Delirium and Neuroimaging: Structural, Functional, Amyloid

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Disclosures

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• Conflicts of interest: none
49 year Female – 16 yrs education
Severe community acquired pneumonia

Hypoxia and hypotension → intubation and mechanical ventilation

48 hours → renal failure, septic shock → ARDS
- 31 days - MV
- 37 days ICU LOS
- 43 days hospital LOS
- 11 days delirium duration

Jackson 2009 SMJ, 102(11):1150-7
MRI, Critical illness and Delirium

- 43 year old
- All with delirium
- 7 normal CT scans

- 6 of 8 had WMH
  - 2 pts. Fazekas grade 1
  - 2 pts. grade 2
  - 2 pts. grade 3

- No
  - Atrophy
  - Ischemic lesions
  - Hemorrhagic lesions

Morandi et al., 2010, Psychiatry 7(9):28-33
67 year old female

Axial Flair
WMHs Grade 3

Left – DWI map
Anterior white matter hypointense

Right – ADC map
Diffuse ADC increase: vasogenic edema

Sharshar et al., 2007 ICM, 33:798-806
Post-Cardiac Surgery

- 130 patients – 18 (13.8%) delirium

- Prevalence of severe WMH higher in patients with delirium
  - Fazekas score = 3
  - OR: 3.9; 95% [CI] 1.2-12.5

- WMH risk factor for development of delirium

Hantano et al. k, 2013, Am J Geriatr Psychiatry; 21(10);938-45)
<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging Modality</th>
<th>N Pts./controls</th>
<th>Cause of delirium</th>
<th>Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koponen et al., 1989</td>
<td>CT</td>
<td>69 / 31</td>
<td>Heterogeneous</td>
<td>Atrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R side focal infarcts</td>
</tr>
<tr>
<td>Figiel et al., 1989</td>
<td>MRI</td>
<td>5 / 55</td>
<td>Antidepressant</td>
<td>Basal ganglia lesions WMHs Cortical Atrophy ↑ VBRs</td>
</tr>
<tr>
<td>Figiel et al., 1990</td>
<td>MRI</td>
<td>10</td>
<td>ECT</td>
<td>Basal ganglia lesions WMHs</td>
</tr>
<tr>
<td></td>
<td>CT / MRI</td>
<td>6</td>
<td>ECT</td>
<td>Basal ganglia lesions WMHs</td>
</tr>
<tr>
<td>Martin et al., 1992</td>
<td>CT / MRI</td>
<td>4 / 10</td>
<td>ECT in Stroke pts.</td>
<td>Caudate Nucleus lesions</td>
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<tr>
<td>Nargaratnam et al., 1995</td>
<td>CT</td>
<td>5</td>
<td>Stroke</td>
<td>R subcortical infarcts</td>
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<tr>
<td>Kishi et al., 1995</td>
<td>CT / MRI</td>
<td>38 / 197</td>
<td>Critical illness (medial and trauma)</td>
<td>SAH / SDH R &amp; L Ischemic lesions</td>
</tr>
<tr>
<td></td>
<td>CT / MRI</td>
<td>49 / 153</td>
<td>Stroke</td>
<td>Cerebral Atrophy WM lesions</td>
</tr>
<tr>
<td>Yokota et al., 2003</td>
<td>Xenon CT</td>
<td>10</td>
<td>Trauma / Medial</td>
<td>↓ CBF frontal, temporal, occipital lobes, caudate, thalamus, lenticular nucleus</td>
</tr>
<tr>
<td>Caeiro et al., 2004</td>
<td>CT / MRI</td>
<td>29 / 189</td>
<td>Stroke</td>
<td>Ischemic lesions</td>
</tr>
<tr>
<td>Samton et al., 2005</td>
<td>CT</td>
<td>22 / 11</td>
<td>Hypoxia, medical, drug intoxication</td>
<td>WMHs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Subcortical atrophy</td>
</tr>
<tr>
<td>Fong et al., 2006</td>
<td>SPECT</td>
<td>22 / 11</td>
<td>Heterogeneous</td>
<td>↓ CBF frontal, parietal, occipital L temporal lobe, pons</td>
</tr>
</tbody>
</table>

Soiza et al., 2008, J Psychosomatic Res, 65:239-48
Sepsis

Before Sepsis

24 days after Sepsis onset

N = 9
4 delirium, 5 coma
2 with normal scans
2 ischemic stroke
5 WMHs
75% abnormal imaging

60 Year old Male
Increase in WMHs

Sharshar et al., 2007 ICM, 33:798-806
79 Year old Female
Increase in extent of WMHs

Sharshar et al., 2007 ICM, 33:798-806
36 Year Old Women

54 Year Old Men

ARDS

Controls

Hopkins 2006 Brain Injury 20;263-71
Delirium Duration and Atrophy
(all P values <0.001)

- 47 Critical ill patients
- Longer duration of delirium associated with greater brain atrophy.

Gunther et al., 2012 CCM, 40(7):2022-32
### rCBF- Hypoactive Delirium

**Critical ill patients**
- Age: 47.5 ± 12.3
- APACHE II: 16.5 ± 5.8

**Yokota et al., 2003 Psychiatry Clin Neurosci 57:337-39**

<table>
<thead>
<tr>
<th>Region</th>
<th>During Delirium</th>
<th>After Recovery from Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First measurement (mL/100 g per min)</td>
<td>Second measurement (mL/100 g per min)</td>
</tr>
</tbody>
</table>
| Whole brain             | 37.8 ± 7.8      | 65.4 ± 18.6                | 0.0056  
| Cortex                  |                 |                            |  
| Frontal (bilateral)    | 38.1 ± 10.6     | 58.7 ± 9.5                 | 0.0010  
| Right frontal           | 38.8 ± 13.3     | 58.2 ± 8.4                 | 0.0007  
| Left frontal            | 37.5 ± 8.4      | 59.2 ± 11.8                | 0.0030  
| Temporal (bilateral)    | 39.6 ± 7.2      | 70.5 ± 7.2                 | 0.0041  
| Right temporal          | 40.7 ± 7.0      | 71.7 ± 17.1                | 0.0120  
| Left temporal           | 38.8 ± 7.7      | 69.3 ± 9.8                 | 0.0013  
| Occipital (bilateral)   | 31.4 ± 7.3      | 60.4 ± 13.1                | 0.0047  
| Right occipital         | 31.6 ± 8.5      | 60.7 ± 13.2                | 0.0045  
| Left occipital          | 31.2 ± 6.3      | 60.1 ± 14.0                | 0.0067  
| Subcortex               |                 |                            |  
| Caudate head (bilateral)| 47.5 ± 16.4     | 88.0 ± 15.2                | 0.0220  
| Right caudate head      | 48.3 ± 18.4     | 88.0 ± 27.6                | 0.0473  
| Left caudate head       | 46.7 ± 17.2     | 85.3 ± 20.8                | 0.0273  
| Thalamus (bilateral)    | 52.4 ± 10.5     | 102.1 ± 21.7               | 0.0045  
| Right thalamus          | 54.4 ± 12.6     | 102.0 ± 25.7               | 0.0055  
| Left thalamus           | 50.2 ± 8.3      | 98.4 ± 23.4                | 0.0044  
| Lenticular nucleus (bilateral)| 50.8 ± 17.4 | 92.3 ± 22.5                | 0.0053  
| Right lenticular nucleus| 49.3 ± 17.8     | 90.1 ± 23.1                | 0.0080  
| Left lenticular nucleus | 52.3 ± 18.1     | 92.3 ± 22.5                | 0.0038  

**Global and Regional Hypoperfusion**
- Hospital Day 35.3 ± 19.3
- Hospital Day 95.5 ± 13.5
SPECT Perfusion Changes in Patients with Delirium.

- Qualitative analysis: 50% changes in frontal & parietal perfusion
- Semi-quantitative analysis: change blood flow ratios L inferior frontal, R temporal, right occipital, and pons
- Inattention associated with perfusion abnormalities – L inferior frontal region
- Delirium vs. No Delirium: change blood flow ratio parietal lobe (n=6)

### Table 1. SPECT Cerebral Blood Flow Studies in Delirium and Related Conditions

<table>
<thead>
<tr>
<th>Reference (Ref. No.)</th>
<th>No. of Patients/Controls</th>
<th>Cause of Onset</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bogousslavsky et al. (10)</td>
<td>1/0</td>
<td>Right thalamic infarction</td>
<td>Right frontal hypoperfusion</td>
</tr>
<tr>
<td>Shih et al. (46)</td>
<td>1/0</td>
<td>Drug withdrawal</td>
<td>Left frontotemporal hypoperfusion</td>
</tr>
<tr>
<td>Kohira et al. (47)</td>
<td>1/0</td>
<td>Hepatic encephalopathy</td>
<td>Cerebellum, basal ganglia, cortical hyperperfusion</td>
</tr>
<tr>
<td>Doyle and Warden (48)</td>
<td>1/0</td>
<td>Cardiotomy</td>
<td>Right temporal-occipital hypoperfusion</td>
</tr>
<tr>
<td>Ohta et al. (49)</td>
<td>1/0</td>
<td>Portal-systemic encephalopathy</td>
<td>Bilateral parietal hypoperfusion</td>
</tr>
<tr>
<td>Kamijo et al. (50)</td>
<td>1/0</td>
<td>Barbiturate withdrawal</td>
<td>Basal ganglia hyperperfusion</td>
</tr>
<tr>
<td>Pittock et al. (51)</td>
<td>1/0</td>
<td>Transplant immunosuppression</td>
<td>Diffuse bilateral decrease</td>
</tr>
<tr>
<td>Ikeda et al. (52)</td>
<td>6/0</td>
<td>Hepatic encephalopathy</td>
<td>Bilateral frontal, parietal, temporal hypoperfusion</td>
</tr>
<tr>
<td>Jalan et al. (53)</td>
<td>8/0</td>
<td>Oral amino acid loading in cirrhosis</td>
<td>Diffusely decreased cortical perfusion; in 4 participants recovery after liver transplant</td>
</tr>
<tr>
<td>Trzepczynski et al. (54)</td>
<td>6/6</td>
<td>Cirrhosis</td>
<td>Bilateral temporal lobe, left superior frontal gyrus, and right parietal and cingulate gyrus decrease</td>
</tr>
<tr>
<td>Strauss et al. (55)</td>
<td>10/9</td>
<td>Hepatic encephalopathy</td>
<td>Right basal ganglia and bilateral frontotemporal hypoperfusion</td>
</tr>
<tr>
<td>O’Carroll et al. (56)</td>
<td>10/10</td>
<td>Cirrhosis</td>
<td>Frontal and basal ganglia hypoperfusion</td>
</tr>
<tr>
<td>Yazgan et al. (57)</td>
<td>12/8</td>
<td>Hepatic encephalopathy</td>
<td>Basal ganglia and occipital increase</td>
</tr>
<tr>
<td>Cattau et al. (58)</td>
<td>13/13</td>
<td>Hepatic encephalopathy</td>
<td>Anterior cingulate decrease</td>
</tr>
<tr>
<td>Fong et al. (59)</td>
<td>22/6</td>
<td>Multiple etiologies in hospitalized medical patients</td>
<td>Bilateral thalamic hypoperfusion</td>
</tr>
<tr>
<td>Ogasawara et al. (60)</td>
<td>5/36</td>
<td>Subdural hematoma</td>
<td>Prefrontal hypoperfusion. Striatal and medial temporal perfusion was higher in more impaired participants</td>
</tr>
<tr>
<td>Gokgoz et al. (61)</td>
<td>6/44</td>
<td>Cardiac surgery</td>
<td>Parietal hypoperfusion in 5</td>
</tr>
<tr>
<td>Gunaydin et al. (62)</td>
<td>7/43</td>
<td>Cardiac surgery</td>
<td>Frontal hypoperfusion in 5</td>
</tr>
</tbody>
</table>

*Note: SPECT = single photon emission computed tomography.*

Alsop et al., 2006, J of Gerontology, 61(12); 1287-93
Longitudinal rCBF in AD

48 patients
Followed over 37 months
Grouped by MMSE scores

rCBF Rapidly Progressing vs. Controls

rCBF Slowly Progressing vs. Controls

rCBF Rapidly vs. Slowly Progressing

Significant decrease in rCBF in frontal, temporal, parietal lobes, and posterior cingulate

Hanyu 2010 J Neurological Sciences, 290, 96-101
DTI – White Matter Integrity

Decreased FA values of the Delirium Group

Shioiri et al, Am J Geriatr Psychia, 2010
A significant decrease in the FA values for the delirium group in
Bilateral thalamus
Bilateral deep white matter  bilaterally
Corpus callosum

Shioiri et al, Am J Geriatr Psychia, 2010
Delirium Duration and Fractional Anisotropy in Corpus Callosum and Internal Capsule

Adjusted for age and sepsis, longer duration of delirium

Gunther et al., 2010 CCM, 40:2022-32
White Matter (FA) and Cognitive Function

Lower FA in ALIC associated with worse attention scores at 3 months
Lower FA in genu CC associated with worse attention scores at 12 months

Morandi et al., 2010 CCM, 40:2182-89
Dorsolateral prefrontal and posterior cingulate activity were inversely correlated in controls, and were strongly correlated during delirium.

Functional connectivity of thalamic and caudate nuclei with subcortical regions were reduced during delirium, recovered after delirium resolution.

Abnormal resting-state functional networks may underlie the pathophysiology of delirium.

Premorbid Risk Factors
Age, Premorbid illness

Illness related factors
Sedatives, narcotics, ICU Tx's, MV, Inflammation, hypoxia

Delirium

Brain Injury / Insult

Cognitive Outcome Impairment / Decline

Outcome Trajectories
Persistent, Progressive, Recovery

Neuroimaging
Potential Areas for Investigation

- Limited studies – even in structural imaging
- Small sample sizes
- Lack of control groups
- Pathophysiology
- Risk factors
- Longitudinal studies
- Beyond clinical imaging - New analysis and modeling methods

- Other Imaging Modalities
  - Amyloid Imaging – amyloid deposition post-delirium
  - Arterial Spin Labeling – blood flow and resting blood flow
  - Blood Brain Barrier imaging – disruption
  - DTI – white matter integrity and connectivity
  - Functional MRI – resting state, stimuli or task responses
  - PET and SPECT neurotransmitter tracers (Ach, DA)

- Does etiology matter?