ALTERED BRAIN FRONTAL WHITE MATTER CELLULAR ENERGY IN CHRONIC HIV INFECTION


1 Neuroscience Research Australia, 2 Centre for Applied Medical Research, St Vincent’s Hospital, UNSW Australia, 3 St. Vincent’s Hospital Imaging Department

HIV-associated Neurocognitive Disorders (HAND)

<table>
<thead>
<tr>
<th></th>
<th>Acquired Impairment in ≥2 Cognitive Abilities</th>
<th>Interferes with Daily Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic Neurocognitive Impairment (ANI)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Mild Neurocognitive Disorder (MND)</td>
<td>YES</td>
<td>MILD</td>
</tr>
<tr>
<td>HIV-Associated Dementia (HAD)</td>
<td>MARKED</td>
<td>MARKED</td>
</tr>
</tbody>
</table>

No Dementia

Dementia

Disclosures

- This project was supported in part by NHMRC project grant ID568746, NHMRC Career Development Fellowship APP1045400 and Abbvie research grant which funded the acquisition of follow-up MRIs (CIA Cysique).
- BJB has received research funding, consultancy fees, and lecture and travel sponsorships from Gilead Sciences, ViiV Healthcare, and MSD.
- LAC has received research support from MSD, Abbvie, Gilead Sciences, and ViiVhealthcare. LAC has received honoraria from Abbvie and ViiVHealthcare.

Background

Long-term brain neurochemical changes are not clearly understood in HIV-infected adults who are aging and are otherwise clinically stable.

Early diagnosis of HAND can help identify individuals at risk for dementia and cognitive impairment. The HIV Neuroimaging Consortium has shown that decreased N-acetylaspartate (NAA) and increased myo-inositol (mI) are associated with HIV infection.

Single Voxel Proton Magnetic Resonance Spectroscopy (SVS) was acquired at baseline and 18 months follow-up

- Single voxel 1H MRS Data acquisition was conducted on a 3T scanner at St. Vincent’s Hospital Imaging department under supervision of KM.
- All spectroscopy data will be acquired using the Philips SMART Brain software allowing accurate repeatable positioning of the voxel.

Our protocol

- PRESS
- TE = 30
- TR = 2000
- CHESS
- 2nd ordershimming
- Ratio to water

CSF Neopterin

Age, HIV duration, AIDS

Mild Neurocognitive Disorder (MND)

HIV-Associated Dementia (HAD)

No Dementia

Dementia

Fracati HAND Diagnostic Criteria, Neurology 2007
Prior to analysis:
- QA Visual inspection in frequency domain while fitting is processed within the time domain
- SVS Fitting:
  - Removal of H2O
  - Quantitation using AMARES
  - H2O reference fitting
  - Amplitudes are recorded.

Frontal white matter spectra

Plausible physiological significance of main brain metabolites for HIV-related brain injury

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Chemical Shift</th>
<th>Normal concentration range</th>
<th>Physiological significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Acety-L-aspartate</td>
<td>2.03 ppm</td>
<td>7.8 mM (6.5-9.7)</td>
<td>Neuronal and axonal integrity/density</td>
</tr>
<tr>
<td>Choline (Cho)</td>
<td>3.2 ppm</td>
<td>1.2 mM (0.8-1.6)</td>
<td>Membrane turnover/Acute neuroinflammation</td>
</tr>
<tr>
<td>Creatine (Cr)</td>
<td>3.0 ppm</td>
<td>4.5 mM (3.4-5.5)</td>
<td>Cellular energetic marker</td>
</tr>
<tr>
<td>Myo-Inositol (mIo)</td>
<td>3.56 ppm (short TE only)</td>
<td>3.8 mM (2.2-6.8)</td>
<td>Glial cell marker/Clinical neuroinflammation</td>
</tr>
</tbody>
</table>

Baseline Study Samples’ Characteristics

<table>
<thead>
<tr>
<th>Study sample demographics</th>
<th>HIV⁻</th>
<th>HIV⁺</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (all males)</td>
<td>42</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.5</td>
<td>54.6</td>
<td>.36</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>15</td>
<td>16</td>
<td>.93</td>
</tr>
<tr>
<td>White English Australian background</td>
<td>95%</td>
<td>99%</td>
<td>.16</td>
</tr>
</tbody>
</table>

Study sample neurocognitive functioning

Follow-up Study Samples’ Characteristics

<table>
<thead>
<tr>
<th>HIV⁺ only</th>
<th>No Follow-up</th>
<th>Follow-up</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52</td>
<td>55</td>
<td>.10</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>13.3</td>
<td>14.1</td>
<td>.43</td>
</tr>
<tr>
<td>Baseline Impaired</td>
<td>54.5%</td>
<td>52.5%</td>
<td>.88</td>
</tr>
<tr>
<td>Always undetectable during study</td>
<td>54.5%</td>
<td>93%</td>
<td>.006</td>
</tr>
</tbody>
</table>

Baseline & follow up neurocognition

HIV+ sample clinical characteristics

**Baseline**
- Median Nadir CD4: 180 [IQR:42-284]
- Median Current CD4: 560 [IQR:362-723]
- Plasma HIVRNA <50 cp/mL (Undetectable): 97.2%
- CSF HIVRNA <50 cp/mL (Undetectable): 97.2% (p=0.001)
- Median HIV duration (years): 159 [IQR:13.1-155]
- Historical AIDS%: 33%
- Only Nadir < 200: 28%
- Median Current cART duration: 19 [IQR:13.5-24]

**Follow-up**
- Median Current CD4: 638 [IQR:438-832] *
- New ADIs: -
- Plasma HIVRNA <50 cp/mL (Undetectable): 94.5%
- Always undetectable: 91.8%

* p<.0001 difference with baseline

FWM Creatine: Cellular energy marker
A History of HAND and neurocognitive decline yield distinct brain cellular energy profiles

- Had HAND & Declining (2.4%)
- Had HAND & Stable (14.3%)
- Never had HAND & Declining (8.3%)
- Never had HAND & Stable (75%)

* Associated with increased CSF neopterin

Conclusions

- Longer-term studies of neurochemical changes in chronic HIV infection are needed to understand the prognostic of Creatine changes at 18 months
- The majority of aging HIV+ persons on stable cART are doing well
- But a non-negligible minority have ongoing disease with two main patterns:
  - Abnormal cellular energy that may reflect initial steps of slow neurodegenerative processes
  - Ongoing HIV-related injury that is associated with low-grade chronic neuroinflammation

- We only presented data in the frontal white matter, therefore these results are partial as we also scanned the Posterior Cingulate Cortex and the Caudate area

Acknowledgements

- Thanks to our research participants for their time

Neuroscience Research Australia

Discover, Conquer, Cure.