Delirium: The Next Frontier

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DSM5 CRITERIA FOR DELIRIUM

- Disturbance in attention and awareness (reduced orientation to the environment)
- 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 an underlying organic etiology or multiple etiologies

Used with permission. American Psychiatric Association, 2013
Why is delirium important?

- Common problem
- Serious complications
- Often unrecognized
- Complex multifactorial etiology
- Potentially preventable contributor to cognitive impairment
Delirium is common

**Delirium Rates**

Hospital:
- Prevalence (on admission) 14-24%
- Incidence (in hospital) 6-56%

Postoperative: 15-53%

Intensive care unit: 70-87%

Nursing home/post-acute care: 20-60%

Palliative care: up to 80%

**Mortality**

Hospital mortality: 22-76%

One-year mortality: 35-40%

Delirium has serious complications

- Delirium associated with:
  - Increased morbidity and mortality
  - Functional and cognitive decline
  - Increased rates of dementia
  - Institutionalization
  - Increased length of stay and healthcare costs
  - Post-traumatic stress disorder
  - Caregiver burden
Patient Experience of Delirium

Patients describe fear, outrage, feeling unsafe, out of control, unprepared.

- “I was afraid, not knowing where I was”
- “I was not able to say what I wanted to say. It was very scary”
- “I was outraged that I should be treated this way with chiming beds and people coming out of walls”

Schmitt EM...Inouye SK. Gerontologist. 2019
Delirium is expensive

Hospital costs (> $8 billion/year)

Post-hospital costs (> $150 billion/year)

• Rehospitalization
• Institutionalization
• Rehabilitation
• Home care
• Caregiver burden

Overview of SAGES Study

• NIH-P01AG031720: “Interdisciplinary Study of Delirium and Its Long Term Outcomes”, started in April 2010, ongoing

• SAGES I cohort:
  – 560 patients age > 70 undergoing major scheduled non-cardiac surgical procedures (orthopedic, colectomy, vascular); no dementia at baseline
  – Interviews with complete neuropsychological battery at pre-operative baseline, 1,2,6 months and every 6 months thereafter
  – All received phlebotomy at baseline, immediate post-op, POD2, 1 month; MRI in subset at baseline/1 yr
SAGES…The Story Unfolds

• >90 papers to date
• Will overview a selected handful to tell the story of some interesting learnings from SAGES
• An ongoing story…
SAGES Study: Delirium Severity measure

Why is delirium severity important?

- Provides a continuous measure to track change over time
- Assess response to treatment
- Monitor clinical course and recovery
- Track burden of care & service utilization
- Advance pathophysiologic understanding and mechanisms
CAM-S Severity Scoring

- Simple additive score based on delirium symptoms.
- For 4-item CAM, scored from 0-7.
- For 10-item CAM, scored 0-19.
  - Detailed scoring instructions at: www.hospitalelderlifeprogram.org
- CAM-S score strongly associated with poor clinical outcomes (LOS, costs, placement, functional/cognitive decline, death)

CAM-S Scores and Length of Stay

SAGES: Natural Experiment

- Major scheduled surgery—presents a “natural experiment” to explore delirium
  - Cannot do RCT
- Significance: Allows us to explore some fundamental questions—about delirium and its outcomes
  - What are the bad outcomes?
  - Who is vulnerable?
  - Are there protective factors—can we build resilience?
  - What are the mechanisms/pathophysiology?
Major surgery: What are the bad outcomes?
Major Postoperative Outcomes

• Delirium is the most frequent postoperative complication in older adults

• Delirium has a greater effect at the population level than all other major complications (Accordion system).
  – Strong associations with:
    • Increase length of hospital stay
    • New institutional discharge
    • 30-day readmission
    • Any adverse outcome

Gleason LJ. JAMA Surg. 2015; 150: 1134-40
POD ≠ POCD

[POD=Postoperative Delirium; POCD=Postoperative Cognitive Decline]

POCD defined by ISPOCD definition (-1.96 SD on 2 tests)
Daiello LA. Anesthesiology. 2019. Epub
Are there protective factors—can we build reserve?
Preoperative Cognitive Performance Dominates Risk for Delirium Among Older Adults

- Risk of delirium is linearly and strongly related to presurgical cognitive performance level, beyond all other risk factors
- Association seen even at levels above the population median, which would be considered unimpaired

Cognitive and brain reserve and the risk of postoperative delirium

- Examined multiple reserve factors in SAGES
- Only the Wechsler Test of Adult Reading (WTAR), measure of premorbid IQ, was associated with delirium risk.
- Each 0.5 SD increase in WTAR associated with 38% reduction in delirium risk (adjusted risk ratio=0.62, 95% CI 0.45–0.85).
- Effect of WTAR disappears when GCP in model
- Lifelong learning and intelligence associated with cognitive reserve

Does delirium lead to long-term cognitive decline?
Short-Term Impact of Delirium
(N=225 cardiac surgery patients)

Short-Term Impact of Delirium (cont)

• Delirium occurred in 46% patients following cardiac surgery in 225 patients
• Cognitive trajectory characterized by abrupt initial decline followed by gradual recovery over 6 months
• Patients did not get fully back to baseline even at 1 year

LONG-TERM COGNITIVE TRAJECTORY AFTER ELECTIVE SURGERY

Longer Term Impact: SAGES Study

• Delirium occurred in 24% patients following major elective surgery in 560 patients

• In both groups, acute cognitive decline at 1 month

• Non-delirium group, recovers above baseline at 2 months, then gradual decline out to 36 mos (above baseline)

• Delirium group, recovers above baseline at 2 months, then gradual decline out to 36 months substantially below baseline (equal to MCI).

DTI Changes at One Year

- At one-year FU in SAGES (n=113), delirium associated with microstructural changes by DTI in frontal, parietal, and temporal white matter (not AD pattern).

Cavallari M. Neurology. 2017; 89: 1020-27
What are the pathophysiologic mechanisms of postoperative delirium?
Importance of Inflammation

• Some inflammation critical for healing
• How much inflammation is too much; when does inflammation become dysfunctional?
• Initial work focused on identifying inflammatory biomarkers in plasma, individually and as a “signature” at sequential timepoints (preop, POD2, 1-month)
## SAGES Inflammatory Biomarkers Studies

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>Cytokine</th>
<th>Marker for Delirium at Timepoint(s)</th>
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</thead>
<tbody>
<tr>
<td>JGMS 2015 (N=75 pairs)</td>
<td>IL-6, IL-2</td>
<td>POD2</td>
</tr>
<tr>
<td>Biopsych 2017 (N=75 pairs)</td>
<td>CRP</td>
<td>PREOP, POD2</td>
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<tr>
<td>JAGS 2017 (N=560)</td>
<td>CRP</td>
<td>PREOP, POD2</td>
</tr>
<tr>
<td>JGMS 2019 (N=75 pairs)</td>
<td>• CRP, AZGP1</td>
<td>PREOP</td>
</tr>
<tr>
<td></td>
<td>• CRP, IL-6, IL-2</td>
<td>POD2</td>
</tr>
<tr>
<td>Ann Surg 2019 (N=36)</td>
<td>CH13L1, CRP, IL-6, Plus others by SOMAScan</td>
<td>Change from PREOP to POD2</td>
</tr>
<tr>
<td>AJGP 2019 (N=547)</td>
<td>COMT genotype (Val/Val “warriors”) protected against increased risk of delirium associated with high CRP</td>
<td>POD2</td>
</tr>
</tbody>
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SAGES: The Next Frontier

- Biomarker “signature” for delirium
- Relationship of systemic inflammation to neuro-inflammation
- Intervention trials to decrease inflammation and prevent postoperative delirium
Why is addressing delirium important?

- Tremendous clinical impact
- Healthcare costs and policy implications
- Indicator of quality of care for elders
- Helps us understand the brain
- Prevention of cognitive impairment and dementia
Interested in Learning More?

• Delirium prevention-HELP
  – www.hospitalelderlifeprogram.org

• Delirium research-NIDUS (Network for Investigation of Delirium: Unifying Scientists)
  – https://deliriumnetwork.org/

• Contact us:
  – AgingBrainCenter@hsl.harvard.edu

• Follow us: @sharon_inouye @NIDUS_Delirium @ElderLifeProg
Join NIDUS & Connect to Delirium Research

NIDUS is an NIA-funded research network dedicated to advancing the study of delirium through development of research resources, career development opportunities, and dissemination of delirium science.
(NIA grant no. R24AG054259, PI: Inouye)

Advance your delirium research by:

- Registering on the NIDUS website [deliriumnetwork.org](http://deliriumnetwork.org) to access our research resources and receive delirium news through our blog and newsletter
- Entering your study in the NIDUS Delirium Research Hub, a database of delirium studies that allows researchers to complete searches and facilitate collaboration
  - Enter here: [https://deliriumnetwork.org/delirium-research-hub/](https://deliriumnetwork.org/delirium-research-hub/)
- Applying for a NIDUS Pilot Grant ($50,000 USD) by November 7, 2019

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