Mechanisms of Neurocognitive Impairment Related to Central Obesity

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Background

• Central obesity and biomarkers of systemic inflammation correlate with cognitive impairment in both HIV+ and HIV- populations.
• Severity of cognitive impairment is associated with increased waist circumference, but not with BMI, in multivariate modeling of the CHARTER metabolic cohort.*
• The mechanisms for this relationship are unknown, but M1 macrophage-mediated inflammation in visceral adipose tissues could play a role.

Overarching hypothesis

In centrally-obese HIV patients who are well-controlled on ART, macrophages in abdominal fat releases mediators that:

- drive systemic inflammation and CNS immune activation, and thereby
- damage the brain and impair cognition.
Obesity inflames visceral fat

Normal adipose tissue  Crown-like structure

M2: “Alternatively Activated”
Anti-inflammatory

M1: “Classically Activated”
Pro-inflammatory
Methods: Patients and Biomarkers

- Cross-sectional study of stored samples from 162 CHARTER patients on ART with HIV plasma VL <1000 copies who were assessed for cognitive impairment (global deficit score = GDS) by the CHARTER NP battery.

- Soluble inflammatory biomarkers were measured in:

  **plasma**
  - IL-6 - Systemic inflammation
  - sCD163 - Monocyte/macrophage activation
  - sCD14 - Monocyte/macrophage activation by LPS

  **CSF**
  - sCD40L - M1 macrophage/microglial phenotype
  - sTNFrII - Pro-inflammatory cytokine
  - MCP-1 - Monocyte chemokine
  - ICAM - Vascular adhesion molecule
  - MMP-9 - Basement membrane integrity
Both waist circumference and IL-6 correlate with cognitive impairment (increased GDS).

**Central Obesity (WC)**

- **Square root of Global Deficit Score** vs **Waist circumference (cm)**

  - Fitted line (with GDS=0)
  - Fitted line (no GDS=0)

<table>
<thead>
<tr>
<th>WC</th>
<th>(n=152)</th>
<th>rho</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.21</td>
<td>0.009</td>
</tr>
</tbody>
</table>

**Systemic Inflammation (log IL-6)**

- **Square root of Global Deficit Score** vs **log IL-6**

  - Fitted line (with GDS=0)
  - Fitted line (no GDS=0)

<table>
<thead>
<tr>
<th>IL-6</th>
<th>(n=152)</th>
<th>rho</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.17</td>
<td>0.04</td>
</tr>
</tbody>
</table>
WC correlates with GDS only in those with the highest tertile (1/3) of IL-6 levels. 

Rho = .07, 

P = .65
IL-6 correlates with GDS only for patients in the highest tertile of WC

<table>
<thead>
<tr>
<th></th>
<th>High Tertile of WC</th>
<th>Low Tertile of WC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-6 vs GDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spearman</strong></td>
<td>0.33</td>
<td>-0.10</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.02</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Difference in slopes: p = 0.03
High IL-6 levels correlated with advancing cognitive impairment (positive GDS slopes) over 3 consecutive annual visits in the highest, but not lowest, IL-6 tertile

<table>
<thead>
<tr>
<th>IL-6 tertile</th>
<th>High</th>
<th>Low</th>
<th>Difference in slopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS slope</td>
<td>Rho = +0.28, P = 0.06</td>
<td>Rho = -0.25, P = 0.11</td>
<td>P = 0.02</td>
</tr>
</tbody>
</table>

Conclusion: Elevated IL-6 appears to mark and/or mediate processes reflecting progression of cognitive impairment.
1) Evaluate complex relationships between predictors, mediators and outcomes

\[
\begin{align*}
\text{Predictor} = WC & \quad \text{Mediator} = \text{Biomarkers} \quad \text{Outcome} = \text{GDS} \\
\beta_1 &= b_1 \\
\beta_2 &= b_2 \\
\beta_3 &= b_3
\end{align*}
\]

2) Models built using regression coefficients

Direct effect: \( \beta_d = \beta_1 \)

Indirect effect: \( \beta_i = \beta_2 \times \beta \)

Total effect: \( \beta = \beta_d + \beta_i = \beta_1 + \beta_2 \times \beta_3 \)

3) Goodness of fit test for the whole model is assessed by p-values with larger p indicating better consistency with data.
Effects of levels of other biomarkers on correlation of IL-6 levels and GDS

<table>
<thead>
<tr>
<th>GDS (SQRT)</th>
<th>High Tertile</th>
<th>Low Tertile</th>
<th>Slope of High vs Low Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCD163</td>
<td>r = 0.31</td>
<td>r = 0.12</td>
<td>P = 0.70</td>
</tr>
<tr>
<td></td>
<td>(p=0.03)</td>
<td>(p=0.42)</td>
<td></td>
</tr>
<tr>
<td>sCD14</td>
<td>r = 0.10</td>
<td>r = 0.18</td>
<td>P = 0.92</td>
</tr>
<tr>
<td></td>
<td>(p=0.50)</td>
<td>(p=0.22)</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>r = 0.10</td>
<td>r = 0.18</td>
<td>P = 0.42</td>
</tr>
<tr>
<td></td>
<td>(p=0.52)</td>
<td>(p=0.22)</td>
<td></td>
</tr>
<tr>
<td>MMP-9</td>
<td>r = 0.10</td>
<td>r = 0.34</td>
<td>P = 0.25</td>
</tr>
<tr>
<td></td>
<td>(p=0.51)</td>
<td>(p=0.01)</td>
<td></td>
</tr>
<tr>
<td>sICAM</td>
<td>r = 0.20</td>
<td>r = 0.22</td>
<td>P = 0.53</td>
</tr>
<tr>
<td></td>
<td>(p=0.18)</td>
<td>(p=0.11)</td>
<td></td>
</tr>
<tr>
<td>sCD40L (CSF)</td>
<td>r = 0.60</td>
<td>r = 0.01</td>
<td>P = 0.09</td>
</tr>
<tr>
<td></td>
<td>(p&lt;0.0001)</td>
<td>(p=0.93)</td>
<td></td>
</tr>
<tr>
<td>sTNFRII</td>
<td>r = 0.08</td>
<td>r = 0.22</td>
<td>P = 0.74</td>
</tr>
<tr>
<td></td>
<td>(p=0.57)</td>
<td>(p=0.12)</td>
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Pathway Model for subgroup with the highest tertile of CSF sCD40L

High tertile sCD40L sub-group

WC → IL-6 → Global Deficit Score

sCD14

Path Model $P = 0.82$
Conclusions

- Inflammation in central fat leads to systemic inflammation and possibly to microglial activation that may mediate neurodegeneration and cognitive impairment.

- Pathway analysis suggests at least two mechanisms – one IL-6 mediated and the other IL-6 independent.

- Therapy for cognitive impairment related to central obesity might target:
  - Reducing central obesity through weight loss, exercise, tesamorelin (a synthetic growth hormone releasing factor), or bariatric surgery, or
  - Anti-inflammatory drugs (eg, NSAIDs, statins, chloroquine)