The Relationship Between Amnestic Mild Cognitive Impairment and Biomarkers of Inflammation Among Adults Living with HIV

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Background

- People living with HIV (PLHIV) may be at greater risk for age-related neurodegenerative disorders such as Alzheimer’s disease dementia and its precursor, amnestic mild cognitive impairment (aMCI).
- aMCI is associated with cognitive and functional decline whereas HIV-associated neurocognitive disorder (HAND) is relatively stable.
- Aging, aMCI and HIV-infection are all associated with increased chronic, low-grade inflammation
  
  » May be a mechanism underlying the increased risk for aMCI among PLHIV, particularly older PLHIV
Memory impairment in HAND is common; therefore, it is hard to distinguish HAND and aMCI

**Differences:**

- HIV-infection is thought to affect frontal and subcortical structures.
  - Memory recall is impaired but recognition is intact
- aMCI is characterized by hippocampal dysfunction & atrophy
  - Memory recall and recognition are both impaired
aMCI Criteria Adapted for PLHIV

- Adapted Jak/Bondi Criteria for aMCI in PLHIV (Bondi et al., 2014; Jak et al. 2009, Sundermann et al. 2018)
  - >-1.0 SD below demographically-corrected normative mean on 2 of 4 memory measures (HVLT-R and BVMT-R recall and recognition)
    - Adaptation: at least one memory test must be recognition
  - aMCI Dx (with or without HAND) is associated with a greater prevalence of amyloid beta in the brains of HIV+ cases

Sundermann et al. (2018)
Aims and Hypotheses

- **Aim 1:** To examine the relationship between age and odds of aMCI
  
  » Hypothesis: Age will relate to greater likelihood of aMCI in PLHIV

- **Aim 2:** To examine how plasma markers of inflammation are associated with group and age
  
  » Hypothesis: A aMCI group x age interaction will indicate plasma biomarkers of inflammation will be highest in older PLHIV with aMCI
Participants & Methods

- 244 persons living with HIV
- Exclusions:
  - Not on antiretroviral therapy
  - Detectable viral load (<50 copies/mL plasma)
  - Current substance use disorder
  - Low premorbid IQ (WRAT<70)
- Plasma inflammation biomarkers measured with immunoassay, adjusted for batch effects, and log-transformed:
  - Tumor necrosis factor-α (TNF-α)
  - Monocyte Chemoattractant Protein-1 (MCP-1)
  - Interleukin-6 (IL-6)
Participant Groups

244 Participants

Meets aMCI criteria?

No

aMCI-

Meets Frascati HAND criteria?

No

HAND-/aMCI-

Yes

aMCI+

(78% with HAND)

Yes

HAND+/ aMCI-

Number of Participants

HAND-/aMCI- 93
HAND+/aMCI- 66
aMCI+ 19

HAND- aMCI- 66
HAND+ aMCI- 66
aMCI+ 19
<table>
<thead>
<tr>
<th>Demographics</th>
<th>HAND-/aMCI- (n=93)</th>
<th>HAND+/aMCI- (n=66)</th>
<th>aMCI+ (n=85)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.4 (9.1)</td>
<td>48.2 (9.8)</td>
<td>50.7 (9.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>39 (42%)</td>
<td>20 (30%)</td>
<td>42 (49%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>78 (84%)</td>
<td>55 (83%)</td>
<td>78 (92%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Education</td>
<td>14.0 (3.0)</td>
<td>13.5 (2.4)</td>
<td>14.1 (2.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>WRAT</td>
<td>105.2 (12)</td>
<td>99.8 (13)</td>
<td>97.7 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV-Disease Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS Status</td>
<td>56 (60%)</td>
<td>42 (64%)</td>
<td>61 (72%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Duration of Infection</td>
<td>11.8 [5.3–19.2]</td>
<td>13.9 [6.0–19.0]</td>
<td>14.2 [5.6–20.8]</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Age increases likelihood of aMCI among PLHIV

Risk of Impairment Group by Age

- **aMCI+**
  - Odds Ratio: 1.02
  - 95% CI: 0.83, 1.05
  - $p = 0.33$

- **HAND+/aMCI-**
  - Odds Ratio: 1.05
  - 95% CI: 1.01, 1.09
  - $p < 0.01$
Older HIV+/aMCI+ PLHIV demonstrated higher TNF-α levels than younger HIV+/aMCI+ PLHIV when compared to the HAND+/aMCI- group ($p<0.01$).
Older HIV+/aMCI+ PLHIV demonstrated higher MCP-1 levels than younger HIV+/aMCI+ PLHIV when compared to the HAND+/aMCI- group (trend level; \( p=0.08 \)).
The group x age interaction for IL-6 was not significant.
Conclusions

- Some inflammatory biomarkers are more associated with older age in aMCI.
- Inflammation may be a mechanism underlying cognitive decline, particularly aMCI, in the context of HIV.
- More research is warranted to further understand this relationship:
  - Longitudinal studies that also include HIV-uninfected adults that examine cognitive trajectories.
  - Analyze inflammatory biomarker association with biomarkers of Alzheimer's disease.
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