The interface between delirium and dementia in elderly adults

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Introduction

- 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[2]

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

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

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

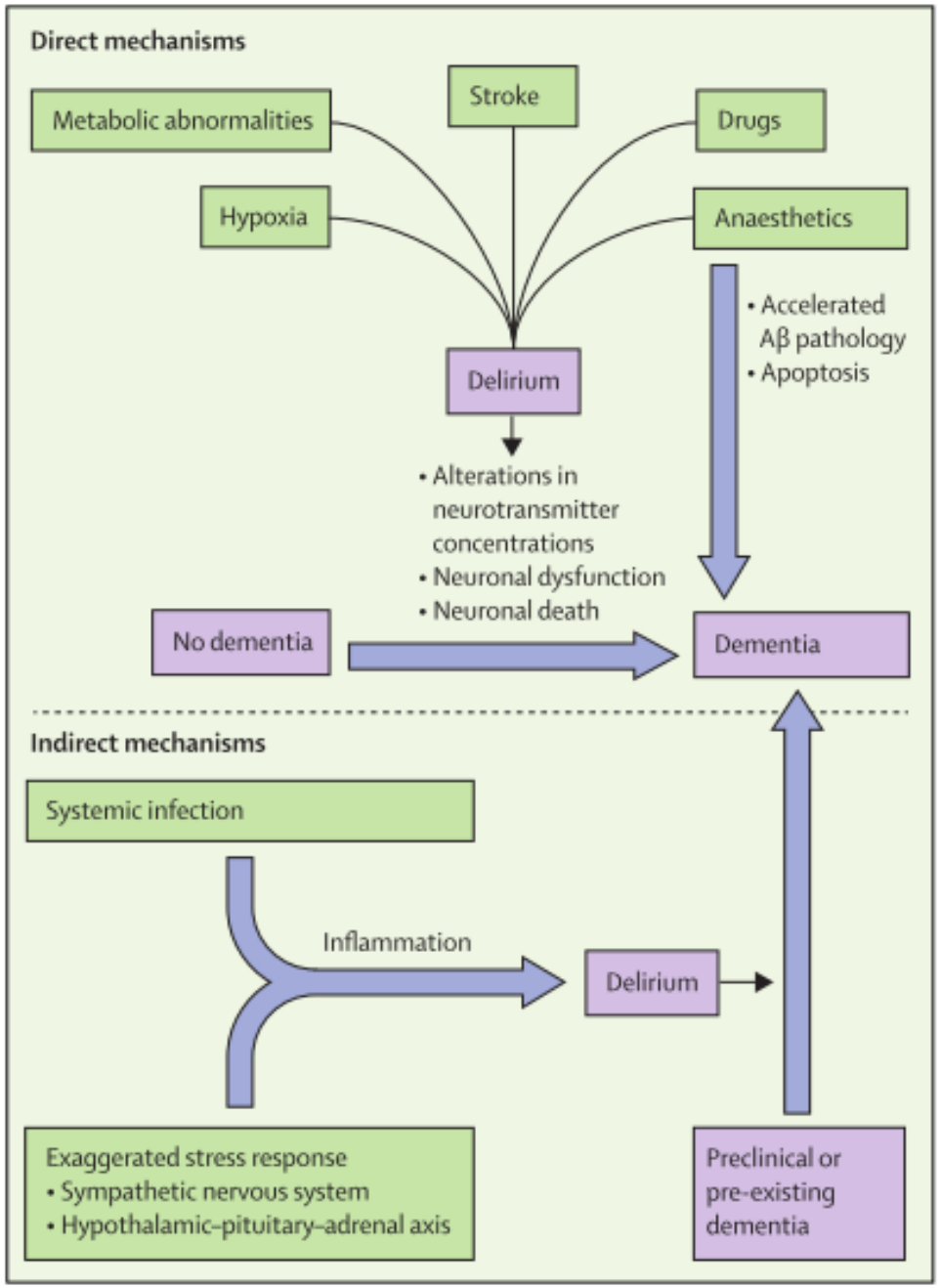

Figure: **A hypothetical model for the pathophysiological relation between delirium and dementia**

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 (eg, drugs, anaesthesia, endotoxins), inflammation, chronic stress, neuronal damage (eg, prolonged ischaemia, hypoglycaemia, shock, sepsis), acceleration of dementia pathology (eg, amyloid β [Aβ] and tau pathology), and diminished cognitive reserve
  - Metabolic derangements or particular drugs (eg, anticholinergics)
    - Alterations in neurotransmitter concentrations (eg, 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 (eg, 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)

	Sample	Sample size	Cognitive baseline	Delirium measure	Mean age at baseline (years)	Patients with delirium	Adjusted effect size (95% CI)
Kennedy et al[22] (2014)	Patients aged ≥65 years admitted to emergency department	700	Documented dementia by chart	Prevalent delirium by CAM	77	9%	OR 4·3 (2·2–8·5)
Koster et al[23] (2013)	Patients aged ≥70 years undergoing elective cardiac surgery	300	MMSE <23	DOSS	74	17%	OR 4·5 (1·9–13·0)
Moerman et al[24] (2012)	Patients aged ≥65 years with acute hip fracture	378	Clinical diagnosis of dementia	Prevalent delirium by DSM-IV	84	27%	OR 2·8 (1·7–4·6)
Bo et al[25] (2009)	Patients aged ≥70 years admitted to medical or geriatric wards	252	SPMSQ to establish presence and severity of cognitive impairment	Incident delirium by CAM	82	11%	RR 2·1 (1·6–2·6)
Rudolph et al[26] (2009)	Patients aged ≥60 years undergoing elective cardiac surgery	122 in development sample; 109 in validation sample	Preoperative MMSE ≤23	Incident delirium by CAM	75	44%	RR 1·3 (1·0–1·7)
Kalisvaart et al[27] (2006)	Patients aged ≥70 years undergoing elective hip surgery	603	Preoperative MMSE <24	Postoperative delirium by DSM-IV and CAM	78	12%	RR 5·5 (3·6–8·6)
Wilson et al[28] (2005)	Patients aged ≥75 years admitted to acute medical wards	100	IQCODE to establish presence of cognitive change over time	Incident delirium by DSM-III	85	12%	OR 3·2 (1·2–9·0)
O'Keeffe et al[29] (1996)	Patients with acute medical admissions to geriatric units	225	Clinical diagnosis of dementia or BDRS ≥4	Incident delirium by DSM-III	82	28%	OR 4·8 (2·0–11·6)
Marcantonio et al[30] (1994)	Patients aged ≥50 years admitted to elective surgical units	1341	TICS <30	Postoperative delirium by CAM	68	9%	OR 4·2 (2·4–7·3)
Pompei et al[31] (1994)	Patients aged ≥65 years with no delirium admitted to acute hospital medical and surgical wards	432 in development sample; 323 in validation sample	MMSE <24 (adjusted for education level)	Incident delirium by DSM-IIIR	74	15%	OR 3·6 (2·1–6·2)
Inouye et al[32] (1993)	Patients aged ≥70 years with no dementia or delirium admitted to acute hospital medical wards	107 in development sample; 174 in validation sample	MMSE <24 on admission	Incident delirium by CAM	79	25%	RR 2·8 (1·2–6·7)

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. IQCODE=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**

	Sample	Sample size	Delirium measure	Cognitive outcome	Mean age at baseline (years)	Patients with delirium	Adjusted effect size (95% CI)
Cognitive function and ageing study[42] (2014)	Population-based sample; multicentre sampling from health authority lists	2197	Algorithmic operationalisation of DSM-IV based on Geriatric Mental State examination	AGECAT-defined dementia at 2 years	77	6%	OR 8·8 (2·8–28·0)
BRAIN-ICU[43] (2013)	Multicentre ICU admissions	821	CAM-ICU	RBANS score at 1 year	61	74%	−5·6 (−9·5 to −1·8) points per day of delirium
Gross et al[44] (2012)*	Memory clinic patients with clinically diagnosed Alzheimer's dementia	263	Retrospective diagnosis of delirium from case notes (validated algorithm)	Worsening of Blessed IMC test score over 5 or more years	78	56%	Additional 1·2 (0·5–1·8) points per year
Saczynski et al[45] (2012)	Patients aged ≥60 years undergoing elective CABG or valve surgery	225	CAM	Trajectory of MMSE change over 1 year	73	46%	Prolonged impairment in recovery
Vantaa 85+[46] (2012)	Population-based sample of all residents aged ≥85 years	553	Participant and informant interview, along with medical record review	Dementia (DSM-IIIR; individual clinician) at 2·5 years	89	13%	OR 8·7 (2·1–35·0)
Fong et al[47] (2009)*	Memory clinic patients with clinically diagnosed Alzheimer's disease	408	Retrospective diagnosis of delirium from case notes (validated algorithm)	Worsening of Blessed IMC test score over 0·7 years	74	18%	Additional 2·4 (1·0–3·8) points
Bickel et al[48] (2008)	Patients aged ≥60 years undergoing elective hip surgery	200	CAM	Cognitive impairment or dementia, or both	74	21%	OR 41·0 (4·3–396·0)
Lundström et al[49] (2003)	Dementia-free patients aged ≥65 years with acute hip fracture	78	DSM-IV	Consensus diagnosis of dementia at 5 years	79	38%	OR 5·7 (1·3–24·0)

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 Aβ1–40:tau and Aβ1–42 :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 Aβ 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 (eg, using lipopolysaccharide [LPS]) or viral infection (eg, 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.

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