EVALUATION OF EARLY CEREBRAL ALTERATIONS IN THE COURSE OF HIV AND HCV INFECTION USING PERFUSION MR IMAGING: IS THE HEPATITIS C VIRUS MORE DANGEROUS FOR THE BRAIN?

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The involvement of the central nervous system (CNS) in the course of HIV infection is already often observed in the early stage of the disease. HIV has been found in the brain within 3 to 6 days after the onset of infection.

Due to similar routes of viral transmission, about 30% of HIV-infected patients are co-infected with the hepatitis C virus (HCV). HIV/HCV co-infection is associated with worse clinical outcomes of both diseases in terms of systemic disease progression and mortality.
Similarly to HIV, HCV can invade the CNS as well. HCV can replicate in leukocytes, including monocytes. The infected monocytes may cross the blood-brain barrier using a process similar to that described for HIV, known as a 'Trojan horse' mechanism.

Moreover, HCV infection is associated with cognitive dysfunction, fatigue, and depression.

Since both viruses can infect the brain and impair CNS function, they may cause alterations in cerebral perfusion.
Aim of the study

- to evaluate changes of rCBV in selected regions of the brain
- to assess the usefulness of PWI in the early detection of HIV as well as HCV-related cerebral circulation abnormalities
- to evaluate the correlations between rCBV values and cognitive tests results, CD4a and CD4n T cell count
- to answer the question: Is the hepatitis C virus more dangerous for the brain?
PWI (Perfusion weighted imaging)

- PWI is a method that brings information on cerebral flow at the capillary level (microcirculation)
• **DCE** — dynamic contrast enhanced imaging (T1- perfusion) parameters of CBV, Ktrans, PS

• **DSC** — dynamic susceptibility contrast enhanced imaging (T2-perfusion) most often used

• **ASL** — arterial spin labeling, without contrast injection
DSC MRI

T2 or T2* - perfusion, dynamic susceptibility weighted imaging,

• Dynamic acquisition after contrast administration, using an automatic injector

• EPI T2*-weighted sequence

Contrast bolus
0.1-0.3 mmol/kg
5-10 ml/s

CBV – Cerebral Blood Volume

Semiquantitative method – rCBV is required

rCBV – relative to cerebellum
Hypoperfusion - ↓ rCBV
Material

- 43 HIV-1-positive patients
- 14 HCV-positive patients
- 18 normal control subjects
Material

- 18 HIV-1 naive (nontreated) (mean age 32.2, M:F 13/5)
- 18 HIV-1 cART-treated (mean age 39.3, M:F 10/8)
- 7 HIV/HCV naive (mean age 32.6, M:F 5/2)
- 14 HCV naive (mean age 39.5, M:F 8/6)
- 18 Control group (mean age 33.87, M:F 13/4)
Material

- The HIV-1 patients group was clinically asymptomatic.
- The amount of CD4 T lymphocytes in all HIV-1 patients was higher than 200 cells/mm$^3$.
- The HCV-positive patients were asymptomatic with only mild liver disease (HAI score of 0-2).
- Normal appearance of the brain in the structural MR images, no pathologic contrast enhancement.
<table>
<thead>
<tr>
<th></th>
<th>HIV-1 naive</th>
<th>HIV-1 cART treated</th>
<th>HIV/HCV naive</th>
<th>HCV naive Genotype 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>33.0</td>
<td>39.3</td>
<td>36.6</td>
<td>39.5</td>
</tr>
<tr>
<td><strong>IDU</strong></td>
<td>6 (28.6%)</td>
<td>6 (30%)</td>
<td>7 (77.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>CD4a T cell (cells/µl) mean</strong></td>
<td>369 - 986</td>
<td>201 - 1040</td>
<td>413 -1014</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>499</td>
<td>599</td>
<td>580</td>
<td>-</td>
</tr>
<tr>
<td><strong>CD4n T cell (cells/µl) mean</strong></td>
<td>300 - 986</td>
<td>3 - 462</td>
<td>10 - 779</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>486</td>
<td>121</td>
<td>441</td>
<td>-</td>
</tr>
<tr>
<td><strong>HIV RNA (copies/ml) mean</strong></td>
<td>3180 - 125000</td>
<td>&lt; 40</td>
<td>4440 - 68321</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>23454</td>
<td>&lt; 40</td>
<td>4727</td>
<td>-</td>
</tr>
<tr>
<td><strong>HCV RNA (IU/ml) mean</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>58672 - 4485492</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>1324553</td>
</tr>
</tbody>
</table>
Methods

- 1.5 T scanner (GE Medical Systems)
- 16-channel HNS coil
- conventional brain MRI

- PWI – DSC method using T2*-weighted echo planar imaging
  (TR 1.900 ms, TE 80 ms, FA 90°, FOV 30 cm, matrix 192 x 128, NEX 1)
  13 slices parallel to ACPC plane, each slice: 8 mm, spacing: 0 cm, time: 1 min 30 s

  contrast bolus – i.v. 0.2 mM/kg, 5 ml/s,
  followed by 20 ml saline flush
Methods – CBV maps

ADW 4.4. GE work station, Functool software

Basal ganglia

Temporoparietal cortices

Frontal cortices

PCG cortex

rCBV normalized to the mean values in the cerebellum

cerebellum

Frontoparietal WM regions
Two cognitive tests were used in order to assess possible deterioration of cognitive functions:

- **Wisconsin Card Sorting Test (WCST)** as a measure of executive function.

- **d2 test of attention - concentration endurance test** as a measure of visual attention.
Methods – statistical analysis

• Analysis of variance followed by the post hoc Tukey LSD test was used for statistical evaluation (significant \( p<0.05 \)).

• Correlations between rCBV measurements and the immunologic data (CD4a, CD4n T cell count) in HIV-1 positive patients as well as the liver histology activity index (HAI) in HCV-positive subjects were estimated using Pearson’s correlation coefficients.

• Additionally, we applied the Bonferroni correction (significant \( p<0.0055 \)): \( p<0.05/n \), where \( n=9 \) variables/testing hypotheses: 9 rCBV measurements).
Results
## Results

<table>
<thead>
<tr>
<th></th>
<th>rCBV</th>
<th>TPR right</th>
<th>TPR left</th>
<th>FC right</th>
<th>FC left</th>
<th>PCG</th>
<th>FPR right</th>
<th>FPR left</th>
<th>BG right</th>
<th>BG left</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>1.27</td>
<td>1.26</td>
<td>1.26</td>
<td>1.26</td>
<td>1.38</td>
<td>0.56</td>
<td>0.56</td>
<td>1.11</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>HIV+ nont</td>
<td>1.16</td>
<td>1.20</td>
<td>1.18</td>
<td>1.12</td>
<td>1.25</td>
<td>0.51</td>
<td>0.54</td>
<td>1.07</td>
<td>1.02</td>
<td></td>
</tr>
<tr>
<td>HIV+ treat</td>
<td>1.16</td>
<td>1.18</td>
<td>1.11</td>
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<td>0.53</td>
<td>0.54</td>
<td>1.06</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
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<td>1.13</td>
<td>1.13</td>
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</table>
Results

TPR - Temporoparietal cortical regions

rCBV

**TPR r**

- **CG**: 1,3
- **HIV-nont**: 1,25
- **HIV-tr**: 1,2
- **HIV/HCV**: 1,15
- **HCV**: 1,1

**TPR l**

- **CG**: 1,3
- **HIV-nont**: 1,25
- **HIV-tr**: 1,2
- **HIV/HCV**: 1,15
- **HCV**: 1,1

### TPR

**RIGHT**

- HIV-1 naive: p = 0.009
- HIV-1 tr: p = 0.007
- HIV-1/HCV: p = 0.007
- HCV: p = 0.010

**LEFT**

- HIV-1 naive: p = 0.03
- HIV-1 tr: p = 0.005
- HIV-1/HCV: p = 0.003
Results

rCBV

FC- Frontal cortical regions

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<thead>
<tr>
<th>FC</th>
<th>RIGHT</th>
<th>LEFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 naive</td>
<td>p = 0.02</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>HIV-1 tr</td>
<td>p = 0.009</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>HIV-1/HCV</td>
<td>p = 0.03</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>HCV</td>
<td></td>
<td>p = 0.03</td>
</tr>
</tbody>
</table>
Results

PCG – posterior cingulate gyrus cortex

PCG

HIV-1 naive p=0.012
HIV-1 tr p=0.033
HIV-1/HCV p=0.045
HCV p=0.045
Results

BG - Basal ganglia

**BG r**

- CG
- HIV-nont
- HIV-tr
- HIV/HCV
- HCV

**BG I**

- CG
- HIV-nont
- HIV-tr
- HIV/HCV
- HCV

<table>
<thead>
<tr>
<th>Condition</th>
<th>RIGHT</th>
<th>LEFT</th>
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<tbody>
<tr>
<td>HCV</td>
<td><strong>p=0.0002</strong></td>
<td><strong>p&lt;0.0001</strong></td>
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BG - Basal ganglia
## Results – Bonferroni correction

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<td>1.29</td>
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</tbody>
</table>

**Note:**
- Bold values indicate significant differences after Bonferroni correction.
There were no statistically significant differences in executive functions measured with all the WCST scales.
Statistical correlation rCBV/WCST

- Temporoparietal cortices:
  - rCBV ROI 3: p = 0.036
  - rCBV ROI 4: p = 0.011

- Right frontal cortex:
  - rCBV ROI 5: p = 0.021

- Left basal ganglia:
  - rCBV ROI 11: p = 0.008
### Statistical correlation rCBV/CD4

#### rCBV/CD4a

<table>
<thead>
<tr>
<th>ROI</th>
<th>ROI 3</th>
<th>ROI 4</th>
<th>ROI 5</th>
<th>ROI 6</th>
<th>ROI 7</th>
<th>ROI 8</th>
<th>ROI 9</th>
<th>ROI 10</th>
<th>ROI 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBV/CD4a</td>
<td>0.524</td>
<td>0.087</td>
<td>0.420</td>
<td>0.225</td>
<td>0.228</td>
<td>0.946</td>
<td>0.900</td>
<td>0.774</td>
<td>0.964</td>
</tr>
<tr>
<td>p value</td>
<td>0.087</td>
<td>0.420</td>
<td>0.225</td>
<td>0.228</td>
<td>0.946</td>
<td>0.900</td>
<td>0.774</td>
<td>0.964</td>
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</tr>
</tbody>
</table>

#### rCBV/CD4n

<table>
<thead>
<tr>
<th>ROI</th>
<th>ROI 3</th>
<th>ROI 4</th>
<th>ROI 5</th>
<th>ROI 6</th>
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<th>ROI 8</th>
<th>ROI 9</th>
<th>ROI 10</th>
<th>ROI 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBV/CD4n</td>
<td>0.100</td>
<td>0.177</td>
<td>0.869</td>
<td>0.724</td>
<td>0.328</td>
<td>0.738</td>
<td>0.907</td>
<td>0.712</td>
<td>0.108</td>
</tr>
<tr>
<td>p value</td>
<td>0.100</td>
<td>0.177</td>
<td>0.869</td>
<td>0.724</td>
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<td>0.738</td>
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</table>

No statistically significant correlation between rCBV and CD4 count
Conclusions
Conclusions

- PWI is capable of depicting rCBV deficits in HIV-1 as well as HCV clinically asymptomatic patients in the early stage of disease.

- Statistically significant decrease of rCBV was observed in the temporoparietal, frontal cortices and the posterior cingulate gyrus, particularly in HIV-1 cART treated, HIV-1/HCV patients as well as HCV patients.

- Hyperperfusion in basal ganglia may be an indicator of brain inflammation in HCV patients.

- HCV-infected patients seem to reveal the most pronounced perfusion changes (significant changes of rCBV values according to the Bonferroni correction).
Conclusions

- rCBV values in both temporoparietal and right frontal cortices, as well as left basal ganglia were correlated with the results of the cognitive tests.
- rCBV value could be a noninvasive neuroimaging biomarker for assessing cerebral microcirculation impairment in HIV and HCV infection.