Central Nervous System Complications of Hepatitis C

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University of California, San Diego
Important Questions Regarding CNS Complications of HCV

Primary Questions
• Does HCV affect the brain?
  – If so, by what mechanisms?
• Does HCV-related brain injury respond to HCV therapy?
• Does HCV infection of the brain limit treatment success?

Related Questions
• What are the best methods to assess HCV’s impact on the brain?
• Can HCV’s effects on the brain be reliably distinguished from those of comorbidities, particularly liver disease, drug and alcohol use, and HIV?
HCV Infection and Replication

Multiple Potential Pathways for HCV-Associated CNS Injury

- Infection of glial cells and brain endothelial cells
  - CNS adaptation
  - Glial activation
  - BBB permeability
- Neurotoxic HCV proteins in the CNS
- Chronic inflammation
- Liver disease
  - Glutamate-related neurotoxicity
- HCV-associated vascular disease
  - Cryoglobulinemia-related vasculitis
- CNS injury from concomitant drug or alcohol use
Autopsy Brain Tissue Supports that HCV can Infect Glial Cells

HCV antigens in brains by heparin columns by WB

NS3 in astrocytes and microglia of HIV+ HCV+

NS5a in astrocytes of HIV+ HCV+ cases


HCV Infects Brain Endothelial Cells

- 10 HCV-infected adults
- Detected HCV RNA in brain tissue but at substantially lower levels than in liver
- Brain endothelial cells expressed HCV entry receptors

Endothelial cell cultures:
- HCV entry and replication
- HCV infection affected endothelial permeability and cellular apoptosis

Fletcher, et al, Gastroenterol 2012;142:634–643
HCV is Associated with Lower Blood-Brain Barrier Permeability

Letendre et al, 18th CROI, 2011, Abstract 408
HCV Can Adapt to Brain Tissue

## Evidence that HCV Can Adapt to the CNS Environment

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morsica</td>
<td>J Med Virology</td>
<td>1997</td>
<td>19</td>
<td>HCV RNA was detected in 5 (26%) and sequences did not differ between CSF and serum</td>
</tr>
<tr>
<td>Radkowski</td>
<td>J Virology</td>
<td>2002</td>
<td>6</td>
<td>HCV RNA detected in brain tissue from 3 (50%)</td>
</tr>
<tr>
<td>Laskus</td>
<td>J Virology</td>
<td>2002</td>
<td>13</td>
<td>HCV sequences were found in 8 (62%) CSF specimens: 4 exhibited differences from other tissues</td>
</tr>
<tr>
<td>Vargas</td>
<td>Liver Transpl</td>
<td>2002</td>
<td>2</td>
<td>HCV RNA sequences from brain differed from consensus serum sequences in both patients</td>
</tr>
<tr>
<td>Forton</td>
<td>J Virology</td>
<td>2004</td>
<td>2</td>
<td>HCV RNA sequences from brain differed from other tissues; Identified 2 unique brain-derived mutations</td>
</tr>
<tr>
<td>Bagaglio</td>
<td>AIDS</td>
<td>2005</td>
<td>21</td>
<td>HCV RNA was detected in 5 (24%); sequences in 2 of these 5 differed from plasma and PBMCs</td>
</tr>
<tr>
<td>Fishman</td>
<td>J Infect Dis</td>
<td>2008</td>
<td>7</td>
<td>Brain HCV sequences differed from liver and blood in 4 (57%)</td>
</tr>
</tbody>
</table>
HCV Core Protein May be Neurotoxic


Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement

Martin Schaefer\textsuperscript{1,2,*}, Lucile Capuron\textsuperscript{3}, Astrid Friebe\textsuperscript{4}, Crisanto Diez-Quevedo\textsuperscript{5}, Geert Robaeys\textsuperscript{6}, Sergio Neri\textsuperscript{7}, Graham R. Foster\textsuperscript{8}, Achim Kautz\textsuperscript{9}, Daniel Forton\textsuperscript{10}, Carmine M. Pariante\textsuperscript{11}

Journal of Hepatology 2012 vol. 57 | 1379–1390

The chart shows the prevalence (%) of various mental health conditions in the general population and HCV patients. The conditions include major depression, anxiety disorder, bipolar disorder, schizophrenia, alcohol abuse, drug abuse, and fatigue. The prevalence is represented by bars with error bars indicating variability.
Early Cognitive Findings from UCSD

Letendre, AIDS, 2005

Cherner, Neurology, 2005
<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Size</th>
<th>Method</th>
<th>People with HCV had…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forton</td>
<td>Hepatology</td>
<td>2002</td>
<td>43</td>
<td>Computer-based</td>
<td>Worse concentration and speed of information processing</td>
</tr>
<tr>
<td>Hilsabeck</td>
<td>JINS</td>
<td>2003</td>
<td>21</td>
<td>4 tests</td>
<td>Worse functioning associated with worse liver fibrosis</td>
</tr>
<tr>
<td>Ryan</td>
<td>Neurology</td>
<td>2004</td>
<td>116</td>
<td>12 tests</td>
<td>Worse executive functioning</td>
</tr>
<tr>
<td>Weissenborn</td>
<td>J Hepatology</td>
<td>2004</td>
<td>45</td>
<td>10 tests</td>
<td>Worse executive functioning and attention</td>
</tr>
<tr>
<td>Martin</td>
<td>JINS</td>
<td>2004</td>
<td>156</td>
<td>1 test</td>
<td>Worse reaction time</td>
</tr>
<tr>
<td>Cherner</td>
<td>Neurology</td>
<td>2005</td>
<td>430</td>
<td>14 tests</td>
<td>Worse functioning in multiple domains</td>
</tr>
<tr>
<td>Letendre</td>
<td>AIDS</td>
<td>2005</td>
<td>526</td>
<td>14 tests</td>
<td>Worse global functioning</td>
</tr>
<tr>
<td>McAndrews</td>
<td>Hepatology</td>
<td>2005</td>
<td>83</td>
<td>9 tests</td>
<td>Worse learning</td>
</tr>
<tr>
<td>Morgello</td>
<td>AIDS</td>
<td>2005</td>
<td>137</td>
<td>14 tests</td>
<td>Worse executive functioning</td>
</tr>
<tr>
<td>Richardson</td>
<td>AIDS</td>
<td>2005</td>
<td>220</td>
<td>8 tests</td>
<td>More frequent global impairment</td>
</tr>
<tr>
<td>Hinkin</td>
<td>J Addict Dis</td>
<td>2008</td>
<td>118</td>
<td>8 domains</td>
<td>Worse learning and memory</td>
</tr>
<tr>
<td>Thiyagarajan</td>
<td>Clin Micro Inf</td>
<td>2010</td>
<td>72</td>
<td>IHDS, CogState</td>
<td>Worse IHDS; Trend worse executive function</td>
</tr>
<tr>
<td>Garvey</td>
<td>PLoS One</td>
<td>2012</td>
<td>81</td>
<td>CogState</td>
<td>Worse processing speed and executive function</td>
</tr>
<tr>
<td>Thames</td>
<td>Neurol Neuroimmunol</td>
<td>2015</td>
<td>96</td>
<td>13 tests</td>
<td>Worse global, processing speed, verbal fluency</td>
</tr>
<tr>
<td>Campagna</td>
<td>Liver Intl</td>
<td>2015</td>
<td>180</td>
<td>6 tests</td>
<td>Worse working memory but cirrhosis and alcohol accounted for more variance</td>
</tr>
</tbody>
</table>
Selected Neurocognitive Findings

Hinkin, J Addict Dis 2008

Thames et al, Neurol Neuroimmunol Neuroinflamm 2015

Campagna, Liver International 2015
Absence of neurocognitive effect of hepatitis C infection in HIV-coinfected people

<table>
<thead>
<tr>
<th>Deficit score</th>
<th>Unadjusted model</th>
<th>Adjusted model (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta^a$</td>
<td>95% Cl</td>
</tr>
<tr>
<td>GDS</td>
<td>0.01</td>
<td>-0.061</td>
</tr>
<tr>
<td>Verbal DDS</td>
<td>-0.036</td>
<td>-0.128</td>
</tr>
<tr>
<td>Executive functioning DDS</td>
<td>0.026</td>
<td>-0.094</td>
</tr>
<tr>
<td>SIP DDS</td>
<td>0.015</td>
<td>-0.068</td>
</tr>
<tr>
<td>Learning DDS</td>
<td>-0.032</td>
<td>-0.148</td>
</tr>
<tr>
<td>Recall DDS</td>
<td>0.064</td>
<td>-0.047</td>
</tr>
<tr>
<td>Work memory DDS</td>
<td>0.027</td>
<td>-0.081</td>
</tr>
<tr>
<td>Motor DDS</td>
<td>-0.004</td>
<td>-0.131</td>
</tr>
<tr>
<td>GDS DDS</td>
<td>0.062</td>
<td>-0.024</td>
</tr>
<tr>
<td>Verbal DDS</td>
<td>0.05</td>
<td>-0.062</td>
</tr>
<tr>
<td>Executive functioning DDS</td>
<td>0.136</td>
<td>-0.012</td>
</tr>
<tr>
<td>SIP DDS</td>
<td>0.064</td>
<td>-0.039</td>
</tr>
<tr>
<td>Learning DDS</td>
<td>0</td>
<td>-0.14</td>
</tr>
<tr>
<td>Recall DDS</td>
<td>0.092</td>
<td>-0.044</td>
</tr>
<tr>
<td>Work memory DDS</td>
<td>0.053</td>
<td>-0.081</td>
</tr>
<tr>
<td>Motor DDS</td>
<td>0.064</td>
<td>-0.095</td>
</tr>
</tbody>
</table>

N = 1,582

Clifford et al, Neurology 2015;84:241–250
Antiretrovirals Might Influence CNS Complications of HCV

Letendre et al, J Neurovirol 2015, Epub, PMID: 26407716
Serum HCV RNA is Not Consistently Associated with Cognition

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Size</th>
<th>Method</th>
<th>People with HCV had…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal</td>
<td>JAIDS</td>
<td>2012</td>
<td>1338</td>
<td>4 tests</td>
<td>In fully adjusted GLM, HCV viremia was <strong>not</strong> associated with scores on any of the cognitive tests</td>
</tr>
<tr>
<td>Clifford</td>
<td>Neurology</td>
<td>2009</td>
<td>172</td>
<td>3 tests</td>
<td><strong>No difference</strong> based on HCV RNA</td>
</tr>
<tr>
<td>Letendre</td>
<td>AIDS</td>
<td>2005</td>
<td>112</td>
<td>14 tests</td>
<td><strong>Higher</strong> HCV RNA associated with worse memory</td>
</tr>
</tbody>
</table>

Letendre, AIDS, 2005

Relationship Between HCV RNA and Cognition May Not be Linear

Letendre, Unpublished Data
Low Levels of HCV RNA in CSF in a Minority of Adults

• Pre-CHARTER CSF supernatants: HCV RNA not detectable in 59 CSF specimens

• CHARTER CSF supernatants: HCV RNA detectable in 5 of 35 CSF specimens (14%): range 77-1,540 IU/mL

• CSF cell pellets: HCV RNA detectable in 2 of 8 (25%): 31 and 64 IU/mL

Letendre, Unpublished Data
HCV Core is More Frequently Present in CSF than HCV RNA

Letendre, Unpublished Data
## Consistent Neuroimaging Findings

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Method</th>
<th>People with HCV had…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forton</td>
<td>Lancet</td>
<td>2001</td>
<td>30</td>
<td>MRS</td>
<td>Worse choline/creatine ratios</td>
</tr>
<tr>
<td>Forton</td>
<td>Hepatology</td>
<td>2002</td>
<td>17</td>
<td>MRS</td>
<td>Worse choline in basal ganglia, white matter</td>
</tr>
<tr>
<td>Taylor</td>
<td>JINS</td>
<td>2004</td>
<td>26</td>
<td>MRS</td>
<td>Worse N-acetyl aspartate</td>
</tr>
<tr>
<td>Weissenborn</td>
<td>J Hepatology</td>
<td>2004</td>
<td>45</td>
<td>MRS</td>
<td>Worse N-acetyl aspartate</td>
</tr>
<tr>
<td>McAndrews</td>
<td>Hepatology</td>
<td>2005</td>
<td>37</td>
<td>MRS</td>
<td>Worse choline, N-acetyl aspartate</td>
</tr>
<tr>
<td>Forton</td>
<td>J Hepatology</td>
<td>2008</td>
<td>25</td>
<td>MRS</td>
<td>Worse myo-inositol</td>
</tr>
<tr>
<td>Gongvatana</td>
<td>J Neurovirol</td>
<td>2011</td>
<td>85</td>
<td>DTI</td>
<td>Worse fractional anisotropy &amp; mean diffusivity</td>
</tr>
<tr>
<td>Heeren</td>
<td>J Cerebral Blood Flow</td>
<td>2011</td>
<td>15</td>
<td>MRI,PET</td>
<td>Worse striatal DA and midbrain SERT availability, glucose metabolism</td>
</tr>
<tr>
<td>Jernigan</td>
<td>J Neurovirol</td>
<td>2011</td>
<td>251</td>
<td>sMRI</td>
<td>Worse volume of abnormal white matter</td>
</tr>
<tr>
<td>Nagarajan</td>
<td>Int J Hepatol</td>
<td>2012</td>
<td>28</td>
<td>L-COSY</td>
<td>Worse myo-inositol; Higher glutathione</td>
</tr>
<tr>
<td>Garvey</td>
<td>PLoS One</td>
<td>2012</td>
<td>36</td>
<td>MRS,PET</td>
<td>Worse myo-inositol; no microglial activation effect</td>
</tr>
<tr>
<td>Grover</td>
<td>J Viral Hepatitis</td>
<td>2012</td>
<td>11</td>
<td>MRS,PET</td>
<td>Worse myo-inositol and microglial activation</td>
</tr>
<tr>
<td>Bladowska</td>
<td>PLoS One</td>
<td>2014</td>
<td>56</td>
<td>PwMRI</td>
<td>Worse blood flow in parietal &amp; frontal cortex</td>
</tr>
<tr>
<td>Thames</td>
<td>Neurol Neuroimmunol</td>
<td>2015</td>
<td>29</td>
<td>MRS</td>
<td>Worse N-acetyl aspartate in parietal white matter, myo-inositol in frontal white matter</td>
</tr>
</tbody>
</table>
Selected Neuroimaging Findings

McAndrews, Hepatology 2005
Bladowska, Eur J Radiol 2013 82: 686–692

Gongvatana, J Neurovirol 2011
Progressive Improvement in HCV Response Rates

Webster et al, Lancet 2015; 385: 1124–35
# Inconsistent Treatment Findings

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capuron</td>
<td>Biol Psychiatr</td>
<td>2005</td>
<td>10</td>
<td><strong>Improved</strong> activation in the anterior cingulate cortex on functional MRI with IFN-α</td>
</tr>
<tr>
<td>Thein</td>
<td>HIV Medicine</td>
<td>2007</td>
<td>34</td>
<td><strong>Improvement</strong> in some measures of cognitive function with SVR</td>
</tr>
<tr>
<td>Zignego</td>
<td>Dig Liver Dis</td>
<td>2007</td>
<td>89</td>
<td><strong>Improved</strong> macrophage IDO activity, plasma TRP and KYN levels and psychopathology after viral clearance</td>
</tr>
<tr>
<td>Comai</td>
<td>Pharmacologic Research</td>
<td>2011</td>
<td>45</td>
<td><strong>Worsened</strong> KYN during treatment, with an increase of the KYN/TRP ratio, an index of IDO activity</td>
</tr>
<tr>
<td>Pattullo</td>
<td>Liver Intl</td>
<td>2011</td>
<td>40</td>
<td><strong>No change</strong> in low NAA in the globus pallidus with viral clearance</td>
</tr>
<tr>
<td>Byrnes</td>
<td>J Hepatology</td>
<td>2012</td>
<td>15</td>
<td><strong>Improved</strong> choline and MI in basal ganglia with SVR, not in non-responders/relapsers</td>
</tr>
<tr>
<td>Cattie</td>
<td>J Neurovirol</td>
<td>2014</td>
<td>40</td>
<td><strong>Worse</strong> neurocognitive performance during IFN-α that did not return to baseline after completion of therapy</td>
</tr>
<tr>
<td>Haroon</td>
<td>Brain, Behavior, &amp; Immunity</td>
<td>2015</td>
<td>31</td>
<td><strong>Worse</strong> glutamate in basal ganglia in older adults during IFN-α</td>
</tr>
</tbody>
</table>
Interferon-Ribavirin Treatment Trial at UCSD

- 40 HCV+ adults starting IFN/RBV therapy
  - Comprehensive medical, psychiatric, and cognitive assessment before and up to 72 weeks after treatment initiation

- After 10 weeks, neurocognitive impairment rose from 27.5% to 47.5% ($p < .05$)
  - Infection with genotype 1 was associated with decline ($p < .05$)

- After 72 weeks, 42.5% remained impaired
  - Only initial 10-week neurocognitive decline predicted persistent impairment
  - Not viral clearance, severity of liver disease, or depressive symptoms

Cattie et al, J Neurovirol 2014, 20: 561-70
Cognitive Performance and Mood Worsened

Cattie et al, J Neurovirol 2014, 20: 561-70
## Direct Acting Antivirals

<table>
<thead>
<tr>
<th>Viral protein</th>
<th>NS3/4A</th>
<th>NS5A</th>
<th>NS5B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Serine protease</td>
<td>Component of HCV replication complex</td>
<td>RNA-dependent RNA polymerase</td>
</tr>
</tbody>
</table>
| Drugs         | Covalent (ketoamide)  
Boceprevir  
Telaprevir  
**Noncovalent (tripeptide or macrocyclic)**  
Faldaprevir  
Simeprevir  
Paritaprevir  
Asunaprevir  
Grazoprevir | Ledipasvir  
Daclatasvir  
Ombitasvir  
Elbasvir  
Samatasvir  
PPI-668 | Nucleoside analogs  
Sofosbuvir  
**Nonnucleoside**  
GS-9669  
Beclabuvir  
Dasabuvir |

## Physicochemical Characteristics of DAA Drugs

### Site of inhibition
- **Sofosbuvir**: Gilead
- **Dasabuvir**: Abbvie
- **Ledipasvir**: Gilead
- **Velpatasvir**: Gilead
- **Ombitasvir**: Abbvie
- **Paritaprevir**: Abbvie

### Molecular Weight
- **Sofosbuvir**: 529.46
- **Dasabuvir**: 533.57
- **Ledipasvir**: 889.01
- **Velpatasvir**: 883.00
- **Ombitasvir**: 975.20
- **Paritaprevir**: 801.91

### Protein Binding
- **Sofosbuvir**: 61-65%
- **Dasabuvir**: > 99.5%
- **Ledipasvir**: > 99.8%
- **Velpatasvir**: > 99.5%
- **Ombitasvir**: 99.9%
- **Paritaprevir**: 97.0-98.6%

### Octanol-Water Partition Coeff.
- **Sofosbuvir**: 1.6
- **Dasabuvir**: 4.3
- **Ledipasvir**: -
- **Velpatasvir**: -
- **Ombitasvir**: 7.4
- **Paritaprevir**: 3.1

### Molecular Transporters Substrate
- **Sofosbuvir**: P-gp, BCRP
- **Dasabuvir**: P-gp
- **Ledipasvir**: P-gp, BCRP
- **Velpatasvir**: P-gp, BCRP
- **Ombitasvir**: P-gp, BCRP, OATP
- **Paritaprevir**: P-gp

*Data provided by Gilead, Abbvie*
New DAA Project in San Diego
Important Questions Regarding CNS Complications of HCV

**Primary Questions**

- Does HCV affect the brain?
  - If so, by what mechanisms?
- Does HCV-related brain injury respond to HCV therapy?
- Does HCV infection of the brain limit treatment success?

**Related Questions**

- What are the best methods to assess HCV’s impact on the brain?
- Can HCV’s effects on the brain be reliably distinguished from those of comorbidities, particularly liver disease, drug and alcohol use, and HIV?
Acknowledgements & Conflicts

Study Volunteers

UC San Diego
- Ronald J. Ellis
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- J. Allen McCutchan
- Edmund Capparelli
- Brookie Best
- Jennifer Marquie
- Florin Vaida

CHARTER or NNTC
- David Clifford
- Justin McArthur
- Ned Sacktor
- Ann Collier
- David Clifford

National Institutes of Health
- ...Mental Health
- ...Drug Abuse
- ...Allergy and Infectious Diseases

Industry
- Cipla
- Gilead Sciences
- Janssen
- Merck & Co., Inc.
- ViiV Healthcare