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Perioperative Delirium and Mild Cognitive Impairment

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To the Editor

Delirium is common in the elderly following major surgery,[1] more so in those who have preexisting reduction of neurocognitive function.[2] And *vice versa*, delirium may predict later cognitive decline during first year after surgery.[3] Furthermore, cognitively normal octogenarians who developed delirium during hospitalization were more likely to be diagnosed with dementia at 3-year follow-up compared to those who did not experience delirium.[4] In another study, 60% of geriatric patients with delirium at hospital admission developed dementia over the next 3 years compared to only 18.5% of those without delirium with an annual incidence of dementia 18.1% versus 5.6% for patients with and without delirium, respectively.[5] Therefore, this suggests an existence of relationship between delirium and later cognitive impairment, but understanding the nature temporality (which is first) of this association is hindered by the paucity of prospective studies. In other words, it is not known whether postoperative delirium is solely related to its precipitating factors (surgery, hospitalization), or whether delirium itself can cause permanent neuronal damage leading to dementia.

While the relationship between dementia and postoperative delirium has been repeatedly established,[6, 7] the association between delirium and mild cognitive impairment (MCI), an intermediate stage between normal cognitive aging and dementia was noted in only two reports.[8, 9] The major controversy remains whether perioperative delirium is simply a marker of vulnerability to dementia, or whether delirium itself can be causative and directly related to neuronal damage leading to dementia.

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In 2004, Mayo Clinic epidemiologists and neurologists assembled a large prospective population-based cohort of non-demented Olmsted County, MN residents (aged 70–89 on October 1, 2004) to study decline in cognitive function with aging.[10–12] The primary aim of the Mayo Clinic Study of Aging (MCSA) is to examine risk factors for progression from normal cognitive function to MCI and dementia.[11–13] Details regarding diagnostic procedures for assessment of cognition and diagnosis of MCI are detailed in prior publications,[10, 11, 13] and in our investigation which is included in this issue of *Mayo Clinic Proceedings*[14] where we examined the association between exposure to surgical anesthesia after age 40 and later development of MCI. The observations reported in this letter use the resources of MCSA[12] and Rochester Epidemiology project[15] to conduct a series of analyses restricted only to patients who underwent surgery after enrollment in MCSA to assess whether: a) preexisting MCI increased likelihood of postoperative delirium, and b) in those characterized as cognitively normal prior to surgery, whether postoperative delirium predicts later MCI.

Delirium can be detected with the standardized confusion assessment method (CAM), a simple test with high sensitivity (94–100%), specificity (90–95%) and interobserver reliability.[16] The CAM instrument examines 4 domains: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM demonstrated convergent agreement with 4 other mental status tests, including the Mini-Mental State Examination.[16] In our practice the CAM has been assessed in all hospitalized patients since 2004 as a part of routine nursing charting.

From electronic medical records we identified all patients in MCSA who were noted to have developed delirium after January 1, 2004 within 72 hours of surgery. We explored whether presence of MCI poses a risk for postoperative delirium, and whether delirium predicts development of MCI, with the following results.

a) There were 688 MCSA participants who had one or more surgeries with general anesthesia following their first MCSA follow-up visit. At the time of their first surgery (index surgery) 126 had been diagnosed with MCI and 562 had not. The types of surgeries performed included orthopedic (n=199), general (n=137), gynecologic/urologic (n=85), ENT (n=48), cardiac with bypass (n=41), neurosurgery (n=34), vascular (n=33), thoracic (n=22), plastic (n=22) and other (n=67). There were 28 patients who experienced postoperative delirium following the index surgery. As expected, the frequency of postoperative delirium was highest in patients undergoing cardiac bypass surgery (8/41, 20%). The frequency of postoperative delirium following the index surgery was significantly higher for those with MCI *vs*. not (16/126, 13% *vs*. 12/562, 2%, respectively; OR (95% C.I.) = 6.6 (3.1, 14.5); $P<.001$, Fisher's exact test). *This suggests that patients with MCI undergoing surgery with general anesthesia may be at increased risk for postoperative delirium*.

b) Of the 562 participants who were cognitively normal at the time of their index surgery, i.e., without a diagnosis of MCI, 409 had a subsequent MCSA follow-up visit, and of these 29 developed incident MCI. The frequency of MCI at the next follow up visit was non-significantly higher in those who experienced postoperative delirium following the index

surgery *vs.* those who did not (2/8, 25% *vs.* 27/401, 7%, respectively; OR (95% C.I.) = 4.6 (0.9, 24.0); *P*=.10, Fisher's exact test).

c) However, since some participants had additional surgeries following their index surgery but before returning for their next MCSA follow-up visit, we also created a variable to indicate any perioperative delirium prior to the next follow-up. Using this as the exposure (risk factor) a similar pattern was observed; the frequency of MCI was 23% (3/13) for participants who had perioperative delirium *vs.* 7% (26/396) for those with delirium (P=.06, Fisher's exact test).

There are several limitations of this analysis. First, statistical power was low because of the low number of events noted. Second, the routine clinical use of the CAM as a means to ascertain delirium has not been validated by research criteria, and the overall incidence of delirium obtained by reviewing medical records appears to be lower than that reported from prospective investigations in earlier time periods.[1] However, any underreporting of delirium is unlikely to be related to the diagnosis of MCI, therefore it should not bias our conclusions.

This exploratory analysis suggests that patients with MCI have a higher likelihood of developing perioperative delirium, which agrees with finding of others.[9] And *vice versa*, in cognitively normal participants at the last assessment prior to surgery, those who experienced postoperative delirium, compared to those not experiencing delirium, tended to be more likely diagnosed with MCI at the first subsequent follow-up (23% *vs.* 7%), however this difference did not reach statistical significance (P = 0.06). Evidence is starting to emerge from epidemiological, clinicopathological, neuroimaging, biomarker, and experimental studies suggesting that delirium and dementia share common pathological mechanisms.[17] Our preliminary results further suggest this intriguing hypothesis and should be tested in future studies.

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Dr. Knopman serves as deputy editor for the journal Neurology and serves on a data safety monitoring board for Lundbeck Pharmaceuticals and for the Dominantly Inherited Alzheimer's Disease Treatment Unit. He has served on a data safety monitoring board for Lilly Pharmaceuticals, served as a consultant to TauRX, was an investigator in clinical trials sponsored by Baxter and Elan Pharmaceuticals in the past 2 years, and receives research support from the National Institutes of Health. Dr. Petersen is the chair of data monitoring committees for Pfizer and Janssen Alzheimer Immunotherapy and has served as a consultant for Roche, Merck, and Genentech. He receives royalties from the publication of Mild Cognitive Impairment by Oxford University Press. Dr. Roberts receives research support from the National Institutes of Health and the Driskill Foundation and previously received research support from AbbVie Health Economics and Outcomes Research.

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List of Abbreviations

CAM	confusion assessment method
MCI	Mild cognitive impairment

MCSA Mayo Clinic Study of Aging

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