Pathophysiology of Delirium

Pratik Pandharipande MD, MSCI
Professor of Anesthesiology and Surgery
Department of Anesthesiology
Vanderbilt University School of Medicine
VA TN Valley Health Care System
Disclosure

- Research grant from Hospira Inc. in collaboration with NIH
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  - Vanderbilt Physician Scientist Award (2003-2005)
  - Foundation of Anesthesia Education and Research (2005-2007)
  - VA Career Development Award (2008-2011)
  - R01 NHLBI (HL111111), NIDUS
Focus

• Prevalent pathophysiological models
• Broad overview
• Focused on a critically ill population
• Supportive or circumstantial evidence through human research
Objectives: Mechanisms of Delirium

- Inflammation/Coagulation
- Endothelial dysfunction
- Neuro-endocrine
- Oxidative Stress
- Neuronal Aging
- Neurotransmitter
- Network Connectivity
Precipitants of Delirium – “End Acute Brain Failure”

- Electrolyte and fluid imbalance
- Neurological disorders and injuries
- Nutritional deficiencies
- Age
- Baseline cognitive functioning
- U-ox or acute substance intoxication & withdrawal states
- Bodily trauma & surgery
- Endocrinopathies
- Baseline psychiatric disorders
- Re or medications and various toxicines
- Anoxia or decreased oxygenation states
- Infections
- Noxious stimuli
- (organ) Failure: Apache Score = severity of medical illness process
- Isolation & sensory deprivation

Delirium Substrates
- Neuronal Aging (NAH)
- Neuroinflammation (NIH)
- Oxidative Stress (OSH)
- Neuroendocrine Dysregulation (NDH)
- Circadian Dysregulation (CDH)
- Melatonin-Tryptophan Dysregulation

Critical Factors
- Network Disconnectivity (NDH)
- Neurone Transmission Disregulation (NTH)

Systems Integration Failure Hypothesis (SIFH)

Acute Brain Failure
- Clinical Delirium Phenotypes
  - Subsyndromal
  - Hypoactive
  - Hyperactive
  - Mixed

Delirium Outcomes
- Full functional (cognitive & physical) recovery
- Variable degree of cognitive & functional deficits (Physical & Neuropsychiatric Morbidity)
- Persistent (or Chronic) Delirium

Morbidity & Mortality

Neurotransmitter Imbalances

- Monoamine Hypothesis (DA, Serotonin, NE)
- Cholinergic Hypothesis
The Monoamine Axis Hypothesis

- Serotonin, dopamine and norepinephrine may play an important role in the pathogenesis of delirium
- Bioavailability of amino acid precursors influence neurotransmitter synthesis by competing with the LAT-1 transporter in the blood brain barrier
  - Tryptophan → Serotonin
  - Tyrosine, Phenylalanine → Dopamine and Norepinephrine

Amino Acids and Delirium

Acute tryptophan depletion dose dependently impairs object memory in serotonin transporter knockout rats

Low Tryptophan Levels Are Associated with Post-Operative Delirium in the Elderly


Tryptophan and Delirium

Tryptophan \rightarrow \text{Serotonin} \rightarrow \uparrow \text{Melatonin} \rightarrow \text{Somnolence} \rightarrow \text{Hypoactive Delirium}

\text{High levels of melatonin metabolites in urine}

\text{Tryptophan} \rightarrow \uparrow \text{N,N'\text{-dimethyltryptamine}} \rightarrow \text{Excitation} \rightarrow \text{Hyperactive Delirium}

\text{Low levels of melatonin metabolites in urine}

Lewis M, 2004 Medical Hypotheses;63;402-06
Tryptophan metabolites and delirium

- Tryptophan
  - 5-hydroxytryptophan
    - 5-hydroxytryptamine (serotonin)
      - Melatonin
        - Sleep regulation and somnolence
  - Kynurenic acid
    - Kynurenine acid
      - Neuroprotective effects
    - 3-hydroxykynurenic acid
      - 3-hydroxyanthranilic acid
        - Quinolinic acid
          - Neurotoxic effects

80-95% conversion by Indoleamine-2,3-dioxygenase (IDO)

Tryptophan Metabolites & Delirium

Days without Delirium or Coma

Kynurenine (μM)

$p = .006$

Role of cholinergic transmission

• Arousal/attention:
  – Cholinergic reticulothalamic pathway
    • Basal forebrain and PPT projections
  – Sensory gating for selective attention
  – Promotes fast, synchronized EEG activity

• Memory/cognition
  – Working, spatial memory
  – Executive function

Overlap of neuroimaging lesions and cholinergic pathways

Clinical studies supporting cholinergic hypothesis


Neuronal Aging
Changes with Aging

- Diminishing physiologic reserve
- Changes in the proportion of stress-regulating neurotransmitters
- Brain blood flow decline, decreased vascular density
- Neuron loss
- Decreased intracellular signal transduction systems
The VISIONS MRI Studies

Discharge

3 Months

Hippocampal

P < 0.001

P = 0.19

Volumes, cm$^3$

P = 0.03

P = 0.03

Days of Delirium In Hospital

Superior Frontal Lobes

2A

2B

2C

2D

3 Systemic and Neuroinflammation
Cytokines, Acetylcholine, & Delirium/LTCI

Systemic insult
- Inflammation
- Endothelial activation

Cholinergic Inhibition of microglial activation

Activated microglia

Delirium

Inflammation and Delirium/LTCI

Old age, incipient neurodegenerative disease, or anticholinergics

Systemic insult
- Inflammation
- Endothelial activation

TNFα

Primed microglia

Reduced cholinergic inhibition of microglia

Overactivated microglia

Neurodegeneration

Severe, prolonged delirium
Further inflammation

Dementia

Inflammatory markers and Delirium

• 1. TNF
• 2. Interleukins (IL6, IL 8 etc)
• 3. Procalcitonin (PCT)
• 4. C-reactive protein (CRP)
• 5. Protein C
Soluble TNF Receptor-1 & Delirium

Protein C & Delirium

$P = .01$

Endothelial Dysfunction, Blood Brain Barrier and Neuronal Injury
Association between Endothelial Dysfunction and Acute Brain Dysfunction during Critical Illness

Christopher G. Hughes, M.D.,* Alessandro Morandi, M.D.,† Timothy D. Girard, M.D.,‡

- Adhesion molecules (E-Selectin)
- Coagulation molecules (PAI-1)
- Angiogenesis markers (Ang 1)
- Blood brain barrier injury (S100B)
Endothelial Dysfunction and Altered BBB Permeability/Neuronal Injury

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Neuroendocrine hypothesis
Neuroendocrine Hypothesis

Vyas et al. Neural Plas 2016
Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study

Jakub Kazmierski, Andrzej Banys, Joanna Latek, Julius Bourke and Ryszard Jaszewski

Table 5 Factors independently associated with delirium after CABG surgery revealed in multivariate stepwise logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT-B</td>
<td>0.016</td>
<td>0.004</td>
<td>1.02 (1.01 to 1.03)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Creatinine concentration</td>
<td>0.015</td>
<td>0.012</td>
<td>1.02 (0.99 to 1.04)</td>
<td>0.191</td>
</tr>
<tr>
<td>Dose of midazolam</td>
<td>0.081</td>
<td>0.028</td>
<td>1.08 (1.03 to 1.15)</td>
<td>0.005</td>
</tr>
<tr>
<td>Preoperative cortisol</td>
<td>0.005</td>
<td>0.002</td>
<td>1.005 (1.001 to 1.009)</td>
<td>0.025</td>
</tr>
<tr>
<td>Depression</td>
<td>2.389</td>
<td>0.954</td>
<td>10.90 (1.68 to 70.67)</td>
<td>0.012</td>
</tr>
<tr>
<td>IL-2 concentration</td>
<td>0.002</td>
<td>0.001</td>
<td>1.002 (1.001 to 1.004)</td>
<td>0.004</td>
</tr>
<tr>
<td>Constant</td>
<td>-12.964</td>
<td>2.725</td>
<td>-</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval; TMT-B, Trial Making Test. *The regression model is statistically significant: \( \chi^2 = 76.889; P < 0.001 \). *Preoperative variable. *Postoperative variable.
Corticosteroids and Transition to Delirium in Patients With Acute Lung Injury

Matthew P. Schreiber, MD, MHS1; Elizabeth Colantuoni, PhD2,3; Oscar J. Bienvenu, MD, PhD3,4; Karin J. Neufeld, MD, MPH3,4; Kuan-Fu Chen, MD, PhD5; Carl Shanholtz, MD6; Pedro A. Mendez-Tellez, MD3,7; Dale M. Needham, MD, PhD3,8,9

Measurements and Main Results: Delirium evaluation was performed by trained research staff using the validated Confusion Assessment Method for the ICU screening tool. A total of 330 of the 520 patients (64%) had at least two consecutive ICU days of observation in which delirium was assessable (e.g., patient was noncomatose), with a total of 2,286 days of observation and a median (interquartile range) of 15 (9, 28) observation days per patient. These 330 patients had 99 transitions into delirium from a prior nondelirious, noncomatose state. The probability of transitioning into delirium on any given day was 14%. Using multivariable Markov models with robust variance estimates, the following factors (adjusted odds ratio; 95% CI) were independently associated with transition to delirium: older age (compared to < 40 years old, 40–60 yr [1.81; 1.26–2.62], and ≥ 60 yr [2.52; 1.65–3.87]) and administration of any systemic corticosteroid in the prior 24 hours (1.52; 1.05–2.21).
Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis
The HYPRESS Randomized Clinical Trial

Didier Keh, MD; Evelyn Trips; Gernot Marx, MD; Stefan P. Wirtz, MD; Emad Abduljawwad, MD; Sven Bercker, MD; Holger Bogatsch, MD; Josef Briegel, MD; Christoph Engel, MD; Herwig Geriach, MD, PhD, MBA; Anton Goldmann, MD; Sven-Olaf Kuhn, MD; Lars Hüter, MD; Andreas Meier-Hellmann, MD; Axel Nierhaus, MD; Stefan Kluge, MD; Josefa Lehmke, MD; Markus Loeffler, MD; Michael Oppert, MD; Kerstin Resener, MD; Dirk Schädler, MD; Tobias Schuerholz, MD; Philipp Simon, MD; Norbert Weiller, MD; Andreas Weyland, MD; Konrad Reinhart, MD; Frank M. Brunkhorst, MD; for the SepNet-Critical Care Trials Group
### Table 2. Primary and Secondary End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (n = 176)</th>
<th>Hydrocortisone (n = 177)</th>
<th>Total (N = 353)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Septic shock, No./total No. (%)</td>
<td>39/170 (22.9) [17.2-30.0]</td>
<td>36/170 (21.2) [15.6-28.1]</td>
<td>75/340 (22.1) [17.9-26.9]</td>
<td>.70</td>
</tr>
<tr>
<td>ITT population</td>
<td>33/156 (21.2) [15.4-28.4]</td>
<td>29/155 (18.7) [13.3-25.7]</td>
<td>62/311 (19.9) [15.8-24.8]</td>
<td>.59</td>
</tr>
<tr>
<td>PP population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality, No./total No. (%)</td>
<td>14/170 (8.2) [5.0-13.4]</td>
<td>15/171 (8.8) [5.4-14.0]</td>
<td>29/341 (8.5) [6.0-12.0]</td>
<td>.86</td>
</tr>
<tr>
<td>28 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>180 d</td>
<td>37/167 (22.2) [16.5-29.0]</td>
<td>45/168 (26.8) [20.7-34.0]</td>
<td>82/335 (24.5) [20.2-29.4]</td>
<td>.32</td>
</tr>
<tr>
<td>ICU</td>
<td>14/172 (8.1) [4.9-13.2]</td>
<td>13/171 (7.6) [4.5-12.6]</td>
<td>27/343 (7.9) [5.5-11.2]</td>
<td>.85</td>
</tr>
<tr>
<td>LOS, median (IQR), d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>9 (6-17)</td>
<td>8 (5-15)</td>
<td>8 (5-16)</td>
<td>.23</td>
</tr>
<tr>
<td>Hospital</td>
<td>25 (16-40)</td>
<td>26 (16-46)</td>
<td>26 (16-43)</td>
<td>.36</td>
</tr>
<tr>
<td>Mechanical ventilation, No./total No. (%) [95% CI]</td>
<td>103/172 (59.9) [52.4-66.9]</td>
<td>91/171 (53.2) [45.8-60.5]</td>
<td>194/343 (56.6) [51.3-61.7]</td>
<td>.21</td>
</tr>
<tr>
<td>MV-free time, median (IQR), d</td>
<td>5 (2-7)</td>
<td>4 (2-7)</td>
<td>4 (2-7)</td>
<td>.34</td>
</tr>
<tr>
<td>RRT, No./total No. (%) [95% CI]</td>
<td>21/172 (12.2) [8.1-17.9]</td>
<td>21/171 (12.3) [8.2-18.0]</td>
<td>42/343 (12.2) [9.2-16.1]</td>
<td>.98</td>
</tr>
<tr>
<td>RRT-free time, median (IQR), d</td>
<td>7 (4-14)</td>
<td>6 (4-12)</td>
<td>7 (4-13)</td>
<td>.35</td>
</tr>
<tr>
<td>SOFA score until day 14, median (IQR)</td>
<td>5.0 (3.5-6.8)</td>
<td>4.7 (3.5-6.5)</td>
<td>4.8 (3.5-6.6)</td>
<td>.69</td>
</tr>
<tr>
<td>Delirium, No./total No. (%) [95% CI]</td>
<td>25/102 (24.5) [17.2-33.7]</td>
<td>11/98 (11.2) [6.4-19.0]</td>
<td>36/200 (18.0) [13.3-23.9]</td>
<td>.01</td>
</tr>
</tbody>
</table>
Oxidative Stress
Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery

Marcos G. Lopez\textsuperscript{a}, Pratik Pandharipande\textsuperscript{a}, Jennifer Morse\textsuperscript{c}, Matthew S. Shotwell\textsuperscript{c},

Partial mediation effect noted
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Network Connectivity
Network Disconnectivity Hypothesis

• Brain is highly organized and interconnected
• Complex integration of sensory information and motor responses
• Delirium represents a failure in integration and processing and an acute breakdown in network connectivity
• Baseline network connectivity (age, cognition) and inhibitory tone determined by neurotransmitter availability

Maldonando J. Int J Geriatr Psychiatry 2017
Delirium associated with a decrease in alpha power and increase in δ power

Measured Phase Lag Index (PLI)- estimates synchronization or the average connectivity strength between EEG channels for a particular band

Mean phase lag index was lower in the α band (8 to 13 Hz) in patients with delirium

δ Band–directed phase lag index was lower in anterior regions and higher in central regions in delirious patients indicating higher information flow toward anterior regions in the δ band.
White Matter Integrity and Delirium

Anterior limb of the internal capsule

Reduced fractional anisotropy = white matter disruption
White Matter Integrity and Delirium

Genu of the corpus callosum

Reduced fractional anisotropy = white matter disruption

Delirium: Complex interplay of numerous mechanisms

Global impairments of cerebral metabolism

Acute glutamate and ACh surge

Proinflammatory cytokine release

Blood brain barrier permeability

Selective reduction of ChAT+ neurons

Increased monoaminergic activity

Decreased ACh synthesis, release

Cholinergic deficit

Delirium

Antimuscarinic Compounds

Exacerbates

IGF-1

Neuroprotection for injured brain

Questions?

Pratik.pandharipande@vanderbilt.edu