Disentangling Delirium and Dementia

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• No conflicts of interest to report

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  – John A. Hartford Foundation

• Hold Milton and Shirley F. Levy Family Chair at Hebrew SeniorLife/Harvard Medical School
DSM5 CRITERIA FOR DELIRIUM

• Disturbance in attention and awareness
• Disturbance develops acutely and tends to fluctuate
• An additional disturbance in cognition, (e.g., memory deficit, language, visuoperceptual)
• Not better explained by a preexisting dementia
• Not in face of severely reduced level of arousal or coma
• Evidence of underlying organic etiology(-ies)

[Characteristics of transience and reversibility]

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DSM5 CRITERIA FOR DELIRIUM

• Evidence of significant cognitive decline from previous level in one or more cognitive domains
• Cognitive deficits interfere with independence in everyday activities
• Deficits do not occur exclusively in the context of a delirium
• Deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)

[Characteristics of chronic and progressive]

Used with permission. American Psychiatric Association, 2013
### Differential Diagnosis: Delirium vs. Dementia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Delirium</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Typically abrupt</td>
<td>Insidious and progressive</td>
</tr>
<tr>
<td>Duration</td>
<td>Hours to day</td>
<td>Months to years</td>
</tr>
<tr>
<td>Attention</td>
<td>Reduced ability to sustain or shift attention</td>
<td>Normal unless severe dementia</td>
</tr>
<tr>
<td>Consciousness</td>
<td>Fluctuating, reduced level of consciousness</td>
<td>Generally intact</td>
</tr>
<tr>
<td>Speech</td>
<td>Can be incoherent, disorganized</td>
<td>Ordered, may have aphasia</td>
</tr>
<tr>
<td>Psychomotor subtypes</td>
<td>Hyperactive/hypoactive forms often present</td>
<td>Psychomotor changes absent or unpredictable</td>
</tr>
</tbody>
</table>

Oh ES...Inouye SK. JAMA 2017; 318:1161-74
Interface of Delirium and Dementia

• Often coexist clinically—delirium superimposed on dementia
• Dementia a leading risk factor for delirium
• Delirium associated with markedly increased risk for dementia (OR=12.5)
• Delirium worsens the cognitive trajectory of dementia
• Pathophysiologic overlap with shared mechanisms

Witlox JAMA 2010; Fong Lancet Neurology 2015
Evidence for Inter-Relationship
“Stacking the Evidence”

• Epidemiologic
• Clinicopathological
• Mechanistic

-------------------------------------------------

• Biomarkers → Dr. Marcantonio
• Neuroimaging → Dr. Asthana
Epidemiologic Evidence
# Dementia: A Risk Factor for Delirium

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Delirium (%)</th>
<th>Adjusted risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy 2014</td>
<td>Emergency department, N=700</td>
<td>9%</td>
<td>OR 4.3 (2.2-8.5)</td>
</tr>
<tr>
<td>Koster 2013</td>
<td>Elective cardiac surgery, N=300</td>
<td>17%</td>
<td>OR 4.5 (1.9-13)</td>
</tr>
<tr>
<td>Moerman 2012</td>
<td>Acute hip fracture, N=378</td>
<td>27%</td>
<td>OR 2.8 (1.7-4.6)</td>
</tr>
<tr>
<td>Bo 2009</td>
<td>Medical or geriatric ward, N=252</td>
<td>11%</td>
<td>RR 2.1 (1.6-2.6)</td>
</tr>
<tr>
<td>Rudolph 2009</td>
<td>Cardiac surgery, development N=122; validation N=109</td>
<td>44%</td>
<td>RR 1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>Kalisvaart 2006</td>
<td>Elective hip surgery, N=603</td>
<td>12%</td>
<td>RR 5.5 (3.6-8.6)</td>
</tr>
<tr>
<td>Wilson 2005</td>
<td>Acute medical ward, N=100</td>
<td>12%</td>
<td>OR 3.2 (1.2-9.0)</td>
</tr>
<tr>
<td>O’Keeffe 1996</td>
<td>Acute medical admissions, N=225</td>
<td>28%</td>
<td>OR 4.8 (2.0-11.6)</td>
</tr>
<tr>
<td>Marcantonio 1994</td>
<td>Elective surgery, N=1341</td>
<td>9%</td>
<td>OR 4.2 (2.4-7.3)</td>
</tr>
<tr>
<td>Pompei 1994</td>
<td>Acute medical/surgical, development N=432; validation N=323</td>
<td>15%</td>
<td>OR 3.6 (2.1-6.2)</td>
</tr>
<tr>
<td>Inouye 1993</td>
<td>Acute medical, development N=107; validation N=174</td>
<td>25%</td>
<td>RR 2.8 (1.2-6.7)</td>
</tr>
</tbody>
</table>

Fong TG et al. Lancet Neurology 2015; 14:823-32
## Delirium: A Risk Factor for Dementia

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Dementia (%)</th>
<th>Adjusted risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFAS 2014</td>
<td>Population-based, N= 2197</td>
<td>23%</td>
<td>OR 8.8 (2.8-28)</td>
</tr>
<tr>
<td>BRAIN-ICU 2013</td>
<td>Multi-centre ICU admissions, N=821</td>
<td>_</td>
<td>-5.6 (-9.5 - -1.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>points per delirium-day</td>
</tr>
<tr>
<td>Gross 2012</td>
<td>Alzheimer’s clinic, N=263</td>
<td>27%</td>
<td>1.2 (0.5-1.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>points per year</td>
</tr>
<tr>
<td>Saczynski 2012</td>
<td>Elective CABG or valve surgery, N=225</td>
<td>_</td>
<td>Prolonged recovery</td>
</tr>
<tr>
<td>Vantaa 85+ 2012</td>
<td>Population-based, N=553</td>
<td>42%</td>
<td>OR 8.7 (2.1-35)</td>
</tr>
<tr>
<td>Fong 2009</td>
<td>Alzheimer’s clinic, N=408</td>
<td>_</td>
<td>2.4 (1.0-3.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>points per year</td>
</tr>
<tr>
<td>Bickel 2008</td>
<td>Elective hip surgery, N=200</td>
<td>53%</td>
<td>OR 41 (4.3-396)</td>
</tr>
<tr>
<td>Lundstrom 2003</td>
<td>Acute hip fracture, N=78</td>
<td>88%</td>
<td>OR 5.7 (1.3-24)</td>
</tr>
</tbody>
</table>

Fong TG et al. Lancet Neurology 2015; 14:823-32
## Adverse Outcomes with Delirium: Dementia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate When Delirium:</th>
<th>No. Studies</th>
<th>Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present n/N (%)</td>
<td>Absent n/N (%)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>217/714 (30%)</td>
<td>616/2243 (27%)</td>
<td>7 HR= 2.0 (1.5-2.5)</td>
</tr>
<tr>
<td>Institutionalization</td>
<td>176/527 (33%)</td>
<td>219/2052 (11%)</td>
<td>9 OR=2.4 (1.8-3.3)</td>
</tr>
<tr>
<td>Dementia</td>
<td>35/56 (63%)</td>
<td>15/185 (8%)</td>
<td>2 OR = 12.5 (1.9-84)</td>
</tr>
</tbody>
</table>

Ref: Witlox J et al. JAMA 2010;304:443-51
Clinicopathological Evidence

- VANTAA 85+ study: population-based, N=553
- Strongest relationship between incident dementia and pathologic measures (tau, amyloid, vascular, Lewy body) in persons *without delirium*
- When delirium included in models, no association with pathologic markers detectable
- Suggestion that pathologic substrates for delirium may be different from conventional dementia pathology.

Mechanistic Evidence

• Animal models and tissue culture studies
• Inflammation: animal models with vulnerable brains administered inflammatory challenge—Lipopolysaccharide (LPS) or polyinosinic:polycytidylic acid (poly I:C) —leading to neuronal death/microglial activation and persistent cognitive deficits
• Microglial priming: Cox 1 and prostaglandin inhibitors protect against LPS-induced cognitive deficits
• Inhalational anesthetics: may induce apoptosis and neurotoxicity, along with changes consistent with AD

Fong TG et al. Lancet Neurology 2015; 14:823-32
Does delirium lead to long-term cognitive decline?
Impact of Delirium at 12 months

• **Aims:** Examine cognitive function over 12 months in 225 patients following elective cardiac surgery.

• **Main Results:**
  – Delirium occurred in 46% patients
  – Cognitive trajectory (by MMSE) characterized by abrupt initial decline followed by gradual recovery over 6 months
  – *Patients with prolonged delirium did not get fully back to baseline at 12 months*

Impact of Delirium at 12 months
(N=225 cardiac surgery patients)

Impact of Delirium at 36 months: SAGES Study

Aims: Examine cognitive trajectory over 36 months in 560 patients without dementia undergoing major elective surgery

Major results:
- Delirium occurred in 24% patients following major elective surgery. Cognitive function measured by GCP composite
- In delirium and non-delirium groups, acute cognitive decline at 1 month
- Non-delirium group, recovers above baseline at 2 months, then gradual decline out to 36 months (above baseline)
- Delirium group, recovers above baseline at 2 months, then gradual decline out to 36 months substantially below baseline, with a slope equivalent to that seen in MCI

LONG-TERM COGNITIVE TRAJECTORY AFTER ELECTIVE SURGERY

Impact of Delirium Severity over 36 months: SAGES Study

Aims: Examine cognitive trajectory over 36 months in 560 SAGES patients without dementia—stratified by tertiles of delirium severity (CAM-S peak)

Major results:
• Delirium occurred in 24% patients following major elective surgery. Long-term cognitive decline (LTCD) measured by slope of GCP composite
• Delirium severity demonstrates a threshold effect with the highest level of severity (sum of CAM-S ≥17) being associated with greatest degree of LTCD at 36 months
• All other groups were not significantly different
• Slope of cognitive decline in highest severity group is \(-0.82\) GCP points/year—equivalent to that of dementia. Important exposure-response relationship.

Impact of Delirium Severity over 36 months: SAGES Study

## Delirium outcomes in persons with Alzheimer’s disease

(N=771 ADRC patients)

<table>
<thead>
<tr>
<th>Adverse Outcomes at 12 months</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>Attributable Risk %</th>
<th>Risk Attributable to Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5.4 (2.3-12.5)</td>
<td>6.2</td>
<td>1 in 16</td>
</tr>
<tr>
<td>Institutionalization</td>
<td>9.3 (5.5-15.7)</td>
<td>15.2</td>
<td>1 in 7</td>
</tr>
<tr>
<td>Cognitive Decline at 1-year</td>
<td><strong>1.6 (1.2-2.3)</strong></td>
<td><strong>20.6</strong></td>
<td><strong>1 in 5</strong></td>
</tr>
<tr>
<td>Any Adverse Outcome</td>
<td>2.2 (1.8-2.7)</td>
<td>12.4</td>
<td>1 in 8</td>
</tr>
</tbody>
</table>

Delirium Accelerates Cognitive Decline Trajectory in Dementia
[Nested cohort of 263 hospitalized patients with AD]

Gross AL Arch Intern Med 2012; 172; 1324; Fong TG Neurology. 2009;72:1570
What we don’t know

• Concept of *complicated delirium*: Delirium that leads to long-term cognitive decline (Akin to injurious falls)
  – Who is at-risk?
  – What are the causes/mechanisms?
  – Are there complex, multifactorial relationships (genetic, environmental, mediation effects between vulnerability and precipitating factors)?
  – How do we prevent?
  – How do we treat?
Preventing delirium may offer the unprecedented opportunity to prevent or ameliorate future cognitive decline.