

COMMENTARY

Characterizing the long-term cognitive impairment following delirium episodes: A call to action

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1 | INTRODUCTION

While the world attempts to recover from one global pandemic, it is useful to turn to the “unfinished business” of meeting the needs of patients living with delirium and dementia. Both delirium and dementia are associated with poor outcomes, including premature transfer to residential care and even death. The relationship between the geriatric syndromes can be, however, thrown into a methodological quagmire, but this should not be a barrier to pursuing fundamental inquiry here. An increasing and sophisticated research base in delirium, frailty, and dementia is essential to improve both our fundamental understanding and the quality of care for patients who experience cognitive impairment following delirium.

2 | THE RELATIONSHIP BETWEEN DELIRIUM AND DEMENTIA

Delirium straddles so many disciplines potentially, including geriatrics and neuroscience, such that it can be simultaneously “everybody’s business” and yet “nobody’s business.”

Behind any cognitive decline after episodes of delirium, there is, however, a neuroscience yet to be properly elucidated. The association between delirium and long-term cognitive decline has been borne out formally in a recent meta-analysis,¹ but geriatricians have known about this association for ages. There is still a specific need to understand more about the individual’s susceptibility to develop cognitive decline after delirium and the trajectories of any cognitive decline. Indeed, the risk of developing cognitive decline is not the same among all people who experience delirium. We actually have

relatively few clues regarding the nature of the cognitive decline, which can happen after delirium. It perhaps seems that the cognitive decline is fastest when delirium episodes happen in patients with a high dementia neuropathological load.² Intriguingly, there is as yet insufficient information as to what the predominant pathology is, nor indeed how heterogeneous the cognitive decline is.

3 | IS THERE A CHOLINERGIC DEFICIT AT ALL ACCOMPANYING THE COGNITIVE DECLINE AFTER DELIRIUM?

Patients who experience a cognitive decline after delirium episodes may be prescribed empirically by their physician a cholinesterase inhibitor, such as donepezil, but there is, as yet, no robust evidence for a fundamental cholinergic deficit in patients experiencing cognitive decline following delirium. Cholinesterase inhibitors increase the availability of acetylcholine at synapses in the brain, but the rationale for their use in cognitive decline following delirium is currently poorly specified.³ Different classes of drugs aimed to be cognitive enhancers, or “nootropics,” are relatively underexplored in the context of cognitive decline after delirium. We have simply not been able to leverage contemporary neuroimaging techniques to study any speculative cholinergic loss following delirium.^{4,5}

In the very old patients, epidemiological study suggests that frailty contributes to the risk for dementia beyond its relationship with the burden of traditional dementia neuropathologies, suggesting that reducing frailty could have important implications for controlling the burden of dementia.⁶ Dementia for the majority is not a simple monogenic disorder, but is marked by complexity and

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comorbidity, especially as the age of patients increase. An important issue therefore is how the genetic and lifestyle factors interact during a life course, in particular whether the genetic risk for dementia can be modified by a healthy lifestyle. Similarly, there may be one fundamental neurotransmitter deficit characterizing any cognitive decline after episodes of delirium.⁷

4 | NEUROLEPTIC SENSITIVITY?

The cholinergic system is, however, not the only neurochemical issue of concern. Suppose that the cognitive decline following delirium takes on predominantly the form of the dementia of Lewy body type. Delirium can be a first presentation of dementia with Lewy bodies, and the early diagnosis of Lewy body dementia is clinically important in terms of avoidance of inappropriate neuropsychopharmacological intervention.⁸ Exposure to the risk of neuroleptic sensitivity may be due to decreased vigilance in a vulnerable patient group.⁹ The observation that a delirium episode is as a sign of a dementia disorder, including even Alzheimer's dementia, alcoholic dementia, or vascular cognitive impairment, perhaps implies that older elderly patients having an episode of delirium should be ideally evaluated and followed up for cognitive decline through integrated systems.¹⁰

5 | A NEED TO UNDERSTAND THE LONGITUDINAL PROGRESSION OF DECLINE

The nature of the initial presentation of cognitive impairment following delirium may be relevant to the subsequent disease progression. As a comparison, for example, it has recently been reported that the specific association between cognitive fluctuations and visual hallucinations, and a poorer prognosis in mild cognitive impairment, may indicate that these are symptomatic of a more aggressive clinical phenotype.¹¹ There has been few or no comprehensive peer-reviewed published studies of the trajectories of cognitive decline in patients after delirium in older age, compared to the more common neurodegenerative disorders, but such an enquiry is important for a number of reasons, including cognitive rehabilitation and intervention trial design.

6 | BIOMARKERS FOR COGNITIVE DECLINE AFTER DELIRIUM

Despite major promises that biomarkers can improve diagnosis, prognosis, prediction, and management, the track record of successful biomarkers, including in the dementia and delirium fields, has not been great. It is plausible that, on admission, both delirium and frailty are independently associated with increased risk of death, beyond that expected from all the acute and chronic health factors, and that delirium and frailty interact in such a way that, although delirium increases the risk of death at all levels of frailty, the relative impact

of this association was greatest in fitter patients.¹² The precise relationship between frailty and delirium remains somewhat enigmatic,¹³ let alone the link between these two and dementia.

7 | CHARACTERIZING THE NONCOGNITIVE FEATURES OF THE DECLINE AFTER DELIRIUM

Research into characterizing what exactly happens concerning the cognitive decline after delirium must extend to identifying the neuropsychiatric symptoms or behavioral and psychological symptoms. Living in the here and now, we do not currently have an adequate characterization of the behavioral symptoms accompanying any decline after delirium. We already know that the behavioral and psychological symptoms can differ significantly among the common diagnoses of dementia, and they therefore differentially affect the care giver's burden.¹⁴ Once the relative frequency of neuropsychiatric disturbances can be ascertained for this patient group, it might be possible to hone in on an evidence base for effective nonpharmacological interventions.¹⁵

8 | CONCLUSION

Possibly the most effective way to prevent any decline which happens after delirium is most likely to prevent the delirium episodes in the first place. We know that dementia increases the risk of delirium, and recurrent delirium increases the risk of dementia. There is undoubtedly an urgent need to break this vicious cycle, and, at the very least, keep tabs of patients in the re-admissions to hospital. That frailty and complexity may be underlying it all in old age must not be a message which is ever obscured. The possibility remains that we are only at the tip of the iceberg in aligning delirium and dementia research and service provision, judging from the huge volume of fundamental geriatric research yet to be performed. Answers to fundamental questions here will have profound implications for the care of persons in the community, in the hospital, and elsewhere.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

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