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The Interface of Delirium and Dementia in Older Persons

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Abstract

Delirium and dementia are two of the most common causes of cognitive impairment in older populations, yet their interrelationship remains poorly understood. Previous studies have documented that dementia is the leading risk factor for delirium; and delirium is an independent risk factor for subsequent dementia. However, a major area of controversy is whether delirium is simply a marker of vulnerability to dementia, whether the impact of delirium is solely related to its precipitating factors, or whether delirium *itself* can cause permanent neuronal damage and lead to dementia. Ultimately, it is likely that all of these hypotheses are true. Emerging evidence from epidemiological, clinicopathological, neuroimaging, biomarker, and experimental studies provide support for a strong interrelationship and for both shared and distinct pathological mechanisms. Targeting delirium for new preventive and therapeutic approaches may offer the sought-after opportunity for early intervention, preservation of cognitive reserve, and prevention of irreversible cognitive decline in ageing.

Introduction

With the unprecedented increases in the proportion of persons over age 75 in most industrialised countries, cognitive impairment is an increasingly frequent problem, calling for a thoughtful and effective approach to its recognition and management. Delirium and

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Author Contributions

All authors contributed to the search strategy, selection of articles, synthesis of information identified in the search, drafting and editing the manuscript or relevant sections thereof. All authors have seen and approved the final version. Dr. Inouye had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of Interests

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dementia are among the most common causes of cognitive impairment in clinical settings, yet they are often either unrecognised or mistaken for each other. Dementia, an insidious neurodegenerative condition, is characterised 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.[12] By contrast, delirium is a syndrome manifesting as an acute change in mental status that is characterised by inattention and disturbance in cognition that develops over a short period of time and tends to fluctuate. Delirium is a common, serious, and often fatal disorder that affects as many as 50% of elderly people in hospital. Typically, there is evidence of a medical and/or multifactorial aetiology.[12] Delirium is preventable in about 30-40% of cases, and is consistently associated with increased mortality, cognitive impairment, and functional decline.[2] Predisposing and precipitating factors for delirium derived from previously validated predictive models are shown in Table 2.[2]

Delirium and dementia can commonly coexist, with pre-existing dementia being a leading risk factor for delirium. While these conditions are recognised as substantially enmeshed, the nature of their interrelationship remains unclear. Moreover, shared pathophysiological mechanisms have been postulated for these syndromes, including cholinergic deficiency, inflammation, and reduced cerebral oxidative metabolism.[1, 2] Fundamental understanding of the interface of delirium and dementia may provide an important opportunity to advance our conceptualisation and treatment approaches to both conditions.

In this review, we will first briefly discuss distinguishing delirium and dementia before examining the current epidemiological, clinical, neuroimaging, biomarker, and experimental evidence linking these disorders. In each of these areas, important gaps in knowledge and future directions for research will be highlighted. Finally, potential mechanisms underlying the links between delirium and dementia and their implications for treatment will be discussed.

Distinguishing delirium from dementia

To date, dementia and delirium have been conceptualised as distinct and mutually exclusive conditions. Indeed, DSM-5 states that dementia should not be diagnosed in the face of delirium, and that delirium should not be diagnosed when symptoms can be “better accounted for by a pre-existing, established, or evolving dementia.”[12] Distinguishing the two diagnoses in the clinical setting can be difficult, even for experienced clinicians. Delirium symptoms can persist for months or even years,[13-18] and the recognised conditions of “persistent delirium” and “reversible dementia” blur the boundaries between these previously demarcated syndromes of cognitive impairment.[1] Distinguishing them is of critical importance, since their evaluation and clinical management are distinct. Signs and symptoms that can be useful to distinguish delirium from dementia are listed in Table 1.[3, 19, 20] Most prominently, with delirium, the onset is typically abrupt over hours to days, whereas with dementia the onset is insidious and progressive over months to years. With delirium, attention and level of consciousness are reduced and fluctuating; with dementia these domains typically remain intact until the advanced stages of dementia. Ultimately, the differentiation may depend on the presence of an acute change in mental status or behaviour

from baseline noted by an informed caregiver, or may be established only in retrospect by resolution of symptoms after precipitating factors have been removed or the acute illness has been treated. In the face of uncertainty, mental status changes should be treated as delirium, until proven otherwise.

Evidence linking delirium and dementia

A major area of controversy is whether delirium is simply a marker of vulnerability to dementia, whether delirium unmasks unrecognised dementia, whether the impact of delirium is solely related to its precipitating factors, or whether delirium *itself* can cause permanent neuronal damage and lead to dementia. Clinically, the development of delirium may have direct "toxic" effects related to periods of lethargy, psychomotor retardation or agitation, and unsafe behaviours. The lethargy and psychomotor retardation may result in immobility and related complications, including but not limited to aspiration pneumonia, respiratory compromise, decreased oral intake with dehydration or malnutrition, pressure ulcers, urinary tract infection, deep venous thrombosis and pulmonary emboli. Psychomotor agitation and unsafe behaviour may lead to falls and use of antipsychotics and other sedative medications or physical restraints, along with their attendant complications. Thus, the occurrence of delirium itself may set off a cascade of noxious stimuli that may adversely impact the brain.

To date, a number of mechanisms have been hypothesised on how delirium may contribute to permanent neuronal damage and dementia. This includes neurotoxicity (e.g., drugs, anaesthesia, endotoxins), inflammation, chronic stress, neuronal damage (e.g., prolonged ischaemia, hypoglycaemia, shock, sepsis), acceleration of dementia pathology (e.g., beta-amyloid (Aβ), tau), and diminished cognitive reserve (Figure 1).[3-6] Certain insults, such as metabolic derangements or particular drugs (e.g., anticholinergics), may directly cause neuronal dysfunction via alterations in neurotransmitters (e.g., acetylcholine deficiency[7] and/or dopamine excess[8]). Hypoxia or cerebral ischaemia may lead directly to cerebral dysfunction, via impaired cerebral blood flow and metabolism. Some anaesthetics may directly facilitate acceleration of Aβ accumulation, leading to apoptosis and cholinergic dysfunction, which in turn may further accelerate or initiate Aβ pathology.[9] Infections or response to a stressor (e.g., surgery or acute illness) can cause neuronal dysfunction through activation of inflammatory mechanisms.[10] Neuronal injury in these cases can occur indirectly through a variety of mechanisms, including altered neurotransmission, apoptosis, and/or activation of microglia and astrocytes, which lead to the production of free radicals, complement factors, glutamate, and nitric oxide.[11] Emerging evidence from epidemiological, clinicopathological, neuroimaging, biomarker, and experimental studies provide support for a strong interrelationship and for both shared and distinct pathological mechanisms.

Epidemiological evidence

Large cohort studies suggest that cognitive impairment and dementia are substantial risk factors for delirium. In the majority of these studies, delirium has been assessed in populations that include patients with dementia. Table 3 summarises studies from a comprehensive review that have examined pre-existing cognitive impairment or dementia as risk factors for delirium in validated predictive models that include adjustment for important

confounding variables.[21-31] The studies include 5,166 participants with mean ages ranging from 68-85 years, recruited from diverse settings, including hospital medical or geriatric medicine wards, emergency department, and surgical services. Cognitive baseline status was determined by a variety of approaches, including brief cognitive screening tests (e.g., Short Portable Mental Status Questionnaire (SPMSQ),[32] Mini-Mental State Examination (MMSE),[33] proxy-based measures (e.g., Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE),[34] Blessed Dementia Rating Scale (BDRS)[35]; clinician diagnosis; or chart documentation of dementia. Delirium was also measured by a variety of approaches, including the Confusion of Assessment Method (CAM),[36] Diagnostic and Statistical Manual (DSM) Versions III, IIIR, and IV,[37-39] and the Delirium Observation Screening Scale (DOSS).[40] The rate of delirium ranged from 9% to 44% across these studies. Baseline cognitive impairment or dementia is a substantial independent risk factor for delirium, consistently increasing delirium risk by 2- to 5-fold (Table 3).

Delirium is an independent risk factor for long-term cognitive decline and dementia, according to a comprehensive review of studies representing a total of 4,745 individuals (Table 4).[41-48] The studies vary in design, including population-based approaches, retrospective analyses of outpatients such as memory clinic patients, evaluation of ICU inpatients and those undergoing elective surgery. Nonetheless, these multiple studies consistently suggest that an episode of delirium carries substantial dementia risk, as well as an altered trajectory of cognitive recovery following surgical procedures. Cognitive outcomes were determined using a variety of measures, including neuropsychological assessments (e.g., Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT),[49] Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),[50] Blessed Information-Memory-Concentration (IMC),[35] MMSE,[33] clinician diagnosis, or consensus panel diagnosis. Despite the multiple methods for operationalising delirium and dementia, the findings are consistent and robust across studies. For example, delirium was consistently associated with a significantly increased risk of both long-term cognitive decline (substantial declines by cognitive testing) and dementia (odds ratios from 6-41), with follow-up periods ranging from 1 to 5 years after baseline evaluation. A meta-analysis[51] involving two studies with 241 total patients demonstrated that delirium was associated with an increased rate of incident dementia, even after controlling for relevant confounders (adjusted relative risk, RR, 5.7, 95% confidence interval, CI, 1.3-24.0). In another study of 225 cardiac surgery patients,[44] delirium resulted in a punctuated decline in cognitive function, followed by recovery over 6-12 months in most patients; however, a substantial proportion, particularly those with prolonged delirium, never returned to baseline. In a study of 821 intensive care unit patients, a longer duration of delirium was independently associated with significantly worse global cognition and worse executive function scores based on a neuropsychological battery at 3 and 12 months follow-up.[42] Moreover, clinical trial evidence has suggested that treatment of delirium was associated with better cognition during follow-up.[52] While not directly linked to delirium, the literature on postoperative cognitive dysfunction also suggests persistent long-term impairment following surgery.[53-55]

Careful follow-up studies have documented that persons with dementia who develop delirium have worse outcomes than those with dementia alone,[56] including increased rates

of re-hospitalisation, institutionalisation, mortality, and subsequent cognitive decline.[57-61] In one study of 771 community-dwelling patients with Alzheimer's disease (AD), after adjustment for confounders, delirium was associated with a greatly increased adjusted risk of death, relative risk of 5.4 (95% CI 2.3-12.5) or institutionalisation, relative risk of 9.3 (95% CI 5.5-15.7). At one year, 21% of those with cognitive decline, 15% of institutionalisations and 6% of deaths were attributable to delirium.[59] In another study of 263 patients with AD, despite the trajectories being similar prior to an index hospitalisation, delirium resulted in a fundamental alteration in the trajectory of cognitive decline with a 2-fold acceleration in rate of decline over the year following hospitalisation, and accelerated decline persisting over the entire the 5-year follow-up period.[43] This study was highly significant in demonstrating that in persons with AD, delirium resulted in a dramatic increase in the rate of cognitive decline over time, and that this change appeared to be irreversible.

Additional long-term follow-up studies looking at outcomes of delirium are still needed to fully understand the impact of this condition. For example, long-term follow-up of a well-characterised cohort who are initially free of dementia at baseline may help to clarify whether incident delirium can lead to new-onset dementia. The patient's individual experience with delirium, including distress, and development of post-traumatic stress disorder has not been fully examined as outcome measures. Lastly, genetic and other important determinants of delirium risk and risk stratification to identify particularly high-risk individuals should be explored. Ultimately, these data will allow for greater support for early identification, prevention, and treatment of delirium.

Clinicopathological evidence

The interaction between delirium and dementia has been shown in a population-based study, Vantaa 85+, examining the impact of delirium (retrospectively determined) on cognitive and functional outcomes.[45] In this cohort of 553 individuals age 85 years and older, delirium increased the risk of incident dementia (odds ratio 8.7, 95% CI 2.1-35). Moreover, consistent with the literature on cognitive trajectories, delirium was associated with worsening dementia severity, new functional deficits, and accelerated decline in cognitive scores. This study also examined the neuropathological correlates of dementia in the presence or absence of a history of delirium. The relationship between dementia and measures of neurofibrillary tau, amyloid burden, apolipoprotein (ApoE) ε4, vascular lesions and Lewy body pathology were strongest in the absence of a delirium history. However, when these pathological markers were assessed in relation to dementia where delirium was *also* part of the history, no associations were detectable. Although not powered to be conclusive, the results suggest that when delirium is part of the dementia trajectory, the pathological substrates may be different from conventional dementia pathology, such as Alzheimer's, vascular or Lewy body pathology. These findings raise the intriguing possibility that the acceleration of cognitive decline following delirium might result from an alternative mechanism leading to neuronal damage.

Studies that include markers of AD pathology, such as CSF or tau and beta amyloid imaging, as well as additional post-mortem studies, will yield significant insight into the

fundamental pathophysiology of delirium and may ultimately help with development of effective treatments.

Neuroimaging evidence

Despite its routine use in clinical practice and a growing number of studies utilising neuroimaging to investigate the pathophysiology and consequences of delirium, there are few studies that provide long-term follow-up or convincing evidence of permanent neurological changes attributable to delirium. Most studies to date have been limited by small sample sizes, inadequate control groups, and the lack of baseline scans prior to delirium.[62, 63] Two studies on the same sample of 47 intensive care unit survivors used volumetric and diffusion tensor imaging at hospital discharge and 3 month follow-up.[64, 65] In the volumetric analysis, longer duration of delirium was significantly associated with greater brain atrophy at hospital discharge and at 3 month follow-up. In addition, duration of delirium was significantly associated with white matter disruption at both hospital discharge and at 3 month follow-up.

The lack of baseline scans in previous studies precludes any strong conclusions about whether the development of delirium itself contributed to subsequent neuroimaging findings. Future studies, with larger cohorts, baseline characterisation, careful selection of controls, and advanced neural anatomic and functional neural imaging measures, may lead to greater understanding of the anatomic and functional links between delirium and dementia.

Biomarker evidence

A range of serum and cerebrospinal fluid (CSF) biomarkers has been considered in the search to understand delirium pathogenesis. Previous work in ICU patients found that elevated levels of baseline inflammatory markers were associated with subsequent delirium.[64, 66] In a pilot study of patients who were critically ill due to infection, the proinflammatory cytokine interleukin (IL)-8 was associated with delirium,[67] whereas in non-infected patients, the antiinflammatory cytokine IL-10 was associated with delirium. These findings suggest that the underlying mechanisms governing the development of delirium in patients with inflammation may differ from those without inflammation.[68] Others have found cytokines such as insulin-like growth factor (IGF)-1, IL-1β and IL-1 receptor antagonist (RA) to be associated with delirium,[69-71] and high levels of interferon (IFN-γ) with low levels of IGF-1 were associated with delirium severity.[72] S100B, a marker of astrocyte damage, has been shown to be elevated in delirium, both in plasma and in CSF.[68, 73, 74] It is not known if these changes in biomarkers are a direct consequence of delirium, a consequence of a separate dementia with progressive neurodegeneration, or both.

Several studies have looked for a direct association between AD biomarkers and delirium. In a cohort of 76 individuals admitted for emergency hip fractures, levels of Aβ1-42, tau, and phosphorylated-tau from CSF were not associated with delirium status, nor did they correlate significantly with IQCODE score, despite a strong association of postoperative delirium with premorbid cognitive decline (as measured by IQCODE).[75] Given the limited sample size, however, the results must be interpreted with caution.

In a more recent study of 557 non-demented patients age ≥70 undergoing major non-cardiac surgery, after adjusting for age, sex, surgical procedure, and preoperative cognitive function, ApoE ε4 and ε2 carrier status were not associated with postoperative delirium. Further, there was no observed association between ApoE and delirium severity or number of delirium episodes. Thus, in a sample with careful exclusion of persons with underlying dementia, ApoE genotype does not appear to confer either risk or protection for postoperative delirium incidence, severity, or duration.[76] The results of both studies are consistent with the Vantaa 85+ epidemiological study of cerebral pathology,[45] suggesting that postoperative delirium might arise through pathophysiological pathways distinct from AD.

In contrast, however, other studies (that did not specifically exclude persons with dementia) have shown a possible association between AD biomarkers and postoperative delirium.[9] In a study of 153 older adults undergoing elective total hip or knee replacement, CSF was obtained during initiation of spinal anaesthesia, and patients were monitored post-operatively for the development and severity of delirium. A significantly higher incidence of delirium was seen among participants with preoperative CSF Aβ40/Tau and Aβ42/Tau ratios in the lowest quartile versus all other quartiles (32% vs. 17%, P=.05 for both comparisons), suggesting a possible threshold effect in the relationship between preoperative AD biomarkers and postoperative delirium. After adjusting for age and sex, lower preoperative CSF Aβ40/Tau and Aβ42/Tau ratios were associated with significantly higher scores on a delirium severity scale ($\beta = -0.12 \pm 0.05$, P=0.018 and $\beta = -0.62 \pm 0.27$, P=0.022, respectively), suggesting that lower CSF Aβ/Tau ratios, similar to ratios seen in AD, are associated with greater delirium severity.[9] Others have found elevated serum Aβ1-42/40 levels are associated with delirium occurrence and correlates with subjective complaints of cognitive-impairment 18-months after the delirium episode.[68] Taken together, these findings suggest that there may be a role for Aβ and Tau in the neuropathogenesis of postoperative delirium, and that delirium may represent the first sign of a (subclinical) dementia process in some cases.

Although these studies are generally small and require cautious interpretation, the accumulating evidence lends support for the impact of delirium itself contributing to and/or being a mediator of permanent cognitive impairment. Future human studies with careful baseline assessment of cognitive function, control for confounding factors such as age and pre-existing dementia, and long-term follow-up with characterisation by neuropsychological testing and neuroimaging, are needed to better address this important area.

Animal models and neuronal tissue culture

Important recent work involving animal models relevant for delirium have demonstrated that in vulnerable animals, systemic inflammatory insults can cause punctuated cognitive decline typical of delirium, followed by persistent acceleration in disease progression typical of dementia.[77] Many experiments have tried to take a clinically relevant experimental approach to delirium by capturing both predisposing and precipitating factors. In these models, underlying pathology/brain vulnerability has been induced by either neurodegeneration associated with prion infection,[78] or through selective and partial lesioning of the cholinergic projections of the basal forebrain.[79] Subsequent to this, the animals are exposed

to an inflammatory challenge to simulate bacterial or viral infection (e.g. lipopolysaccharide (LPS) or polyinosinic: polycytidylic acid (poly I:C), respectively).[80, 81] 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, and similar deficits are observed with inflammation superimposed upon either of these underlying neurodegenerative models. Thus, such animal models provide an opportunity to probe specific pathophysiological pathways in delirium and dementia.[82] Other studies using a single dose of LPS to induce an inflammatory insult comparable to sepsis in humans, a frequent contributor to delirium, have found that inflammation via inducible nitric oxide synthase contributes to neuronal death, microglial activation, decreased regional blood flow, and loss of cholinergic activation,[83-85] with persistent cognitive deficits in attention, executive function, and working memory.

Microglial priming has been demonstrated in chronic neurodegeneration[78] and ageing,[86] whereby microglia elaborate a more aggressive inflammatory response to peripheral inflammation compared with either younger or non-diseased animals. The acute insult triggers acute, transient[81] and fluctuating[87] cognitive deficits during T-maze testing, and further neurodegeneration[78] and acceleration of disease trajectory is observed.[77] Other studies using this model have shown microglia express cyclo-oxygenase (COX) 1 and synthesise prostaglandins. Selective inhibition of COX-1 or non-selective inhibition with ibuprofen are protective against systemic LPS or IL-1β-induced cognitive deficits respectively.[88] Inflammation was sufficient, but microglial priming was not essential, for similar deficits reproduced in cholinergic-deficient mice, which could be blocked by donepezil.[80] This suggests an important interplay between acetylcholine deficiency and systematic inflammation but the observation that worsening neurodegeneration makes animals progressively more susceptible to the cognitively disrupting effects of LPS[87] implicates several different neuronal networks.

Previous studies in human neuronal cell culture have demonstrated that exposure to some inhalational anaesthetics (e.g., isoflurane, sevoflurane) may induce neurotoxicity, including apoptosis, caspase activation, A-β oligomerisation and accumulation, neuroinflammation, and mitochondrial dysfunction,[6, 89] whereas this effect is not seen with other agents (e.g. desflurane, nitrous oxide and propofol).[90]

Animal models and neuronal tissue culture studies have already begun to explore pathophysiological pathways that may identify future targets for intervention. Other areas will need to be explored, including neurotransmitter dysregulation, oxidative stress, and aberrant stress response. Advancing these mechanistic studies will be critical, and ultimately will represent the primary means for understanding the pathophysiology of delirium. Initial studies focused on inflammation have suggested the impact of delirium itself may contribute to and/or be a mediator of permanent cognitive impairment. Taken together, these experimental studies provide strong support for the pathophysiological linkage between delirium mechanisms and long-term cognitive impairment or dementia, and further studies are necessary to confirm and extend these findings.

Conclusion

Ultimately, it is likely that delirium serves multiple roles: it is a marker of vulnerability, unmasks unrecognised dementia, mediates the effects of noxious insults, and itself leads to permanent neuronal damage and dementia. There is little doubt that occurrence of an episode of delirium can signal underlying vulnerability of the brain with decreased cognitive reserve and increased risk for future dementia.[91] Delirium reflects a decompensated cognitive state under stress conditions, and its presence implies diminished cognitive reserve. In some cases, delirium may bring previously unrecognised cognitive impairment to medical attention. Moreover, there is no question that severe precipitating factors of delirium, such as prolonged hypoglycaemia or hypoxaemia, can lead to neuronal death and permanent cognitive impairment. It is also possible that delirium may mediate the impact of many factors, such as general surgery, anaesthesia, critical illness, acute respiratory distress syndrome, prolonged intubation, or sepsis, on long-term cognitive outcomes.

Unraveling the inter-relationship of delirium and dementia poses myriad challenges highlighting the barriers to addressing this important area. Given the lengthy prodromal stage of dementia along with its unpredictable progression, knowledge of the baseline state and trajectory of any cognitive changes are essential. The target population often is frail, with multiple medical co-morbidities, and delirium may go undetected, thus active surveillance is essential. Refinement of distinct diagnostic criteria and demarcation of the overlap syndrome will be critical to differentiate the two conditions. Identification of the contribution of the presence of delirium is a paramount first step; however, a dose-response relationship with delirium severity and duration will help to strengthen causal inference. Appropriate control for confounding factors, without over-controlling, will be necessary to evaluate the contribution of delirium itself, as well as the mediation effects of other precipitating insults by delirium. Moreover, the presence of delirium poses numerous logistical challenges, including informed consent, ethical dilemmas, and challenges to conducting procedures and neuroimaging in the face of older adults with agitation, behavioural disturbances, severe illness, multi-morbidity, and frailty.

Acknowledging delirium as a determinant of chronic cognitive impairment obliges us to broaden our understanding of dementia. Recognising that slowly evolving neurodegenerative processes may be accelerated by delirium necessitates the consideration of the long-term impact of acute illness and other precipitants on the vulnerable brain. Thus, delirium may serve as an important model system for research, offering a unique approach to advance our understanding of cognitive disorders and dementias more generally. The frequency and acuity of delirium and its associated serious adverse outcomes make it a highly promising area for investigation. The development of delirium may help to identify persons who are vulnerable to cognitive decline through genetic predisposition, diminished cognitive reserve, or the presence of unrecognised dementia. Investigation of delirium also provides a window to observe the link between brain pathophysiology and behavioural manifestations, which may hold broader implications for other neurological and psychiatric disorders. Moreover, advancing the understanding of the pathogenesis of delirium will be critical to identify preventable factors which can lead directly to neuronal injury, and thus, permanent cognitive sequelae. Implementing therapies for prevention of delirium holds

particular relevance for their potential to delay or alter both the typical cognitive ageing process as well as the progression of cognitive decline in persons with dementia. Finally, targeting delirium for new therapeutic approaches may offer the much sought-after opportunity for early intervention, preservation of cognitive reserve capacity and prevention of irreversible cognitive decline in ageing.

PANEL

Search strategy and selection criteria

We conducted an initial systematic search of Medline, Ovid SP, Embase, and Science Citation Index from 1950-2012. The Ovid search terms included “exp Delirium/ep [Epidemiology]” “delirium.mp” “acute confusion”.mp “metabolic encephalopathy”.mp, with equivalent terms used in the other databases. There were no language restrictions. Articles were selected by hand-review of the results of the search on the basis of relevance to delirium and dementia. Subsequently, an updated systematic search was conducted in PubMed from 2000 – 2015 using the following search strategy: (“dementia”[MeSH Terms] OR “dementia”[All Fields]) AND (“delirium”[MeSH Terms] OR “delirium”[All Fields]). For all articles, including systematic and comprehensive reviews, tables and reference listings generated were reviewed for additional pertinent articles.

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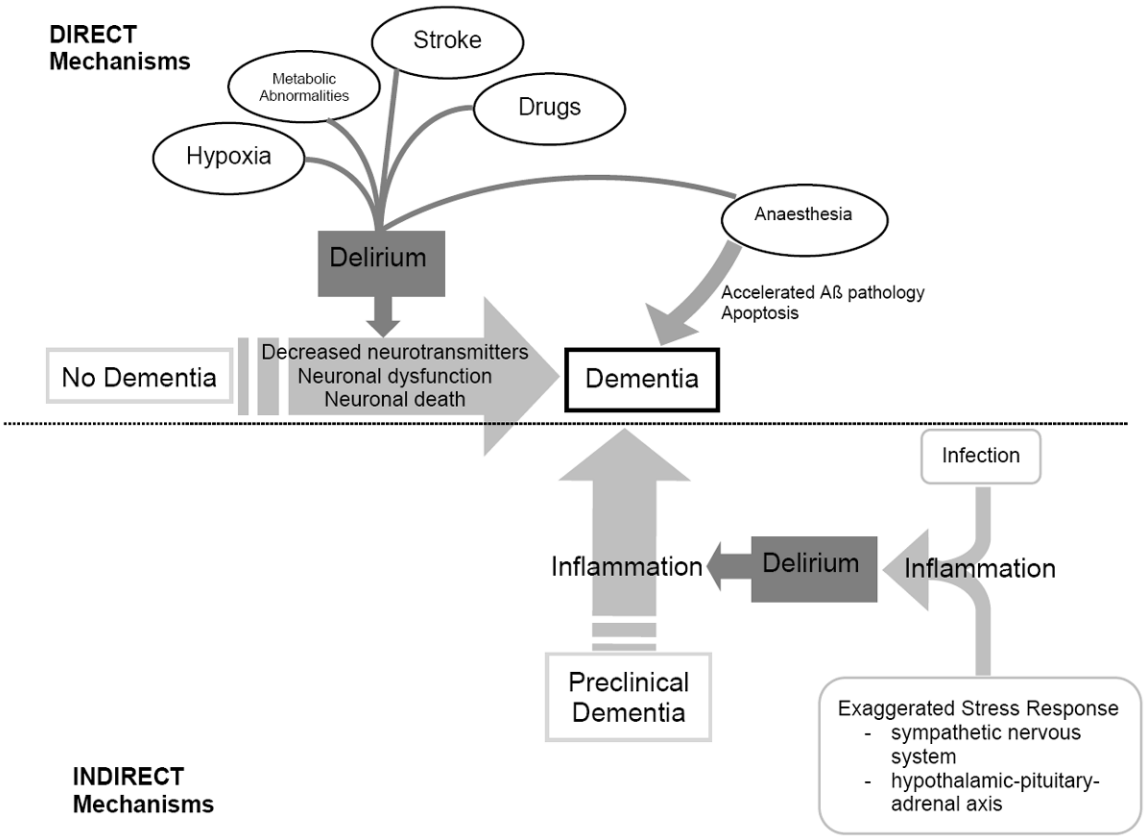

Figure 1.

A hypothetical model for the pathophysiologic interrelationship between delirium and dementia. Delirium is a known risk factor for new onset dementia, and this may arise via direct mechanisms such as hypoxia, metabolic abnormalities, stroke, or medications. In turn, delirium is associated with neuronal dysfunction, alterations in neurotransmitters, and neuronal death and this could lead directly to dementia. There is also growing evidence that certain anesthetics associated with postoperative delirium may alter Aβ, which in turn may indicate a role for new onset dementia. Delirium is also likely to be a marker of vulnerability in patients with pre-existing dementia, and might accelerate existing dementia. This may occur indirectly, for example, via inflammation triggered by systemic infection or exaggerated response to a stressor.

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Table 1

Comparative features of delirium and dementia

Feature	Delirium	Dementia
Onset	Abrupt, though initial loss of mental clarity may be subtle	Insidious and progressive
Duration	Hours to days (though can be prolonged)	Months to years
Attention	Reduced ability to focus, sustain, or shift attention is a hallmark feature, occurring early in presentation	Normal unless severe dementia
Consciousness (awareness of the environment)	Fluctuating (making assessment at multiple timepoints necessary), reduced level of consciousness and impaired orientation	Generally intact
Speech	Incoherent, disorganised; distractible in conversation	Ordered, may develop anomia or aphasia
Other features	Caused by underlying medical condition, substance intoxication, or medication side effect; Hyperactive, hypoactive, and mixed forms of psychomotor disturbance are possible; disruption in sleep duration and architecture; perceptual disturbances	Caused by underlying neurological process (e.g. beta-amyloid plaque accumulation in Alzheimer's disease), with symptoms varying depending on underlying pathologies (e.g. fluctuations in cognition are a feature of Lewy body dementia)

Note that there is substantial overlap between these syndromes; they may coexist in an individual patient.

Table 2

Predisposing and precipitating factors for delirium*

Predisposing Factors	Precipitating Factors
Dementia or pre-existing cognitive impairment	Medications: • Polypharmacy • Psychoactive medication use • Sedative-hypnotic use
History of delirium	Use of physical restraints
Functional impairment	Use of bladder catheter
Sensory impairment: • Vision impairment • Hearing impairment	Physiologic and metabolic abnormalities: • Elevated BUN/creatinine ratio • Abnormal sodium, glucose, or potassium • Metabolic acidosis
Comorbidity/severity of illness	Infection
Depression	Any iatrogenic event
History of transient ischaemia/stroke	Major surgery
Alcohol abuse	Trauma or urgent admission
Older age	Coma

*From validated predictive models for delirium[2]

Table 3

Baseline cognitive impairment/dementia as independent risk factor for delirium from predictive models

Study (year)	Population	Cognitive baseline	Delirium measure	Mean age (years)	% delirium	Effect size (adjusted) (95% CI)
Kennedy (2014)[21]	Emergency department, age ≥ 65 years (n=700)	Documented dementia by chart	Prevalent delirium by CAM	77	9%	OR 4.3 (2.2 to 8.5)
Koster (2013)[22]	Elective cardiac surgery, age ≥ 70 years (n=300)	MMSE < 23	DOSS	74	17%	OR 4.5 (1.9 to 13)
Moerman (2012)[23]	Acute hip fracture, age ≥ 65 years (n=378)	Clinical diagnosis of dementia	Prevalent delirium by DSM-IV	84	27%	OR 2.8 (1.7 to 4.6)
Bo (2009)[24]	Patients age ≥ 70 years admitted to medical or geriatric ward (n=252)	SPMSQ for presence and severity of cognitive impairment	Incident delirium by CAM	82	11%	RR 2.1 (1.6 to 2.6)
Rudolph (2009)[25]	Planned cardiac surgery, age ≥60 years (development n=122; validation=109).	Pre-operative MMSE ≤ 23	Incident delirium by CAM	75	44%	RR 1.3 (1.0 to 1.7)
Kalisvaart (2006)[26]	Elective hip surgery, age ≥ 70 years (n=603)	Pre-operative MMSE <24	Postoperative delirium by DSM-IV and CAM	78	12%	RR 5.5 (3.6 to 8.6)
Wilson (2005)[27]	Patients aged ≥ 75 years admitted to an acute medical ward (n=100)	IQCODE to establish presence of cognitive change over time	Incident delirium by DSM-III	85	12%	OR 3.2 (1.2 to 9.0)
O'Keeffe (1996)[28]	Acute medical admissions to geriatric medicine unit (n=225)	Clinical diagnosis of dementia or BDRS ≥4	Incident delirium by DSM-III	82	28%	OR 4.8 (2.0 to 11.6)
Marcantonio (1994)[29]	Elective surgical admissions, age ≥ 50 years (n=1341)	TICS <30	Post-operative delirium by CAM	68	9%	OR 4.2 (2.4 to 7.3)
Pompei (1994)[30]	Acute hospital medical and surgical admissions, age ≥ 65 years with no delirium (development n=432; validation n=323)	MMSE < 24 (education adjusted)	Incident delirium by DSM-III-R	74	15%	OR 3.6 (2.1 to 6.2)
Inouye (1993)[31]	Acute hospital medical admissions, age ≥ 70 years with no dementia or delirium (development n=107; validation n=174)	MMSE < 24 on admission	Incident delirium by CAM	79	25%	RR 2.8 (1.2 to 6.7)

BDRS Blessed Dementia Rating Scale; CAM Confusion Assessment Method; DOSS Delirium Observation Screening Scale; IQCODE Informant Questionnaire for Cognitive Decline in the Elderly; MMSE Mini-Mental State Examination; OR odds ratio; RR relative risk; SPMSQ Short Portable Mental Status Questionnaire; TICS Telephone Interview for Cognitive Status.

Table 4

Delirium as an independent risk factor for long term cognitive decline and dementia

Study (year)	Population	Delirium measure	Cognitive outcome	Mean age at baseline (years)	% delirium	Effect size (adjusted) (95% CI)
CFAS (2014)[41]	Population-based; multi-centre sampling from Health Authority lists (n=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 to 28)
BRAIN-ICU (2013)[42]	Multi-centre ICU admissions (n=821)	CAM-ICU	RBANS score at 1 year	61	74%	-5.6 (-9.5 to -1.8) points per day of delirium
Gross (2012)[43]*	Memory clinic patients with clinically diagnosed Alzheimer's dementia (n=263)	Retrospective diagnosis of delirium from case notes (validated algorithm)	Worsening on Blessed IMC score over up to 5 years	78	56%	Additional 1.2 (0.5 to 1.8) points per year
Saczynski (2012)[44]	Elective CABG or valve surgery patients age ≥60 years (n=225)	CAM	Trajectory of MMSE change over 1 year	73	46%	Prolonged impairment in recovery
Vantaa 85+ (2012)[45]	Population-based; all residents age ≥85 (n=553)	Participant and informant interview, along with medical record review	Dementia (DSM-III-R; individual clinician) at 2.5 years	89	13%	OR 8.7 (2.1 to 35)
Fong (2009)[46]*	Memory clinic patients with clinically diagnosed Alzheimer's dementia (n=408)	Retrospective diagnosis of delirium from case notes (validated algorithm)	Worsening on Blessed IMC score over 0.7 years	74	18%	Additional 2.4 (1.0 to 3.8) points
Bickel (2008)[47]	Elective hip surgery patients age ≥60 years (n=200)	CAM	Cognitive impairment and/or dementia	74	21%	OR 41 (4.3 to 396)
Lundstrom (2003)[48]	Acute hip fracture patients, dementia-free, age ≥ 65 years (n=78)	DSM-IV	Consensus diagnosis of dementia at 5 years	79	38%	OR 5.7 (1.3 to 24)

*Related analyses with some overlap of data. AGECAT Automated Geriatric Examination for Computer Assisted Taxonomy; Blessed IMC Blessed Information-Memory-Concentration scale; BRAIN-ICU Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors; CABG Coronary artery bypass grafting; CAM Confusion Assessment Method; CAM-ICU Confusion Assessment Method-ICU; CFAS Cognitive Function and Ageing Study; DSM Diagnostic and Statistical Manual of the American Psychiatric Association; RBANS Repeatable Battery for the Assessment of Neuropsychological Status.