Delirium accelerates cognitive decline in Alzheimer disease

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ABSTRACT

Objective: To examine the impact of delirium on the trajectory of cognitive function in a cohort of patients with Alzheimer disease (AD).

Methods: A secondary analysis of data collected from a large prospective cohort, the Massachusetts Alzheimer's Disease Research Center's patient registry, examined cognitive performance over time in patients who developed (n = 72) or did not develop (n = 336) delirium during the course of their illnesses. Cognitive performance was measured by change in score on the Information-Memory-Concentration (IMC) subtest of the Blessed Dementia Rating Scale. Delirium was identified using a previously validated chart review method. Using linear mixed regression models, rates of cognitive change were calculated, controlling for age, sex, education, comorbid medical diagnoses, family history of dementia, dementia severity score, and duration of symptoms before diagnosis.

Results: A significant acceleration in the slope of cognitive decline occurs following an episode of delirium. Among patients who developed delirium, the average decline at baseline for performance on the IMC was 2.5 points per year, but after an episode of delirium there was further decline to an average of 4.9 points per year ($p = 0.001$). Across groups, the rate of change in IMC score occurred about three times faster in those who had delirium compared to those who did not.

Conclusions: Delirium can accelerate the trajectory of cognitive decline in patients with Alzheimer disease (AD). The information from this study provides the foundation for future randomized intervention studies to determine whether prevention of delirium might ameliorate or delay cognitive decline in patients with AD. *Neurology*® 2009;72:1570–1575

GLOSSARY

AD = Alzheimer disease; **CDR** = Clinical Dementia Rating; **IMC** = Information-Memory-Concentration subtest of the Blessed Dementia Rating Scale; **MADRC** = Massachusetts Alzheimer's Disease Research Center; **MGH** = Massachusetts General Hospital.

Identification of factors that impact cognitive trajectory in Alzheimer disease (AD) may lead to effective secondary prevention strategies. Studies have shown that older age,[1,2] male gender,[3] genetic predisposition,[4] rapid onset disease,[5] higher dementia severity,[4] and high degree of medical comorbidity[2] can influence cognitive decline over time, but these factors are not modifiable. A potentially preventable condition that may impact cognitive trajectory and which occurs in up to 66%–89% of patients with AD during hospitalization[6-8] is delirium. This syndrome is characterized by acute changes in cognition and attention, and is often the physiologic consequence of a medical disturbance or complication, such as infection, labora-

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tory derangements, adverse medication effects, or surgery. A diverse nomenclature for delirium has emerged, including terms such as acute confusional state, acute brain syndrome, or toxic-metabolic encephalopathy. For the purposes of this research these terms are considered to refer to the same syndrome, and are generalized under the broad characterization of acute brain failure. Like heart failure, brain failure can be conceptualized as a syndrome resulting from multiple and diverse etiologies, and contributing to poor outcomes independent of specific causes.

This study examines cognitive trajectory in a cohort of patients with AD before and after an episode of delirium. We hypothesize that the occurrence of delirium results in more rapid cognitive decline, independent of relevant covariates. Ultimately, if delirium irreversibly impacts cognitive decline in patients with AD, this finding would hold substantial clinical implications for delirium prevention and management.

METHODS

Setting and subjects. Potential study participants were consecutive patients seen at the Memory Disorders Unit of the Massachusetts Alzheimer's Disease Research Center (MADRC) at Massachusetts General Hospital (MGH) from January 1, 1991, through June 30, 2006. The MGH Memory Disorders Unit evaluates approximately 200–250 new patients each year, and is the primary memory clinic serving the MADRC, a specialized research center that has been funded by the National Institute of Aging/NIH since 1984. The MGH is a 900-bed Harvard-affiliated acute care teaching hospital with over 45,000 admissions and 433,000 outpatient visits per year.

Patients included in the study were diagnosed with probable or possible AD by an attending neurologist in the MGH Memory Disorders Unit using National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association guidelines.[9] All patients had a minimum of three observations at about 6-month intervals to determine cognitive trajectory. Written informed consent for use of their clinic data for research was obtained jointly from the patients and their family members, next of kin, health care proxy, or count-appointed guardian, according to procedures approved by the MGH institutional review board.

Clinical evaluation. Patients were assessed at entry to the cohort and approximately every 6 to 7 months thereafter, following a uniform protocol at the Memory Disorders Unit clinic. Baseline evaluation included collection of the following variables: age, sex, race and ethnicity, education, and presence of comorbid medical conditions including thyroid disorder, heart disease, hypertension, hypercholesterolemia, diabetes mellitus, liver disease, kidney disease, cancer, pulmonary disorders, or stroke. Dementia-related information included family history of dementia, duration of dementia symptoms before diagnosis, and dementia severity. Dementia severity was rated across all timepoints using the MGH Dementia Severity Rating scale, an in-house scale created at the MADRC, which rates general levels of functional dependence (range 0–5, with 5 indicating profound impairment). For patients enrolled after 2002, the Clinical Dementia Rating (CDR) scale[10] was also used to assess dementia severity. Cognitive testing was conducted at baseline and approximately every 6 months using the Information-Memory-Concentration (IMC) section of the Blessed Dementia Scale,[11] further described below.

Identification of delirium. Delirium and its date of onset was identified among cohort members hospitalized at MGH during the course of the study by using a previously validated chart review method[12] based on recognition of key terms or presence of mental status or behavioral changes by trained clinical chart abstractors. In a previous study, the chart-based method demonstrated a sensitivity of 74%, specificity of 83%, likelihood ratio of 4.4, and overall agreement of 82% (kappa = 0.41) for delirium diagnoses.[12] To verify reliability of ratings, interrater reliability assessments were conducted among the three actual chart reviewers for the present study, and demonstrated an agreement of 100% (kappa = 1.0) for delirium ratings across 21 cases.

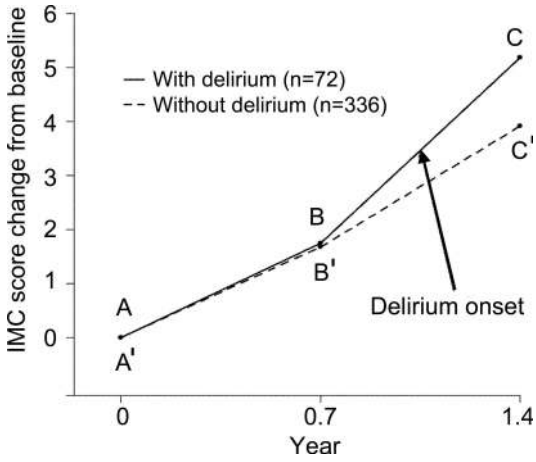
Outcome. The primary outcome for this study was rate of cognitive decline, as measured by changes in the IMC score over time. The IMC is a well-validated, widely used summary measure that measures domains of orientation, memory, knowledge of personal information/current events, and performance on three concentration tests. IMC scores range from 0 to 37, with higher scores indicating impairment.[11]

Statistical analyses. For all patients, three sequential study timepoints were identified (labeled A, B, and C in the figure). In the delirium group, all timepoints were defined relative to the date of onset of the delirium. For example, point B represents the MADRC assessment most proximal but prior to the delirium. In the nondelirium group, point B was randomly chosen from among multiple assessments except for the first or last visit. In both groups, point A represents the MADRC visit prior to point B and point C represents the next visit after point B. For these analyses, the date of delirium onset was required to fall in the interval between points B and C. To assure that the selection of timepoints in the nondelirium group did not bias our results, a random selection of timepoints was performed for this group five times and the analysis was replicated in each of the derived datasets. For this analysis, time period AB was considered as the baseline interval (prior to delirium), and BC was the outcome interval (including delirium occurrence).

Crude changes in IMC score across baseline (AB) and outcome (BC) intervals in delirium and the nondelirium groups were calculated. Because there was some variability in assessment intervals, an annualized change in the slope of IMC scores for both intervals was used in all analyses. Using a paired *t* test, baseline slope and the outcome slope for both groups was compared. The crude change and slope among those with and without delirium was also assessed.

To calculate adjusted slopes, a linear mixed regression model was used and controlled for age, sex, education, dementia severity score, duration of symptoms prior to diagnosis, family history of dementia, and number of comorbid medical conditions. Time was included as a random effect. The hypothesis that cognitive change is greater after delirium was tested. Change was anticipated to be constant between the two study intervals for the nondelirium group.

Figure **Cognitive trajectories of patients with Alzheimer disease with and without delirium**



This figure depicts the slopes of the cognitive trajectories in patients with Alzheimer disease over time in our cohort. The median time to delirium from point B was 0.3 years (75% interquartile range, 0.13–0.45 years). The slopes are based on the changes in the Blessed Information-Memory-Concentration (IMC) subscore over time, and the scores presented are calculated adjusting for baseline differences. These slopes are derived from linear mixed models adjusted for relevant covariables (age, sex, educational level, Massachusetts General Hospital dementia severity rating score, duration of dementia symptoms before diagnosis, family history of dementia, and number of comorbid medical diagnoses). The solid line indicates the trajectory for patients with delirium (n = 72) and the dashed line indicates the trajectory for patients without delirium (n = 336).

A small number of missing values were present for duration of symptoms before diagnosis (3%) and number of comorbid medical diagnoses (4%) for the delirium group and for education (2%), family history of dementia (0.3%), dementia severity score (1%), duration of symptoms before diagnosis (1%), and number of comorbid medical diagnoses (2%) for the nondelirium group.

All analyses were conducted using the SAS version 9.1 statistical analysis program (SAS Institute, Cary, NC). All statistical tests were two-tailed, and an alpha level of less than 0.05 was used to indicate statistical significance.

RESULTS A total of 990 patients were potentially eligible to participate. Over the course of the study, 195 patients were hospitalized at MGH and underwent chart review. A total of 112 of these patients were confirmed to have developed delirium. For some of these patients, the date of delirium onset did not fall in the outcome interval BC; that is, occurred either after timepoint C (n = 13), or delirium occurred during the baseline AB interval (n = 27). These patients were excluded from primary analysis. The remaining patients who developed delirium during the outcome interval BC had a median time to delirium from point B of 0.3 years (75% interquartile range, 0.13–0.45 years). Thus, a total of 72 patients were used to determine cognitive trajectory for the delirium group.

Of the remaining 878 patients, 540 were excluded due to a caregiver report of acute illness or possible delirium or hospitalization outside the MGH that could not be confirmed by medical record review, and 2 were excluded due to lack of follow-up visits during the target (6-month) time interval. Thus, 336 patients were included in the nondelirium comparison group.

The characteristics of the patients in the overall cohort (n = 408) and the delirium (n = 72) and nondelirium (n = 336) subgroups are shown in table 1. Compared with the nondelirium group, the delirium group was significantly older, more likely to be male, had less years of formal education, and had more comorbid illnesses. The patients with delirium were significantly more likely to have a positive fam-

Table 1 **Characteristics of the Massachusetts Alzheimer's Disease Research Center study sample**

Characteristic*	Overall (n = 408)	Delirium (n = 72)	Nondelirium (n = 336)	*p* Value†
Age at initial visit in analysis, y	73.9 ± 8.1	76.9 ± 6.6	73.2 ± 8.3	0.001
Male	176 (43.1)	39 (54.2)	137 (40.8)	0.04
Race/ethnicity, nonwhite	24 (5.9)	4 (5.6)	20 (6.0)	0.92
Education, y	13.9 ± 3.5	13.0 ± 3.4	14.1 ± 3.4	0.02
Number of medical diagnoses	1.3 ± 1.2	1.7 ± 1.3	1.3 ± 1.1	0.01
Family history of dementia	22 (5.4)	8 (11.1)	14 (4.2)	0.02
Baseline Blessed IMC score	11.1 ± 6.7	9.7 ± 5.4	11.4 ± 6.9	0.04
Baseline MGH dementia severity score	2.1 ± 0.9	2.1 ± 0.8	2.1 ± 0.8	0.54
Duration of symptoms before diagnosis, y	3.1 ± 2.1	2.6 ± 1.5	3.2 ± 2.2	0.01

Values are mean ± SD or n (%).
*Missing values were present for the following: race (n = 3 in nondelirium group); education (n = 8 in nondelirium group); family history of dementia (n = 1 in nondelirium group); baseline dementia severity score (n = 4 in nondelirium group); duration of symptoms before diagnosis (n = 2 in delirium group and n = 4 in nondelirium group); and medical diagnosis (n = 1 in delirium group and n = 5 in nondelirium group).
†For comparisons of all characteristics in delirium vs nondelirium groups.
IMC = Information-Memory-Concentration test; MGH = Massachusetts General Hospital.

Table 2 Comparison of cognitive score change at baseline vs outcome interval

	Baseline interval	Outcome interval	*p* Value
Delirium patients (n = 72)			
IMC score change ± SE	2.1 ± 0.4	3.9 ± 0.6	0.02
Slope (points/year) ± SE	3.1 ± 0.7	5.4 ± 0.8	0.05
Adjusted slope (points/year)* ± SE	2.5 ± 0.4	4.9 ± 0.7	0.001
Nondelirium patients (n = 336)			
IMC score change ± SE	1.8 ± 0.2	2.1 ± 0.3	0.54
Slope (points/year) ± SE	2.9 ± 0.4	3.3 ± 0.5	0.55
Adjusted slope (points/year)* ± SE	2.4 ± 0.3	3.2 ± 0.3	0.07

*Adjusted for age, sex, educational level, number of comorbid medical diagnoses at baseline visit, family history of dementia, Massachusetts General Hospital dementia severity rating score, and duration of dementia symptoms before diagnosis.
IMC = Information-Memory-Concentration test.

ily history of dementia and shorter duration of dementia-related symptoms prior to diagnosis. These baseline differences were controlled for in subsequent analyses. Of note, the delirium group showed less cognitive impairment by IMC scores at baseline compared to the nondelirium patients. Finally, there were no significant differences between the two groups in baseline MGH dementia severity score or duration of follow-up in the analyses.

In order to correlate the MGH Severity Scale with the more widely used CDR scale,[10] a Spearman correlation coefficient was calculated. In 4,296 paired ratings, the Spearman correlation coefficient for the CDR and MGH Severity Scale was 0.87 ($p < 0.0001$), confirming a high degree of correlation.

Comparisons of changes in cognitive scores or slopes at baseline and outcome interval for delirium and nondelirium patients are presented in table 2. For the delirium group, results are shown for the 72 patients who had complete data available. The crude change in Blessed IMC scores was significantly greater in the outcome interval compared with the baseline interval (3.9 vs 2.1, $p = 0.02$). The rates of change for baseline and outcome intervals were 3.1 and 5.4 points per year ($p = 0.05$). There was a significant acceleration in the adjusted mean slope after delirium, 4.9 points per year, compared to the baseline interval prior to delirium, 2.5 points per year ($p = 0.001$). To verify the results in the entire delirium group (n = 112), the analyses were repeated using multiple imputation to model adjusted slopes for the interval prior to and with delirium, and found an adjusted mean slope of 3.8 points per year after delirium, in comparison to 2.2 points per year at baseline ($p = 0.02$, data not shown).

For the nondelirium group of 336 patients (table 2), there was no significant difference in the change in Blessed IMC scores between baseline and outcome interval (1.8 vs 2.1, $p = 0.54$). In addition, no significant differences were found between unadjusted slopes (2.9 vs 3.3, $p = 0.55$) or adjusted slopes (2.4 vs 3.2, $p = 0.07$). These results indicate no significant acceleration of change in cognitive decline in the outcome interval in the nondelirium group.

The figure depicts the adjusted model implied slope (annualized change in Blessed IMC) of the cognitive performance over time in the cohorts with and without delirium. These slopes, derived from linear mixed regression models adjusting for relevant covariables as described in Methods, again demonstrate the significant acceleration in the slope of cognitive decline after delirium.

DISCUSSION This study demonstrates that incident delirium accelerates the trajectory of cognitive decline in hospitalized patients with AD. Prior studies have shown that patients with dementia who develop delirium have increased rates of hospitalization, institutionalization, and mortality.[6,13-15] In this sample, after adjusting for baseline differences, the change in score on the Blessed IMC prior to an episode of delirium was 2.5 points per year, consistent with prior reported increases in patients with AD of about 3 points per year.[16-18] In the delirium group, the relative change in IMC score doubled from 2.5 points per year at baseline to a postdelirium rate of 4.9 points per year. In comparisons across groups, the rate of change in IMC score occurred about three times faster in those who had delirium compared to those who did not. In other words, these data estimate a 53% absolute increase in the rate of change. From a clinical standpoint, this study suggests that over 12 months, patients with AD who become delirious experience the equivalent of an 18-month decline compared to those who do not experience delirium.

Delirium used to be viewed as a transient cognitive disorder, but research has shown that delirium is not always temporary and can often result in persistent functional[19,20] and cognitive losses among general medical hospitalized elderly. For example, delirium has been linked to long-term cognitive impairment, as demonstrated by lower Mini-Mental State Examination scores and lowered performance on tasks of executive functioning, attention, and processing speed.[14,21-23] Furthermore, subjective memory complaints, newly diagnosed dementia, and need for long-term care have been associated with delirium in elderly patients after hospitalization[24] or hip surgery.[25,26] While these studies demonstrate adverse long-term outcomes, this study is noteworthy in that it demonstrates the adverse impact of an episode of delirium on cognitive trajectory in patients with AD.

There are a number of strengths of this study. First is the relatively large sample size from the well-

characterized MADRC cohort. Second, although baseline differences emerged between the patients with AD with and without delirium, these factors were controlled in all subsequent analysis. Of note, these differences, including age, male gender, lower baseline education, and higher number of comorbid illnesses, are well described risk factors for delirium[27] and such group differences were not unexpected. The delirium group demonstrated lower baseline IMC scores on average than the nondelirium group. While this difference was significant, the impact of lesser degrees of cognitive impairment at baseline would be a conservative bias. An analysis using baseline IMC scores in the logistic regression model was conducted (data not shown) and the results did not substantively alter the findings of our study. Further, substantially worsened cognitive functioning in the delirium group despite this baseline difference lends support for the robustness of the finding. Third, duration of follow-up time was consistent in the analyses. Fourth, the time of delirium onset was identified from medical chart review. Finally, this work is proof of concept for what is commonly observed in clinical practice, that is, older patients—particularly those with dementia—may decline at a faster rate or never fully recover their cognitive function following an episode of delirium.

Bias may have been introduced into the analysis by missing data, or by excluding those patients who experienced delirium before a baseline cognitive trajectory could be established (n = 27), or who lacked a final measure to establish their trajectory following delirium (n = 13). To evaluate for the possibility of survivor bias in the 72 patients with data at all three timepoints, the analyses were repeated using multiple imputation for missing observations to model adjusted slopes in all 112 patients with delirium, and still demonstrated significant acceleration in cognitive trajectory following delirium.

There are limitations in the current study that should be noted. First, this was a single site study with a low representation of minorities and findings may not be generalizable to all patient populations. Second, the diagnosis of delirium was made by chart diagnosis, and although a validated method was utilized,[12] some cases of delirium may have been missed due to lack of documentation. Moreover, duration and severity of delirium could not be determined by chart review, which represents an important area for future investigation. Third, while inclusion of an additional timepoint post-delirium (point D) would have been ideal, we were unable to conduct such analyses due to substantial attrition from this frail, elderly, cognitively impaired cohort over time (55% did not have point D). An important limitation of the current analysis is that the concurrent effects of delirium, which may not have resolved during the delirium interval (BC), may confound the cognitive trajectory. Future studies with longer-term follow-up post-delirium will be required to validate our findings. Fourth, 43% of the hospitalized patients (83 of 195) did not develop delirium, and the effects of hospitalization on cognitive trajectory could not entirely be disentangled from the current study. Finally, not all patients in the MADRC cohort had complete chart reviews or hospitalization data.

Replication of this study is needed to confirm that delirium alters the trajectory of cognitive decline in AD. Other important features that might affect cognitive trajectory will need to be studied, including more diverse populations, longer time periods, and specific causes, duration, and severity of delirium. If delirium does indeed precipitate a more rapid decline in dementia severity, such a finding would necessitate changes in the standard of care for patients with dementia. For example, patients with AD would need to be monitored closely for delirium, and when in high-risk settings, delirium prevention strategies should be utilized. It has been previously shown that multicomponent risk factor strategies,[28] proactive geriatric consultation,[7] educational interventions targeted toward staff,[29] and avoidance of medications with high risk for delirium can be beneficial. Treating patients as outpatients where the risk of delirium may be lower could be another potential strategy for minimizing delirium. The area of delirium among hospitalized patients with AD has been largely unaddressed.[30] Given their high risk of accelerated long-term decline, new approaches to care for these patients to improve early identification and prevention of delirium are greatly needed.

Ultimately, the information derived from this study provides the foundation for future randomized intervention studies to determine whether prevention of delirium might ameliorate and/or delay cognitive decline in patients with AD. Understanding the pathophysiologic mechanisms for how delirium impacts cognitive trajectory in dementia is another area of important future work.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Peilin Shi, Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, MA.

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