The interface between delirium and dementia in elderly adults

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Dementia
- An insidious neurodegenerative condition, is characterized by chronic and progressive cognitive decline from a previous level of performance in one or more cognitive domains that interferes with independence in everyday activities.

Delirium
- A syndrome manifesting as an acute change in mental status that is characterized by inattention and disturbance in cognition that develops over a short period of time with a fluctuating course of symptoms.

- As many as 50% of people older than 65 years
- Preventable in about 30–40% of cases
Introduction

- Two of the most common causes of cognitive impairment in older populations
- Interrelation remains poorly understood
- Dementia is the leading risk factor for delirium
- Delirium is an independent risk factor for subsequent development of dementia
- Delirium
  - a marker of vulnerability to dementia
  - precipitating factors
  - itself can cause permanent neuronal damage
Panel: Predisposing and precipitating factors for delirium from validated predictive models

Predisposing factors
- Dementia or pre-existing cognitive impairment
- History of delirium
- Functional impairment
- Sensory impairment—eg, vision impairment and hearing impairment
- Comorbidity or severity of illness
- Depression
- History of transient ischaemia or stroke
- Alcohol abuse
- Older age

Precipitating factors
- Polypharmacy, use of psychoactive or sedative-hypnotic drugs
- Use of physical restraints
- Use of bladder catheter
- Physiological and metabolic abnormalities—eg, high blood-urea-nitrogen:creatinine ratio, abnormal sodium, glucose, or potassium concentrations in serum, hypoxaemia, or metabolic acidosis
- Infection
- Any iatrogenic event
- Major surgery
- Trauma or urgent admission to hospital
- Coma
Distinguishing delirium from dementia

- Dementia and delirium - distinct and mutually exclusive conditions (DSM-V)
- Distinguishing between the two diagnoses in the clinical setting can be difficult
  - Persistent delirium and reversible dementia
  - Delirium symptoms can persist for months or even years
<table>
<thead>
<tr>
<th></th>
<th>Delirium</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Abrupt, although initial loss of mental clarity can be subtle</td>
<td>Insidious and progressive</td>
</tr>
<tr>
<td>Duration</td>
<td>Hours to days (although it can be prolonged in some cases)</td>
<td>Months to years</td>
</tr>
<tr>
<td>Attention</td>
<td>Reduced ability to focus, sustain, or shift attention is a hallmark feature that occurs early in presentation</td>
<td>Normal except in severe dementia</td>
</tr>
<tr>
<td>Consciousness (ie, awareness of the environment)</td>
<td>Fluctuating (thus assessment at multiple timepoints is necessary); reduced level of consciousness and impaired orientation</td>
<td>Generally intact</td>
</tr>
<tr>
<td>Speech</td>
<td>Incoherent and disorganised; distractible in conversation</td>
<td>Ordered, but development of anomia or aphasia is possible</td>
</tr>
<tr>
<td>Cause</td>
<td>Underlying medical condition, substance intoxication, or side-effect of drugs</td>
<td>Underlying neurological process (eg, amyloid β plaque accumulation in Alzheimer’s disease)</td>
</tr>
<tr>
<td>Other features</td>
<td>Hyperactive, hypoactive, and mixed forms, as determined by the type of psychomotor disturbance, are possible; disruption in sleep duration and architecture; perceptual disturbances</td>
<td>Symptoms vary depending on underlying pathology (eg, fluctuations in cognition are a feature of Lewy body dementia)</td>
</tr>
</tbody>
</table>

These two syndromes have substantial overlapping features and can coexist in an individual patient.

Table 1: Comparative features of delirium and dementia
Evidence linking delirium and dementia

Figure: A hypothetical model for the pathophysiological relation between delirium and dementia
Evidence linking delirium and dementia

- Epidemiological evidence
- Clinicopathological evidence
- Neuroimaging evidence
- Biomarker evidence
- Animal models and neuronal tissue culture
Evidence linking delirium and dementia

- Several mechanisms hypothesized to explain how delirium might contribute to permanent neuronal damage
  - Permanent neuronal damage
    - Neurotoxicity (e.g., drugs, anaesthesia, endotoxins), inflammation, chronic stress, neuronal damage (e.g., prolonged ischaemia, hypoglycaemia, shock, sepsis), acceleration of dementia pathology (e.g., amyloid β [Aβ] and tau pathology), and diminished cognitive reserve
  - Metabolic derangements or particular drugs (e.g., anticholinergics)
    - Alterations in neurotransmitter concentrations (e.g., acetylcholine deficiency, dopamine excess)
  - Hypoxia or cerebral ischemia
    - Impaired cerebral blood flow and metabolism
Evidence linking delirium and dementia

- Anaesthetics
  - directly facilitate acceleration of Aβ accumulation, leading to apoptosis and cholinergic dysfunction, which in turn could further accelerate or initiate Aβ pathology.
- Infections or response to a stressor (e.g., surgery or acute illness)
  - cause neuronal dysfunction through activation of inflammatory mechanisms
- Indirectly through altered neurotransmission, apoptosis, activation of microglia and astrocytes
  - Production of free radicals, complement factors, glutamate, and nitric oxide
Evidence linking delirium and dementia

- Epidemiological evidence
  - Dementia with delirium ranged from 9% to 44%
    - Baseline cognitive impairment or dementia is an important independent risk factor for delirium
    - Increasing delirium risk by 2-5 times
  - Delirium was consistently associated with a significantly increased risk of both long-term cognitive decline (ie, substantial declines on cognitive testing) and dementia (odds ratios 6–41)
<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample size</th>
<th>Cognitive baseline</th>
<th>Delirium measure</th>
<th>Mean age at baseline (years)</th>
<th>Patients with delirium</th>
<th>Adjusted effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy et al (2014)</td>
<td>Patients aged ≥65 years admitted to emergency department</td>
<td>700</td>
<td>Documented dementia by chart</td>
<td>Prevalent delirium by CAM</td>
<td>77</td>
<td>9%</td>
</tr>
<tr>
<td>Koster et al (2013)</td>
<td>Patients aged ≥70 years undergoing elective cardiac surgery</td>
<td>300</td>
<td>MMSE &lt;23</td>
<td>DOSS</td>
<td>74</td>
<td>17%</td>
</tr>
<tr>
<td>Moerman et al (2012)</td>
<td>Patients aged ≥65 years with acute hip fracture</td>
<td>378</td>
<td>Clinical diagnosis of dementia</td>
<td>Prevalent delirium by DSM-IV</td>
<td>84</td>
<td>27%</td>
</tr>
<tr>
<td>Bo et al (2009)</td>
<td>Patients aged ≥70 years admitted to medical or geriatric wards</td>
<td>252</td>
<td>SPMSQ to establish presence and severity of cognitive impairment</td>
<td>Incident delirium by CAM</td>
<td>82</td>
<td>11%</td>
</tr>
<tr>
<td>Rudolph et al (2009)</td>
<td>Patients aged ≥60 years undergoing elective cardiac surgery</td>
<td>122 in development sample; 109 in validation sample</td>
<td>Preoperative MMSE ≤23</td>
<td>Incident delirium by CAM</td>
<td>75</td>
<td>44%</td>
</tr>
<tr>
<td>Kalisvaart et al (2006)</td>
<td>Patients aged ≥70 years undergoing elective hip surgery</td>
<td>603</td>
<td>Preoperative MMSE &lt;24</td>
<td>Postoperative delirium by DSM-IV and CAM</td>
<td>78</td>
<td>12%</td>
</tr>
<tr>
<td>Wilson et al (2005)</td>
<td>Patients aged ≥75 years admitted to acute medical wards</td>
<td>100</td>
<td>ICODE to establish presence of cognitive change over time</td>
<td>Incident delirium by DSM-III</td>
<td>85</td>
<td>12%</td>
</tr>
<tr>
<td>O’Keeffe et al (1996)</td>
<td>Patients with acute medical admissions to geriatric units</td>
<td>225</td>
<td>Clinical diagnosis of dementia or BDRS ≥4</td>
<td>Incident delirium by DSM-III</td>
<td>82</td>
<td>28%</td>
</tr>
<tr>
<td>Marcantonio et al (1994)</td>
<td>Patients aged ≥50 years admitted to elective surgical units</td>
<td>1341</td>
<td>TICS &lt;30</td>
<td>Postoperative delirium by CAM</td>
<td>68</td>
<td>9%</td>
</tr>
<tr>
<td>Pompei et al (1994)</td>
<td>Patients aged ≥65 years with no delirium admitted to acute hospital medical and surgical wards</td>
<td>432 in development sample; 323 in validation sample</td>
<td>MMSE &lt;24 (adjusted for education level)</td>
<td>Incident delirium by DSM-III</td>
<td>74</td>
<td>15%</td>
</tr>
<tr>
<td>Inouye et al (1993)</td>
<td>Patients aged ≥70 years with no dementia or delirium admitted to acute hospital medical wards</td>
<td>107 in development sample; 174 in validation sample</td>
<td>MMSE &lt;24 on admission</td>
<td>Incident delirium by CAM</td>
<td>79</td>
<td>25%</td>
</tr>
</tbody>
</table>

CAM=Confusion Assessment Method. OR=odds ratio. MMSE=Mini-Mental State Examination. DOSS=Delirium Observation Screening Scale. DSM=Diagnostic and Statistical Manual of Mental Disorders. SPMSQ=Short Portable Mental Status Questionnaire. RR=relative risk. ICODE=Informant Questionnaire on Cognitive Decline in the Elderly. BDRS=Blessed Dementia Rating Scale. TICS=Telephone Interview for Cognitive Status.

Table 2: Baseline cognitive impairment and dementia as an independent risk factor for delirium from predictive models
<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample size</th>
<th>Delirium measure</th>
<th>Cognitive outcome</th>
<th>Mean age at baseline (years)</th>
<th>Patients with delirium</th>
<th>Adjusted effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive function and ageing study (2014)</td>
<td>Population-based sample; multicentre sampling from health authority lists</td>
<td>2197</td>
<td>Algorithmic operationalisation of DSM-IV based on Geriatric Mental State examination</td>
<td>AGECAT-defined dementia at 2 years</td>
<td>77</td>
<td>6%</td>
</tr>
<tr>
<td>BRAIN-ICU (2013)</td>
<td>Multicentre ICU admissions</td>
<td>821</td>
<td>CAM-ICU</td>
<td>RBANS score at 1 year</td>
<td>61</td>
<td>74%</td>
</tr>
<tr>
<td>Gross et al (2012)*</td>
<td>Memory clinic patients with clinically diagnosed Alzheimer’s dementia</td>
<td>263</td>
<td>Retrospective diagnosis of delirium from case notes (validated algorithm)</td>
<td>Worsening of Blessed IMC test score over 5 or more years</td>
<td>78</td>
<td>56%</td>
</tr>
<tr>
<td>Saczynski et al (2012)</td>
<td>Patients aged ≥60 years undergoing elective CABG or valve surgery</td>
<td>225</td>
<td>CAM</td>
<td>Trajectory of MMSE change over 1 year</td>
<td>73</td>
<td>46%</td>
</tr>
<tr>
<td>Vantaa 85+ (2012)</td>
<td>Population-based sample of all residents aged ≥85 years</td>
<td>553</td>
<td>Participant and informant interview, along with medical record review</td>
<td>Dementia (DSM-III-R; individual clinician) at 2-5 years</td>
<td>89</td>
<td>13%</td>
</tr>
<tr>
<td>Fong et al (2009)*</td>
<td>Memory clinic patients with clinically diagnosed Alzheimer’s disease</td>
<td>408</td>
<td>Retrospective diagnosis of delirium from case notes (validated algorithm)</td>
<td>Worsening of Blessed IMC test score over 0-7 years</td>
<td>74</td>
<td>18%</td>
</tr>
<tr>
<td>Bickel et al (2008)</td>
<td>Patients aged ≥60 years undergoing elective hip surgery</td>
<td>200</td>
<td>CAM</td>
<td>Cognitive impairment or dementia, or both</td>
<td>74</td>
<td>21%</td>
</tr>
<tr>
<td>Lundström et al (2003)</td>
<td>Dementia-free patients aged ≥65 years with acute hip fracture</td>
<td>78</td>
<td>DSM-IV</td>
<td>Consensus diagnosis of dementia at 5 years</td>
<td>79</td>
<td>38%</td>
</tr>
</tbody>
</table>

DSM=Diagnostic and Statistical Manual of Mental Disorders. AGECAT=Automated Geriatric Examination for Computer Assisted Taxonomy. OR=odds ratio. BRAIN-ICU=Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in Intensive Care Unit Survivors. ICU=intensive care unit. CAM=Confusion Assessment Method. RBANS=Repeatable Battery for the Assessment of Neuropsychological Status. IMC=Information-Memory-Concentration. CABG=coronary artery bypass grafting. MMSE=Mini-Mental State Examination. *Related analyses with some overlap of data.

Table 3: Delirium as an independent risk factor for long-term cognitive decline and dementia.
Evidence linking delirium and dementia

- A meta-analysis involving two studies with a total of 241 patients
  - Delirium was associated with an increased rate of incident dementia
  - Even after controlling for relevant confounders (adjusted relative risk 5.7, 95% CI 1.3–24.0).

- In another study of 225 patients who had undergone cardiac surgery,
  - Delirium resulted in a punctuated decline in cognitive function, followed by recovery over 6–12 months in most patients
  - A substantial proportion, particularly those patients with prolonged delirium, never returned to baseline

- In a study of 821 ICU patients
  - A longer duration of delirium was independently associated with significantly worse global cognition and worse executive function scores on the basis of a neuropsychological battery at 3-month and 12-month follow-up
Evidence linking delirium and dementia

- Clinicopathological evidence (Vantaa 85+)
  - The effect of delirium (determined retrospectively) on cognitive and functional outcomes
    - In this cohort of 553 individuals aged 85 years or older, delirium increased the risk of incident dementia (odds ratio 8.7, 95% CI 2.1–35.0)
    - Delirium was associated with increased dementia severity, new functional deficits, and accelerated decline in cognitive scores
  - Acceleration of cognitive decline following delirium might result from an alternative mechanism leading to neuronal damage
    - In the absence of a delirium history
      - neurofibrillary tau, amyloid burden, apolipoprotein E (APOE) ε4 variant, vascular lesions, and Lewy body pathology were strongest
    - Which delirium was also part of the history
      - no associations
Evidence linking delirium and dementia

- Neuroimaging evidence
  - Two studies on 47 ICU survivors used volumetric analysis and DTI at hospital discharge and 3-month follow-up
  - In the volumetric analysis
    - Longer duration of delirium was significantly associated with greater brain atrophy (at hospital discharge and at 3-month follow-up)
    - Duration of delirium associated with white matter disruption (both at hospital discharge and at 3-month follow-up)
Evidence linking delirium and dementia

• Biomarker evidence
  • In a pilot study of patients who were critically ill owing to infection
    • Infection
      • Proinflammatory cytokine interleukin 8 was associated with delirium
    • Non-infected
      • antiinflammatory cytokine interleukin 10 was associated with delirium
  • Other studies have shown cytokines such as insulin-like growth factor (IGF)-1, interleukin 1β, and interleukin 1 receptor antagonist to be associated with delirium
  • Interferon γ and low concentrations of IGF-1 was associated with delirium severity
  • S100B, a marker of astrocyte damage
    • High concentrations in both the plasma and the CSF of patients with delirium
Evidence linking delirium and dementia

- Direct result vs Indirect association
  - In a cohort of 76 individuals admitted to hospital for emergency hip fractures
    - Concentrations of Aβ1–42, tau, and phosphorylated tau in CSF -> not associated with delirium status
  - In a more recent study of 557 non-demented patients aged 70 years or older undergoing major non-cardiac surgery
    - APOE ε4 and APOE ε2 carrier status -> not associated with postoperative delirium
    - No associations between APOE genotype and delirium severity or the number of delirium episodes
  - Postoperative delirium might arise through pathophysiological pathways that are distinct from those in Alzheimer’s disease
Evidence linking delirium and dementia

- **Direct result** vs indirect association
  - In a study of 153 older adults aged 64–80 years (mean 71 years [SD 5]) undergoing elective total hip or knee replacement
    - Preoperative CSF A\(\beta_{1-40}:\tau\) and A\(\beta_{1-42}:\tau\) ratios in the lowest quartile versus all other quartiles
      - Significantly higher incidence of delirium (32% vs 17%, p=0.05 for both comparisons)
  - Suggest a role for A\(\beta\) and \(\tau\) in the neuropathogenesis of postoperative delirium
    - Delirium could represent the first sign of a (subclinical) dementia process in some cases
Evidence linking delirium and dementia

- Animal models and neuronal tissue culture
  - Dementia induced either by neurodegeneration associated with prion infection, or through selective and partial lesioning of the cholinergic projections of the basal forebrain
  - Exposed to an inflammatory challenge to simulate bacterial infection (e.g., using lipopolysaccharide [LPS]) or viral infection (e.g., using polyinosinic:polycytidylic)

- In these models, acute peripheral inflammation induced by LPS or poly(I:C)
  - Leads to acute deficits in cognition and motor function (analogous to delirium)

- Other studies using a single dose of LPS to induce sepsis
  - Inflammation via inducible NOS
    - Contributes to neuronal death, microglial activation, decreased regional blood flow, and loss of cholinergic activation, with persistent cognitive deficits in attention, executive function, and working memory
Conclusions and future directions

- Delirium is likely to interface with dementia on many levels
  - Marker of vulnerability of the brain
  - Unmasks unrecognized dementia
  - Mediates the effects of noxious insults
  - Itself leads to permanent neuronal damage and dementia
Conclusions and future directions

- Refinement of distinct diagnostic criteria
  - Demarcation of the overlap syndrome will be crucial
- Dose–response relation of dementia with delirium severity and duration
  - Strengthen causal inference
- The frequency and acuity of delirium and its associated serious adverse outcomes make it a highly promising area for investigation
Conclusions and future directions

• The presence of delirium could help to identify
  • Genetic predisposition
  • Diminished cognitive reserve
  • Unrecognized dementia

• Understanding of the pathogenesis of delirium
  • Crucial to identify modifiable or preventable factors
    • That lead directly to neuronal injury and thus permanent cognitive sequelae

• Prevention of delirium
  • Delay or alter both the typical cognitive ageing process and dementia.
감사합니다.