV be used in the management of HAND?
14. What can be done to prevent HAND?
“A Specter is haunting Europe…”

Multicenter European Prevalence Study of Neurocognitive Impairment and Associated Factors in HIV Positive Patients

- Cross-sectional
- 448 HIV-positive patients
- London, Copenhagen, Minsk, Rome
- NCI was defined as a normalized Z score <= -1 in at least 2 out of 5 cognitive domains
- Mean age was 45.8 years, 84% male, 87% white, 56% university educated
- Median CD4 count 550 cells/mm3, 89% on cART

<table>
<thead>
<tr>
<th>HAND</th>
<th>% Overall Study Sample</th>
<th>% of pts Without Confounding Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall NCI</td>
<td>35%</td>
<td>31.8%</td>
</tr>
<tr>
<td>Overall HAND</td>
<td>26.1%</td>
<td>31.9%</td>
</tr>
<tr>
<td>ANI</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>MND</td>
<td>4.9%</td>
<td>6%</td>
</tr>
<tr>
<td>HAD</td>
<td>0.9%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
Peripheral Control and HAND

- Pérez-Valero et al. reported proportions of NC decline of 15%, 18.5%, 22.3% and 26% for HIV-negative, always suppressed, sometimes suppressed and always detectable HIV-positive patients, respectively. Comparing to HIV-negative subjects, higher rates of NC decline were detected in HIV-positive patients always detectable in plasma.

- Nightingale et al. reported an 18% vs 0% of patients with CSF/plasma discordance between patients with low level plasma viremia and those with durable plasma suppression.

No significant difference in terms of cognitive symptoms, International HIV Dementia Scale score, functional impairment on the Instrumental Activities of Daily Living scale, or anxiety and depression testing.
Does Escape matter?

- Cerebrospinal fluid HIV escape (CVE) and residual CSF replication (RCR) have been described in approximately 10% and 12-42% of adequately treated patients, respectively.

<table>
<thead>
<tr>
<th>CVE</th>
<th>Pathophysiology</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Asymptomatic CVE</td>
<td>CSF blips</td>
<td>19.1/1000/year</td>
</tr>
<tr>
<td></td>
<td>Persistent (virological failure, compartementalization)</td>
<td>9.8/1000/year</td>
</tr>
<tr>
<td></td>
<td>Slow suppression</td>
<td>8.5/1000/year</td>
</tr>
<tr>
<td>Neurosymptomatic CVE</td>
<td>Virological failure</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Compartmentalization</td>
<td></td>
</tr>
<tr>
<td>Secondary CVE</td>
<td>Replication related to another infection with inflammation</td>
<td>Few reports</td>
</tr>
</tbody>
</table>

Kugathasan R et al, CID 2017  
Eden A et al, JID, 2010  
Anderson AM et al, JID, 2017  
Perez Valero, 6° Symposium on HIV and Psychiatry, 2013
Occasional low-level CSF HIV-RNA in 36% of patients

The presence of quantifiable virus correlated with CSF immune activation, but no with neuronal damage

None of the cases progressed to clinically symptomatic disease

In the vast majority of cases, **CSF virus likely represented a benign CSF viral blip**

Low-level CSF HIV-RNA is common during suppressive ART: 42.3%
AIMS OF THE STUDY

1. To assess the prevalence of RCR among patients with neurocognitive impairment

2. To assess whether RCR is associated with ongoing intrathecal inflammation
MATERIALS AND METHODS

Inclusion Criteria:
- Age ≥ 18 years old
- Naïve or treated patients complaining of neurological or cognitive disturbances and receiving a lumbar puncture and a complete cognitive assessment within 12 months apart

Exclusion Criteria:
- Patients with CNS opportunistic infections, neoplastic, traumatic, vascular or neurodegenerative disorders
- Active drug or alcohol abuse (within 6 months apart)
- A Beck depression inventory score (BDI-II) ≥30
- An Hamilton Anxiety Rating Scale (HAM-A) score ≥ 30
MATERIALS AND METHODS

- We recorded:
  - **Immunovirological and epidemiological data**
  - **CSF and plasma HIV-RNA** were quantified using PCR CAP/CTM v.2 assay (CAP/CTM, Roche Molecular System, Branchburg, NJ, **detection limit: 20 copies/mL**)
  - **CSF biomarkers**: tau, p-tau, neopterin, S100beta (ELISA), Tourtellotte index and CSF-serum albumin ratio (CSAR) (Immunoturbidimetric methods)

- **RCR** was defined as CSF HIV-RNA 1 Log10 greater than the corresponding plasma viremia or >20 cp/mL if plasma HIV RNA <20 copies/mL or as any case of CSF HIV-RNA between 1-19 cp/mL in the presence of TND in plasma

- **HAND** diagnosis was made according to **Frascati criteria** through a neurocognitive battery assessing 8 cognitive domains

- Variables are described as median (interquartile range) and analyzed through non-parametric tests
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Enrolled population (n=100)</th>
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<tbody>
<tr>
<td>Female</td>
<td>25 (25%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>47 (41-54)</td>
</tr>
<tr>
<td>Educational level, years</td>
<td>8 (8-13)</td>
</tr>
<tr>
<td>Risk factors:</td>
<td></td>
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<tr>
<td>MSM</td>
<td>46 (46%)</td>
</tr>
<tr>
<td>Previous IDU</td>
<td>29 (29%)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (25%)</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>93 (93%)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Hepatitis coinfection</td>
<td>27 (27%)</td>
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<tr>
<td>Naive</td>
<td>45 (45%)</td>
</tr>
<tr>
<td>Plasma VL &lt;20 cp/mL, patients</td>
<td>32 (32%)</td>
</tr>
<tr>
<td>Duration of suppression, months</td>
<td>31 (6.5-74.1)</td>
</tr>
<tr>
<td>Plasma HIV-RNA, ( \log_{10} ) cp/mL</td>
<td>5.13 (2.72-5.74)</td>
</tr>
<tr>
<td>CD4+ T cell count, cell/mmc</td>
<td>110 (41-398)</td>
</tr>
<tr>
<td>CD4+ nadir, cell/mmc</td>
<td>67 (24-143)</td>
</tr>
<tr>
<td>Type of HAART:</td>
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<tr>
<td>NNRTIs</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td>PIs</td>
<td>22 (40%)</td>
</tr>
<tr>
<td>INSTIs</td>
<td>8 (14.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (32.7%)</td>
</tr>
<tr>
<td>CPE score</td>
<td>7 (6-8)</td>
</tr>
</tbody>
</table>

- HAND were diagnosed in 40 patients (40%):
  - 27 ANI
  - 11 MND
  - 2 HAD
  - 34 patients presented neurocognitive deficits not fulfilling Frascati criteria

Total=100

- 26% Normal
- 27% ANI
- 11% MND
- 2% HAD
- 34% Deficit
RESULTS - 1

- CVE was observed in 8 subjects (8%):
  - 7 in treated and suppressed (TS) patients (21.9%)
  - 1 in treated and non suppressed (TnS) individuals (4.3%)

- CVE was marginally more common in neurocognitive impaired versus not impaired patients among both:
  - TS subjects (28% vs. 0%, p=0.3)
  - TnS subjects (5.3% vs 0%, p=0.9)
Among TS patients, a higher prevalence of detectable CSF HIV RNA was observed in subjects with NC deficits compared to those without any cognitive impairment (14/25, 56% vs 0/7, 0%; p 0.0073)

Between TS patients with and without NC deficits no differences in terms of:
- CPE score: no deficit 7 (7-7) vs deficit 6.5 (6-8), p= 0.341
- Current CD4 T cell count: no deficit 356 (120-825) vs deficit 441 (164-784), p=0.804
- CD4 nadir: no deficit 21 (11-493) vs deficit 120 (37-197), p=0.316
Among TS patients, RCR was significantly associated with higher values of CSF S100beta (135 pg/mL vs 84 pg/mL), Tourtelotte index (5.5 vs 0) and CSAR (6.2 vs 3.9).

No difference in terms of tau, ptau and neopterin
LIMITATIONS

- Cross-Sectional Retrospective study
- Lack of longitudinal analysis; we couldn’t differentiate CSF blips from persistent CSF escape
- Small Sample Size
- Definition of RCR
- Limit of detection of the assay we used
- Lack of data regarding patient compliance with HAART therapy
- Risk of overestimating NC deficit due to our large battery and inclusion of NC impairment not fulfilling Frascati criteria
CONCLUSIONS

- **CVE** was found to be **more common in neurocognitive impaired** versus not impaired patients, although not statistically significant.

- Among TS patients:
  - we described a statistically significant **higher prevalence of RCR in subjects with neurocognitive deficits** compared to those without any cognitive impairment.
  - **RCR** was **associated with** evidence of **BBB impairment, neuroinflammation and astrocytosis**, in accordance with Nightingale S et al. (Cytokine, 2016) and Edén A et al. (JID, 2016)
These findings support the need to improve understanding of the mechanisms of CNS injury in the cART era and of the clinical management of RCR.

The NC decline in TS patients may be explained by:

- A detrimental role for RCR in terms of NC performance due to BBB impairment, astrocytosis and persistent neuroinflammation:

- The Legacy Effect:

\[
\text{Residual CSF Replication} \rightarrow \text{CNS Damage} \rightarrow \text{HAND}
\]

\[
\text{No HAART} \quad \begin{array}{c}
\text{Immunological impairment} \\
\text{& Sanctuary damages}
\end{array} \rightarrow \begin{array}{c}
\text{HAART} \\
\text{Residual immune impairment} \\
\text{Irreversible CNS damage} \\
\end{array} \rightarrow \begin{array}{c}
\text{RCR} \\
\text{HAND}
\end{array}
\]
DISCUSSION

- Despite the lack of consensus on the management of RCR, the higher prevalence of such a condition in TS patients with NC deficits would prompt towards the **indication for lumbar puncture in suppressed patients with neurocognitive deficits**, if confirmed on larger longitudinal cohorts.

- Further studies should evaluate the **prevalence of neurocognitive deficits not fulfilling Frascati criteria** among HIV-positive patients and should assess their role in the evolving spectrum of HAND:
  - Are they meaningful or the result of an inherent overestimation of the available diagnostic tools?
  - Should they be considered as a prior step to ANI?

- Among the patients with an initial diagnosis of neuropsychological deficit not fulfilling Frascati criteria 29% evolved towards ANI and 16% towards MND.

- The majority of patients newly diagnosed with HAND came from the subgroup of patients with neuropsychological deficit not fulfilling Frascati criteria.

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Vassallo M et al, AIDS, 2014
Thank you for your attention

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