Delirium and Post-Delirium Encephalopathy

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Gerald Nora MD, PhD

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Disclosures

Nothing to disclose
Goals of this talk

1. Distinguish the characteristics of both acute delirium and also post-delirium encephalopathy.

2. Describe similarities and differences between the mechanisms of traumatic brain injury and delirium.

3. Identify pharmacologic and non-pharmacologic interventions for prevention and treatment of delirium.

4. Identify potential pharmacologic and non-pharmacologic interventions for patients with post-delirium encephalopathy.

Outline

• Delirium 101

• Post-delirium Encephalopathy

• Mechanisms of Brain Injury in Delirium

• Future Directions

• Potential Interventions
Scope of the Talk

The focus of this talk is on systemic and environmental causes of delirium.

TBI, CVA, PRES, Meningitis, Seizures are excluded.

Perioperative delirium is excluded.

Delirium 101
Definition of Delirium

1. Disturbance of consciousness: reduced focus or attention.

2. Cognitive change: memory, language, orientation, or perception.

3. Acute onset and fluctuating course.

Hyperactive: overt hallucinosis, psychomotor agitation
Hypoactive: seemingly well-behaved, more common

Historical Perspective

Called “phrenitis” by Hippocrates

1959 review characterized delirium as “brain failure”

Multiple terms and etiologies frustrated early research

DSM-IV (TR); Albrecht et al., 2015

Morandi et al., 2008; Engel and Roman, 1959
Epidemiology

Incidence: 11-14% in general medicine patients.

Mortality risk increased ~1.4-2.0 fold (or greater in ICU).

Length of stay: increased by 5-10 days.

Cost: $38-152 Billion dollars in the USA annually.

Inouye et al., 2014; Ely et al., 2004; Maldonado, 2013

Post Delirium Encephalopathy
Increased dependence in functional activities.

~50% of survivors with complaints of memory deficits; >70% in ARDS. (Hopkins and Jackson, 2006)

BRAIN-ICU Study

Tracked 893 ICU patients.
Tracked ICAM assessments in ICU.
3- and 12-month neuropsych battery.

(Pandharipande et al., 2013)
Delirium: “Time is Brain”

Proposed Characteristics of PDE

Deficits in executive function and memory.

Chronic as opposed to fluctuating course.

Attention is stable.

Potentially some overlap with post-concussive symptoms.

Alternative term used is “Post-ICU Syndrome”.

Pandharipande et al., 2013
Mechanisms of Delirium and PDE

Iacobone et al, 2009

Cerebral Malperfusion
Cerebral Perfusion: A Delicate Balance

Original Lassen Model vs Modern Data

- Tzeng and Ainslie, 2014; Tan, 2012; Lucas et al., 2010

Cerebral Perfusion: Deficits in Concussion

- 92 mTBI patient prospective study.
- SPECT within 72 hours of injury.
- SPECT abnormal in 63% of patients.
- Correlated with LOC, PTA, and PCS.

Gowda et al., 2006; Yuh et al, 2014
Delirium and Malperfusion

sPECT abnormalities in 11 of 22 delirious older patients.

Plurality of patients septic.

Normalized perfusion with resolution of delirium.

About 10 case series and reports with supporting data.

Fong et al., 2006; Alsop et al, 2006

Delirium and Malperfusion Key Points

Some striking correlations with the TBI literature.

Limited but suggestive data on perfusion abnormalities even in non-septic patients with delirium.
Inflammation and Amyloid in CTE

Repetitive TBI mouse model shows increased deposition of amyloid over time.

Inflammation and neurotoxicity associated with tau-deposition in CTE.

Meehan et al., 2015; Uryu et al, 2002
Inflammation and Amyloidogenesis in Delirium

S100B associated with astrocyte activation in brain.

CSF IL-6 and Serum IL-8 and IL-10 correlated with delirium.

Alteration of amyloid metabolism in delirium.

Van Munster et al., 2004; Khan et al., 2011; Maldonado, 2013

Microglia activation in delirium

Retrospective case control post-mortem of 9 delirious patients and six age-matched controls.

Van Munster et al., 2011
Microglia activation in delirium

Van Munster et al., 2011

Statins May Modify Course of Delirium

Prospective cohort study of 763 patients in ICU

588 developed delirium defined by CAM-ICU.

257 used statins pre-admission.

197 used statins in ICU.

Early benefit with early statin use in sepsis.

Morandi et al., 2014
Key Points

Correlation of delirium and neuroinflammation.

Suggests how delirium can cause, not just unmask dementia.

Further work on amyloid and tau pathology would be useful.

Neurotransmitter Imbalance
Frontal Lobes and Dopamine in Delirium

Orbifrontal cortex modulates aggression in non-human primates.

Acetylcholine-dopamine imbalance exists in delirium.

Restraints, noxious stimuli provoke imbalance.

Fong et al., 2009; Nelson and Trainor, 2007

Antipsychotics and Delirium: Dopamine Excess (?)

Randomized controlled trials show less severe delirium for atypical and typical antipsychotics.

One perioperative study showed prophylactic benefit in an RCT.

*Must differentiate between hyperactive and hypoactive delirium!*

Wang et al., 2012; Fong et al., 2009
Delirium and Acetylcholine Deficiency

Elevated serum cholinesterase is associated with delirium.

Anticholinergic drugs are classic causes of delirium.

Nicotine withdrawal associated with delirium.

Donepezil in hip fracture patients had no benefit in small RCT.

Overshott et al., 2008; Hessler et al, 2014

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Benzodiazepines in Delirium

Imbalance of GABAergic activity can lead to paradoxical agitation.

Associated with executive dysfunction in BRAIN-ICU Study.

Burst supression in ICU predicts subsequent delirium.

Fong et al., 2009; Pandharipande et al, 2006, 2013; Brown et al., 2011
Every time you give a benzodiazepine to a delirious patient, God kills a puppy.

Please, think of the puppies.

H/T Dr. Camiolo-Reddy
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Post-Delirium Encephalopathy

Brain Atrophy after ARDS

15 ARDS patients vs. age- and sex-matched controls.

Did not assess delirium but post-dc cognition followed.

Hopkins et al., 2006
Hypothesis: Acetylcholine and Microglia Activation

Acetylcholine has an anti-inflammatory effect on microglia.

Inadequate acetylcholine leads to uncontrolled microglia activation.

Microglia lead to acetylcholinergic neuron death.

Van Gool et al., 2010
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Delirium

- Inflammation
- Neurotransmitter imbalance
- Metabolic dysfunction
  - Sepsis
  - SIRS
  - Amyloid

Metabolic dysfunction
  - Malperfusion
  - Oxidative stress
  - Nutrition/lytes

Delirium and Evolution to PDE

- Inflammation
- Neurotransmitter imbalance
- Neuron death
  - Sepsis
  - SIRS
  - Amyloid

Metabolic dysfunction
  - Malperfusion
  - Oxidative stress
  - Nutrition/lytes
Open Questions

Is PDE a new “miserable minority”?

Neurophysiology of delirium subtypes.

The role of discharge medications in PDE.

Amyloid and tau pathology in post-delirium patients.

Tracking chronic neuroinflammation.

So Now What?
Clinical Implications

Assessment of post-ICU patients’ return to former activities and cognitive screening.

Consider neuropsychological evaluation if patient struggling >3-6 months.

Clean up medications.

Assess sleep, PTSD/depression.

Address physical activity.
So Now What? Pharmacology

Less is probably more, especially with senior citizens.

Poor evidence for donepezil/rivastigmine acutely, none for PDE.

Could consider medication if a younger patient is out of delirium with cognitive deficits.

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Bibliography


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