Definition

Delirium = acute cerebral dysfunction

Fluctuation or change baseline mental status
- Changed level of consciousness
  - less aware of surroundings, decreased focus, attention deficit (depression, apathy), disorganized thinking
- Change in cognition
  - Memory disturbance, disorientation, speech disorders
  • Hallucinations, delusions

Delirium mechanism

1. **Imbalance neurotransmitters and neuroinflammatory mediators**
   - \(\Delta\) dopamine, \(\Delta\) Acetylcholine (β 0)
   - Haloperidol = dopamine-blocker
   - \(\Delta\) GABA, serotonin, noradrenaline, histamin, glutamin...

2. **Occult diffuse brain injury**
   - Seizures: severe hypotension, hypoxia
   - Inflammation
     - \(\Delta\) delirium in pts with high crp ~ BBB disruption
     - Role of cytokines (IL-1, IL-2, TNF) ~ neurotransmitters

3. **Genetic predisposition**: Apolipoprotein E4 genotype
   - \(\Delta\) delirium duration
   - More pronounced vulnerability to drug related brain toxicity

Risk factors

- **Not Modifiable**
  - Age
  - Cognition
  - Hypertension

- **Modifiable**
  - Alcohol
  - Smoking
  - Renal depend.
  - Hypotension
  - Sepsis
  - Metabolic Δ
  - USUS

DISEASE SEVERITY

Patient-centered
- Illness related
- ICU acquired
- USUS

- Hypotension
- Sepsis
- Metabolic Δ

Continuum of cognitive dysfunction

- **In the ICU**
  - Delirium
  - Acute stress disorder
  - Anxiety
  - Depression

- **Outside ICU**
  - Cognitive dysfunction
  - PTSD
  - Anxiety
  - Depression

Impairment of:
- Attention
- Concentration
- Memory
- Executive function

MMSE (global), Trailmaking test A/B, Digit span, A01, IADL, Verbal fluence test, Verbal learning test...

Delirium prevalence

- **11 – 87% of all ICU admissions**
- Disease severity, ventilation, delirium score used, relation with sedation

Effect of sedation level on the prevalence of delirium when assessed with CAM-ICU and ICDSC

In the ICU

Outside ICU
Cognitive Impairment (CI) - short term

- At hospital discharge
  - ARDS studies: 70% - 100% of patients
  - Mixed ICU studies: 39% - 51%
  - Sakuramoto et al. mixed ICU 79 pts with LOS >2days
  - Cognition evaluation by MMSE

Averaged ICDS score OR 1.6 (1.02 - 2.55 ; P=0.004)

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

- Prospective cohort 1194 patients for severe sepsis
  (US residents 1998-2008, original 9223 respondents)
  - 516 survived severe sepsis, 4517 patients non-sepsis episode
  - Biennial interviews cognition and HRQOL

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Change in Individual ADLs and Instrumental ADLs by Baseline Functioning

No limitations (n=269)  Mild/Moderate limitation (n=195)  Severe limitation (n=159)

Wide range of new difficulties across the array of activities.

Long-term Cognitive Impairment after Critical Illness

- 821 pts with respiratory failure or shock, CAM-ICU and SOFA 30 days + Cogn. Function at 3 / 12 months post ICU

Global cognition + executive functions 0 at 12 months

CI = mild TBI in 40% (3m) → 34% (12 m)
  - Alzheimer in 25% (3m) → 24% (12m)

BRAIN-ICU
Bringing To Light The Risk Factors And Incidence Of Neuropsychological Dysfunction in ICU Survivors

Independent of sedative, age, pre-existing CI, comorbidity, organ failure, duration ICU

The New England Journal of Medicine
October 5, 2013

The Adult Respiratory Distress Syndrome Cognitive Outcomes Study (ACOS)

Long-Term Neuropsychological Function in Survivors of Acute Lung Injury


Am J Respir Crit Care Med. 190, 62, pp 1084-1105, Jan 15, 2014

Subset of FACT: Fluid and Catheter Treatment Trial: Liberal vs conservative fluid management in ALI

Ventilation days -2.5d (P=0.04)

75 patients (<1001 patients)

Telephone-based neuropsychological evaluation

- Test battery of 45-60 minutes
  - Memory, verbal fluency, executive function

Table 2: Association with Long-term Cognitive Impairment in Survivors of ALI

- CI ~ mild TBI in 40% (3m) → 34% (12 m)
  - Alzheimer in 25% (3m) → 24% (12m)

Global cognition + executive functions 0 at 12 months

International journal of medicine

Cost-Effectiveness of Biannual Cognitive Screening in ICU Survivors

Independent of sedative, age, pre-existing CI, comorbidity, organ failure, duration ICU
Delirium in the Intensive Care Unit and Subsequent Long-term Disability Among Survivors of Mechanical Ventilation


- Study within the Awakening and Breathing Controlled (ABC) Trial
- 84% experienced delirium (1/2 ≥ 2d; 1/4 ≥ 5d)
- 126 eligible patients

84% experienced delirium (1/2 ≥ 2d; 1/4 ≥ 5d)

126 eligible patients

Functional outcomes during follow-up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3-months</th>
<th>12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL disability</td>
<td>33% (28/89)</td>
<td>32% (29/92)</td>
</tr>
<tr>
<td>IADL disability</td>
<td>17% (13/76)</td>
<td>5% (3/55)</td>
</tr>
<tr>
<td>Impaired Physical Health Status</td>
<td>84% (62/74)</td>
<td>80% (64/80)</td>
</tr>
<tr>
<td>Worse or Much Worse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor/Sensory Factor Score</td>
<td>62% (46/74)</td>
<td>73% (41/56)</td>
</tr>
</tbody>
</table>

The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: The VISIONS cohort magnetic resonance imaging study

- Prospective study 47 ICU pts with sepsis / respiratory failure
  - 70% had delirium during ICU stay, > 25% during at least 3 days
  - MRI and cognitive functions at discharge, 3 and 12 m post-ICU

Results:
- Duration delirium ¨ brain volume (discharge hosp, 3m)
- ¨ brain atrophy at 3 months ¨ cognitive deficit 12 months

Histopathology

- Brain autopsy in patients with critical illness + delirium
  - Mean age: 55 yrs
  - No history of dementia,
  - Ischemic and hypoxic/hypoxic hippocampal lesions in 5/7 patients

Janz et al. JCC 2010

Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: The Activity and Cognitive Therapy in ICU (ACT-ICU) trial

- 82 patients, 3 groups (Phys+Cogn+Phys/0) start 24hrs post ICU admission

Feasibility study
Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial

- 82 patients, 3 groups, (Phys/Cogn+Phys/0) start 24hrs post ICU admission

### Table 3: 3-month follow-up outcomes

<table>
<thead>
<tr>
<th></th>
<th>Used care (n = 32)</th>
<th>Physical therapy (n = 10)</th>
<th>Cognitive + physical therapy (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary follow-up outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS (days)</td>
<td>10 (8-13)</td>
<td>11 (9-13)</td>
<td>10 (9-13)</td>
<td>0.20</td>
</tr>
<tr>
<td>Secondary follow-up outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU retention (days)</td>
<td>21 (16-25)</td>
<td>18 (14-22)</td>
<td>20 (16-24)</td>
<td>0.06</td>
</tr>
<tr>
<td>APACHE II</td>
<td>25 (18-35)</td>
<td>26 (22-35)</td>
<td>25 (21-34)</td>
<td>0.98</td>
</tr>
<tr>
<td>NRS-10 (0-10)</td>
<td>8 (6-9)</td>
<td>8 (6-9)</td>
<td>9 (6-9)</td>
<td>0.25</td>
</tr>
<tr>
<td>Katz ADL (activities of daily living)</td>
<td>0.00 (0.00)</td>
<td>1.00 (1.00)</td>
<td>0.00 (0.00)</td>
<td>0.69</td>
</tr>
<tr>
<td>IADL ( instrumental activities of daily living)</td>
<td>2.0 (1.0-3.0)</td>
<td>2.0 (1.0-3.0)</td>
<td>2.0 (1.0-3.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>EQ-5D VAS (health-related quality of life)</td>
<td>73 (54-88)</td>
<td>70 (62-89)</td>
<td>75 (54-88)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

### Conclusion

- Critical illness and delirium ➔ short-term + long-term cognitive dysfunction
- Longer duration of delirium ➔ more cognitive impairment
- Impact on quality of survivorship on very long term
- More studies on how to improve long-term CI:
- Identify which patients can improve?
- Identify which rehabilitation efforts work?