From Acute Confusion to Chronic Decline: The Cognitive Impact of Delirium in Older Adults

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ABSTRACT

Delirium is prevalent in healthcare settings, leaving susceptible older adults at risk for persistent cognitive impairment, prolonged care needs, morbidity, and mortality. In older adult patients, delirium often arises from acute medical illnesses, infections, medications, and comorbidities, with age and underlying dementia increasing susceptibility. Its complex pathophysiology involves systemic inflammation, neurotransmitter dysregulation, disrupted brain metabolism, and physiological cycle disturbances. While delirium causes acute cognitive impairments, patients are often left with persistent dysfunction. Moreover, patients with pre-existing cognitive impairment are at higher risk for developing dementia or accelerated cognitive decline in the wake of a delirium episode. Delirium also worsens long-term quality of life, increasing risk for functional disability and need for institutional care. Prevention and management strategies focus on prophylaxis, early intervention, multicomponent programs, and pharmacological interventions, while ongoing research seeks to identify biomarkers and improve delirium detection and long-term management.

KEYWORDS: delirium, dementia, cognitive impairment, geriatric

INTRODUCTION

Delirium is a common medical condition that disproportionately affects older adults. Among hospitalized older adults, the incidence of delirium ranges from 10% on general medical floors, 20 to 45% following major surgeries, and up to 85% of patients in intensive care units.[1,2] When delirium occurs in the emergency department, 57–83% of cases are missed and often misattributed to dementia or psychiatric illness, and 25% of these patients are discharged home.[3] Known sequelae of delirium include increased risk of morbidity and mortality, prolonged hospital stays, increased hospital-acquired infections, poorer quality of life, and increased admissions to short- and long-term post-acute care facilities.[4]

Historically, delirium has been conceptualized as an acute confusional state associated with psychomotor disturbances and its cognitive effects were believed to be fully reversible. However, increasing reports of persistent post-delirium cognitive impairment in the medical literature of the mid-1980s motivated researchers to question the "transient" impact of delirium on the aging brain. Current evidence suggests that persistent cognitive dysfunction following an episode of delirium is not infrequent among susceptible older patients, particularly for those with pre-existing dementia. In one study, only 4% of patients who experienced delirium while hospitalized demonstrated full resolution of symptoms at discharge, and 60% experienced persistent symptoms six months later.[4,5] Given the potentially long-lasting impact of delirium on cognitive and functional outcomes, prevention, early identification, and treatment of delirium remains paramount for patients, families, caregivers, and healthcare systems, and may play a pertinent role in dementia prevention. Therefore, the primary objective of this paper is to summarize current knowledge of the acute and long-term cognitive impacts of delirium.

DIAGNOSTIC CRITERIA AND SUBTYPES

Delirium, defined by the *Diagnostic and Statistical Manual, 5th edition, Text Revision* (DSM-5 TR), is characterized by a disturbance in attention and accompanied by reduced awareness of the environment (Criterion A), occurring acutely with frequent fluctuations in severity (Criterion B) with additional disturbances in memory, orientation, language, visuospatial ability, or perception (Criterion C), which are not better explained by a pre-existing, established, or evolving neurocognitive disorder (Criterion D). Likewise, there is more evidence for a direct physiological consequence of another medical condition, toxin, substance, or multiple etiologies (Criterion E).[6]

Delirium has been classified into four phenotypes based on psychomotor/physical activity and level of arousal; these include hypoactive, hyperactive, mixed, and subsyndromal.[1,3,7] Hypoactive delirium is characterized by diminished motor activity and speech output, hypersomnolence, and lethargy, with or without perceptual disturbances.[3,7] As such, this subtype is often misattributed to medication effects, depression or fatigue. Hyperactive delirium typically presents with increased activity, (e.g., wandering, hypervigilance, restlessness, paranoia, agitation), sometimes accompanied by euphoria, and hyperverbal and pressured speech.

Although hyperactive delirium is slightly less prevalent than the hypoactive subtype,[7] it is more commonly recognized by clinicians. Mixed delirium features alternations between hypoactive and hyperactive episodes, leading to the classic "waxing and waning" presentation associated with delirium.[7] Patients with subsyndromal delirium exhibit one or more diagnostic features of delirium, but do not meet standard criteria. Subsyndromal delirium often goes unrecognized; leaving patients at elevated risk for negative outcomes post-discharge relative to hospitalized patients without delirium.[1]

Although this phenotypic construct is most utilized in delirium research, evidence suggests potential application for clinical prognostication as well. Of clear clinical relevance, variation in pathological mechanisms, precipitants, risk, and etiologic factors among delirium subtypes has been reported. Likewise, phenotypic prognoses may vary; hypoactive delirium, relative to hyperactive and mixed phenotypes, has been associated with the most detrimental prognosis, including higher short- and long-term mortality rates.[3,8] Amongst all phenotypes, delirium severity is correlated with increased length of hospitalization, likelihood of nursing home placement, increased re-admission within 30 days, worsened functional impairment, and overall morbidity.[3,9,10]

COGNITIVE IMPACT OF DELIRIUM

Associations between delirium and subsequent cognitive dysfunction have been observed across research populations, with and without premorbid cognitive disorders.[11] In longitudinal studies, cognitively unimpaired older adults who develop delirium show greater rates of decline and increased risk for progression to dementia than their peers who did not develop delirium.[12,13] For example, a large prospective study of cognitive aging in people 85 years or older found that participants who developed delirium during follow- up experienced a faster rate of decline in MMSE scores, relative to those without a history of delirium.[14] Results of a subgroup analysis of participants without cognitive impairment at baseline showed that delirium was associated with a nearly nine-fold increased risk of incident dementia. Likewise, Mohanty et al reported that postoperative delirium was associated with substantially elevated odds of a new dementia diagnosis (odds ratio [OR] 13.9; 95% confidence interval (CI), [12.2–15.7]) in the year following a major elective surgery.[15] More recently, a 2020 meta-analysis that included 24 observational studies of cognitive outcomes in older adult, general medical or surgery patients found that delirium was associated with worse post-discharge cognitive performance at three months or longer, across all studies.[16]

Factors influencing post-delirium outcomes

Premorbid cognitive function is arguably the most consistent and robust predictor of incident delirium, as well as post-delirium cognitive outcomes. While delirium has been identified as an independent risk factor for developing new-onset dementia, it is also strongly associated with accelerated cognitive decline among those with cognitive disorders, including mild cognitive impairment (MCI), Alzheimer's Disease (AD), and other neurodegenerative dementias.[11,14,17]

Compared to hospitalized patients with delirium, but no baseline cognitive impairment, patients with pre-existing dementia experienced more severe long-term cognitive and functional decline following delirium, as well as a 2.6-fold increase in risk of dying.[11,18] Researchers have also hypothesized that individuals with AD dementia may be particularly vulnerable to prolonged post-delirium cognitive deficits.[19] Associations of delirium with accelerated cognitive decline in AD have been shown to be independent of dementia severity, demographic factors, and pre-delirium rate of cognitive decline in some studies.[20]

The often-subtle cognitive deficits associated with MCI are rarely recognized or documented in clinical settings,[21,22] so it is not unexpected that relatively little is known about the impact of delirium. Notably, a recently proposed longitudinal study, MDDCohort (Mild Cognitive Impairment Delirium Dementia), will evaluate the rate of coversion from MCI to dementia following delirium.[23] Findings from a subgroup analysis of patients with MCI in a large prospective study of older adults undergoing major elective surgeries, demonstrated that patients with MCI developed postoperative delirium at twice the rate of those with normal cognition (adjusted relative risk (RR)=1.9, 95% confidence interval (CI) [1.3, 2.7]), and were at highest risk for moderately severe (RR=2.3, 95% CI [1.1–4.6]) or severe delirium (RR=4.6, 95% CI[2.0, 10.8]), compared to those without MCI or delirium.[24] Furthermore, patients with MCI and delirium were less likely to be discharged home, and at one month after surgery, this group was more likely to have developed new impairments in tasks associated with higher-level cognitive functions (e.g., handling finances, cooking, managing medications).

Last, recent results from the U.K. Delirium and Population Health Informatics Cohort (DELPHIC), a community-based study of cognitive aging, suggests that relationships between baseline cognitive function and long-term outcomes after delirium may be more complex than previously appreciated. As reported by Tsui et al, participants with strong baseline cognitive abilities had a lower risk of incident delirium, shorter duration, and lower delirium severity; however, this group experienced a larger post-delirium drop in cognitive scores, and were more likely to develop MCI during follow-up than those without delirium.[20,25]

Delirium: cause or catalyst of cognitive decline?

Taken together, the current literature suggests the potential for a bidirectional relationship between delirium and

cognitive impairment, such that presence of either may increase the incident risk of the other.[26] However, the question of whether post-delirium cognitive sequalae represent the unmasking of unrecognized dementia, an accelerant of preclinical neurodegeneration, or a direct cause of new onset of cognitive impairment, cannot be completely resolved with observational data. Advances in neurobiology research contribute additional insights into the nature of these relationships.

OVERVIEW OF DELIRIUM NEUROBIOLOGY

The underlying pathophysiology and associated neurologic and cognitive changes of delirium are complex, and multiple theories have been proposed.[4] Evidence supports the involvement of several potential mechanisms, including inflammation, immune response, abnormal brain energy metabolism, disruption in neurotransmitter function, cellular-signaling, and network connectivity, and neuronal injury and degeneration.[4,11,27] One systematic review across 32 studies examined markers of inflammation in delirium and found consistently elevated levels of serum CRP, TNF-α, IL-8, and IL-6.[28,29] The association between incident delirium and inflammatory markers may be due to the powerful cascade effect of the systemic inflammatory response resulting in the release of cytokines and leukocytes, reduced integrity of the blood-brain barrier, and risk for perivascular swelling, neuroinflammation, decreased oxygen perfusion, ischemia, and neuronal apoptosis.[4,29-31] Acetylcholinesterase deficiency and increased serum anticholinergic levels have also been associated with increased risk and severity of delirium, with improved levels associated with delirium resolution.[3,32,33] One hypothesis posits that a cumulative effect of neurotransmitter dysfunction and hampered brain network connectivity may reduce sensory processing and integration, resulting in delirium.[1] This may explain why the use of medications that alter neurotransmission, like opioids, may induce delirium.[29] Abnormalities in the above mechanisms, as well as alterations in melatonin and cortisol levels, may also explain why disruptions in sleep-wake cycles and heightened physiological stress are also implicated in cognitive changes and delirium onset.[4,31,34,35]

Several neurobiological mechanisms overlap between delirium and dementia. One pertinent and thorough review by Fong & Inouye[27] summarizes the current evidence for several shared mechanisms, including neuroinflammation, neuronal injury, neuroanatomical structural abnormalities, and AD-specific biomarkers. Novel research is being conducted on the potential use of related biomarkers for early detection or prediction of delirium, including apolipoprotein E isoforms, cortisol signaling, pro-inflammatory cytokines, neurodegenerative marker S100B, copeptin and 6-sulfatoxymelatonin levels, neurofilament light, and MRI-based brain atrophy.[36-38] Other unique approaches for prediction and detection of delirium include EEG and transcranial doppler.[27] The substantial overlap in mechanisms shared by delirium and dementia supports observations of frequent cooccurrence and mutual exacerbation.

NEUROPSYCHOLOGY OF DELIRIUM

Though acute change in cognitive functioning is a key characteristic of delirium, full neuropsychological evaluation is not typically pursued during acute episodes. Due to the nature of delirium, it is challenging to accurately evaluate higher-level cognitive abilities that require intact attention (e.g., problem solving). Other factors common in delirium (e.g., agitation, drowsiness) and inpatient settings (e.g., distracting noises, cognitive effects of medications) can also confound cognitive test performance. However, clinicians may use brief cognitive testing or simplified test measures to assess basic domains of cognitive impairment and track changes over time.

Many assessment tools are available to characterize diagnosis, subtype, symptom severity, and relevant risk factors for delirium,[39] including the Confusion Assessment Method,[40] Family Confusion Assessment Method,[41] Memorial Delirium Assessment Scale,[42] Delirium Rating Scale Revised-98,[43] and Mini-Mental Status Exam (MMSE).[44] These assessments are relatively easy to administer and, except for the MMSE, they are publicly available for clinical use. The first four utilize clinical observation or collateral report to evaluate for relevant symptoms and show moderate to strong sensitivity and specificity for identifying delirium (CAM 94%, 89%; FAM-CAM 74%, 91%;[45] DRS-R98 83–88%, 79–88%; MDAS 71%, 94%).[42,46] The MMSE can be used to assess severity and domain-specific cognitive impairments during delirium (e.g., language, attention, and memory). However, the MMSE has poor specificity for differentiating cognitive impairment due to delirium from other causes.[47] Impairment on such cognitive screeners without improvement following resolution of acute delirium symptoms may warrant further neuropsychological evaluation. Before attempting cognitive assessment with an individual with suspected delirium, clinicians should determine patient engagement to ensure accuracy of test findings. Though no formal tests of engagement have been developed for delirium specifically, clinicians can use behavioral observation and informal approaches. For example, assessing quality and nature of performance on certain MMSE items, including basic orientation questions, object identification, phrase repetition, and simple command following, may help gauge the patient's capacity to engage in more comprehensive assessment.

Attention, memory, language, and visuospatial abilities are commonly impaired in delirium and some simple bedside tasks can be administered to better gauge these abilities.[48] Attention can be assessed in delirium using a range of tasks, including digit span, spatial span, vigilance, serial

7s, and months of the year backwards (MOTYB).[48-50] Clinicians may also assess for deficits in expressive and receptive language using tasks of confrontation naming, and comprehension.[51]Interestingly, impaired written signature is quite specific to impairments in visual perception and visuospatial abilities are often reported in delirium, and patients may perform significantly worse.[52,53] Short- and long-term tests of memory can also be administered; however, it can be difficult to determine.[48]

Considering the significant overlap in cognitive symptoms between delirium and dementia,[54] there is no one task that can differentiate the two. However, subtle differences have been found on tests of verbal memory (dementia<delirium) and visual perception, and test combinations may be even more accurate (e.g., vigilance, MOTYB). The Cognitive Test for Delirium (CTD) was also specifically designed to evaluate cognitive abilities in patients with delirium and involves tasks of orientation, memory, comprehension, and vigilance. Patients with delirium perform significantly worse on the CTD (Total Score 9.5 ± 5.0) than patients with dementia (Total Score 24.5 ± 1.9) suggesting good discriminability.[55] Although often infeasible, cognitive evaluation before and after delirium may be the most useful to track post-delirium cognitive changes and guide decision-making concerning future treatments and support.

DELIRIUM PREVENTION AND MANAGEMENT

Since the cognitive and functional effects of delirium may persist long after the acute episode has resolved, taking measures to prevent and ameliorate delirium are critical. Risk for delirium has been associated with several factors, including older age, preexisting cognitive impairment, certain medical and psychiatric comorbidities, acute medical events, polypharmacy, certain medications and medical interventions, and treatment setting.[25,27,30,56-59] Though some of these risk factors are unalterable (e.g., age), several are modifiable and should be addressed to prevent or mitigate the effects of delirium. Non-pharmacological approaches include tailoring hospital environments (e.g., consistent reorientation to time using calendars), having a family member present, promoting physical functioning (e.g., ensuring use of visual and hearing devices), confirming proper hydration and nutrition, and preventing common complications (e.g., falls, urinary incontinence, and feeding disorders), all of which may increase delirium risk.[60,61] Additionally, the utilization of brief cognitive screeners (i.e., MMSE, MoCA) may help predict heightened delirium risk and establish a neurocognitive baseline. Serial cognitive monitoring may therefore promote early detection of delirium as well as dementia.

Drug toxicity and polypharmacy may precipitate delirium or prolong its duration, particularly in older adults with pre-existing health conditions. Anticholinergic medications, antipsychotics, benzodiazepines, and opioids have long been recognized as key triggers for delirium, although the frequency of association varies across different studies. Deprescribing deliriogenic medications and assessing medication withdrawal sequelae are recommended approaches to decrease delirium risk.[30,62] Pharmacologic prophylaxis of delirium has also been investigated, though not formally recommended since evidence from randomized trials is sparse and interpretation of effectiveness is challenging due to heterogeneity across treatment settings and patient populations. One meta-analysis of 58 studies showed favorability for the use of ramelteon, as well as promise for olanzapine, risperidone, and dexmedetomidine to reduce delirium incidence.[63] Evidence for use of medications to ameliorate acute delirium is also mixed. Some research has found that use of haloperidol plus lorazepam and alpha-2 agonist dexmedetomidine (depending on the patient population) may improve delirium outcomes;[62,64] however, various other studies have not found haloperidol to be superior to placebo for treatment of delirium on all-cause, post-hospitalization, or short-term mortality.[65,66] In general, findings on the general use of antipsychotics, opioids, benzodiazepines, statins, serotonin agonists, and cholinesterase inhibitors to mitigate delirium are unclear,[64] and as such, the deprescription of medications should be of primary consideration.[64-66]

CONCLUSIONS

Although delirium may be an acute medical event, the residual effects of delirium can be long-lasting and have significant implications for daily functioning and cognitive outcomes. The neurobiological mechanisms underpinning cognitive consequences of delirium and associated neurological diseases are multifaceted, complex, and, seemingly, overlapping. Patients with preexisting cognitive impairment, including those with MCI and dementia, are at greater risk for incident delirium, and episodes of delirium can exacerbate or incite new cognitive impairments. Presently, there are several measures that clinicians can take to reduce risk and screen for delirium, including integration of non-pharmacological and pharmacological approaches to patient care, and use of well-validated measures to detect and track delirium symptoms. Though completing neuropsychological testing before and after delirium is rarely feasible, subsequent outpatient evaluations can help track future changes and provide additional insights for treatment and support. Future research pursuing additional insights into the neurobiological mechanisms of delirium will hopefully support the development and implementation of additional approaches for prevention, detection, and treatment.

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