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"Delirium superimposed on dementia is associated with prolonged length of stay and poor outcomes in hospitalized older adults"

Donna M. Fick, RN, PhD, FAAN[1,2], **Melinda R. Steis, RN, PhD**[3], **Jennifer L. Waller, PhD**, and **Sharon K. Inouye, MD, MPH**[4,5]

[1]School of Nursing, The Pennsylvania State University, Boston, MA

[2]Department of Psychiatry, Penn State College of Medicine, Boston, MA

[3]Orlando Veterans Administration Medical Center, Boston, MA

[4]Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

[5]Institute for Aging Research, Hebrew Senior Life, Boston, MA

Abstract

Background—Current literature does not identify the significance of underlying cognitive impairment and delirium on older adults during and 30 days following acute care hospitalization.

Objective—Describe the incidence, risk factors, and outcomes associated with incident delirium superimposed on dementia.

Design—24-month prospective cohort study

Setting—community hospital

Patients—139 older adults (>65 years) with dementia

Methods—This prospective study followed patients daily during hospitalization and one month post-hospital. Main measures included dementia (Modified Blessed Dementia Rating Score, IQ CODE), daily mental status change, dementia stage/severity (Clinical Dementia Rating, Global Deterioration Scale), delirium (Confusion Assessment Method), and delirium severity (Delirium Rating Scale-Revised-98). All statistical analysis was performed using SAS 9.3 and significance with an alpha level of 0.05. Logistic regression, analysis of covariance or linear regression was performed controlling for age, gender and dementia stage.

Results—The overall incidence of new delirium was 32% (44/140). Those with delirium had a 25% short term mortality rate, increased length of stay and poorer function at discharge. At one month follow-up, subjects with delirium had greater functional decline. Males were more likely to develop delirium and for every one unit increase in dementia severity (Global Deterioration Scale), subjects were 1.5 times more likely to develop delirium.

Corresponding author: Donna M. Fick, PhD, GCNS-BC, FGSA, FAAN Distinguished Professor, School of Nursing, The Pennsylvania State University and Department of Psychiatry, Penn State College of Medicine 201 Health and Human Development East, University Park, PA 16802 814 865-9325 (phone) 814 574 1716 (cell) 814 865-3779 dmf21@psu.edu.

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Conclusions—Delirium prolongs hospitalization for persons with dementia. Thus, interventions to increase early detection of delirium have the potential to decrease the severity and duration of delirium and to prevent unnecessary suffering and costs from the complications of delirium and unnecessary readmissions to the hospital.

INTRODUCTION

Much attention has been given recently to hospitalized older adults, the critical 30 day period and post-hospital syndrome.[1] What is missing from this dialogue is the contribution and significance of underlying cognitive impairment. By 2050, 14 million older persons in the United States are expected to have dementia.[2] Increasing numbers of older adults diagnosed with dementia are hospitalized and are at increased risk of developing delirium—in fact, delirium occurs in over half of hospitalized persons with dementia.[3] Further, current evidence suggests that delirium may accelerate the clinical course and trajectory of cognitive decline, and may be associated with considerably worse long-term outcomes, including prolonged hospitalization, rehospitalization within 30 days, nursing home placement, and death.[3–6] However, the problem of delirium superimposed on dementia (DSD) remains a neglected area of investigation in hospitalized patients. Delirium is superimposed on a dementia when an acute change in mental status (characterized by a fluctuating course, inattention, and either disorganized thinking or altered level of consciousness) is layered on top of a preexisting dementia.[4]

Despite the poor outcomes and high prevalence of DSD, little is known about the natural history in hospitalized older adults with dementia. Delirium studies often exclude persons with dementia, even though the prevalence of DSD is extremely high in both community (13–19%) and hospital (40–89%) populations and associated with higher costs and utilization compared to dementia and delirium alone.[4,5,7] In one study, annual costs for DSD were $9566 compared to $7557 for dementia alone.[7] The few risk factor studies of DSD were conducted in ICU or long-term care settings.[8,9]

The purpose of this study was to describe the incidence, risk factors, and outcomes associated with incident delirium in a prospective cohort of hospitalized older adults with dementia. The study aims were to: 1) estimate the incidence of new delirium in hospitalized persons with dementia, 2) identify the risk factors associated with incident delirium superimposed on dementia in this sample, and 3) describe the outcomes associated with development of delirium, and 4) evaluate the contributions of delirium severity and duration to outcomes.

METHODS

This 24-month prospective cohort study recruited and enrolled consecutive hospital admissions with dementia in a 300 bed community hospital in central Pennsylvania from July, 2006 through November, 2008. Data were collected daily from patients during hospitalization followed by a one-month post-hospitalization interview with patients and their caregivers in the community setting. Patients were included if they spoke English, had been hospitalized fewer than 24 hours, and met the screening criteria for dementia. Patients were excluded if they had any significant neurological condition associated with cognitive impairment other than dementia (e.g. brain tumor), a major acute psychiatric disorder, were unable to communicate, or had no caregiver to interview. The interviewers included experienced research assistants (RAs) who were either registered nurses or trained in a health-related field. All staff training of instruments were done with scripted training manuals and video training using manuals for the CAM. After training was completed, final interrater reliability assessments were conducted until staff reached 100% agreement. The

RAs were blinded to the aims and completed over 10 hours of training. Inter-rater reliability checks were conducted on 10% of the sample in the field with > 90% agreement attained on all instruments. This study was reviewed by and approved by The Pennsylvania State University Institutional Review Board (IRB) and consent was received from all subjects.

Study Measures

Dementia was defined by meeting all three criteria of a Modified Blessed Dementia Rating Score (Blessed) of greater than 3, an Informant Questionnaire on Cognitive Dementia (IQCODE) of ≥ 3.3, and documented dementia symptoms of at least 6 months' duration prior to current illness.[10–12] The Mini-Mental State Examination (MMSE), purchased from Psychological Assessment Resources, Inc., was used to measure change from day to day and aid in the measurement of delirium, but was not used to establish the diagnosis of dementia. Both the Clinical Dementia Rating (CDR)[13] scale and the Global Deterioration Scale (GDS)[14] were used to measure dementia stage and severity.

Delirium and delirium severity were defined according to the validated Confusion Assessment Method (CAM) algorithm;[15] the Delirium Rating Scale-Revised-98 (DRS-R-98) was used for delirium severity.[16] In a recent review, the CAM showed an overall sensitivity of 94% and specificity of 89%.[17] In the present study, delirium was measured in a comprehensive and structured interview that involved the MMSE and CAM criteria, and was based on a 24-hour period of observations, interviews with nurses and family members and chart review. The CAM was completed daily during patient hospitalization and the follow-up interviews. The CAM assesses four criteria including, acute and fluctuating nature, inattention, disorganized thought, and altered level of consciousness. Delirium was recorded by the research staff as present or absent each day based on full CAM criteria. Since the goal of the present paper focused on full CAM delirium, subsyndromal delirium is not presented in this paper

Delirium duration was defined as the number of days with a positive rating. Data were collected daily from patients during hospitalization, followed by a single interview at one-month post-hospitalization with patients and their caregivers. Most interviews were in person.

Delirium Risk Factors—Central nervous system-active (CNS-active) drug use was defined by 2005 American Hospital Formulary Services classification.[18] The Beers criteria were used to define potentially inappropriate medication use.[19] The Cornell scale for depression in persons with dementia was used, with cut point of 12 indicating depression.[20] Functional status change was measured via the Katz Index of Activities of Daily Living (ADLs) and Lawton instrumental activities of daily living (IADL) change scores.[21] Co-morbid conditions were classified with a weighted index that took into account both the number and seriousness of different co-morbid diseases.[22] Pain was measured using the PAIN AD scale.[23] Dehydration was defined using the BUN/ creatinine ratio and/or any chart diagnosis of dehydration. Admission lab values (Blood urea nitrogen--BUN, creatinine) were abstracted from the medical records.

Primary Outcomes—The primary outcomes measured were full CAM delirium, index hospitalization length of stay, cognitive decline (change in MMSE and GDS scores), death and functional status change (change from baseline to discharge score). One month mortality was measured by chart review and follow-up family interviews performed at one month via telephone or in person interviews. Mortality was not verified by additional methods.

Statistical Analysis

All statistical analysis was performed using SAS 9.3 and statistical significance was assessed using an alpha level of 0.05 unless otherwise noted. Descriptive statistics were calculated on all characteristics by incident delirium status.

Potential risk factors for incident delirium were examined using chi-square and t-tests, where appropriate. Simple proportional hazards models were used to estimate the relative risk (RR) and 95% confidence interval (CI) for incident delirium. A stepwise model building procedure under a proportional hazards model was used to build a final model for incident delirium that contained all variables that were statistically significant at the 0.05 alpha level or which had a RR of 1.5 or greater. Adjusted RR and corresponding 95% CI were determined. The outcome in each model was the number of days from admission to an incident delirium diagnosis. Subjects without incident delirium were censored using their length of stay as the total number of days they were at risk for developing delirium.

Finally, to examine the relationships between incident delirium, maximum incident delirium severity, and the number of inpatient days positive for delirium with the outcomes of death, impaired in 2 or more IADLs at follow-up, impaired in 2 or more ADLs at follow-up, length of stay, change in IADLs from admission to follow-up and change in ADLs from admission to follow-up, logistic regression (for the dichotomous outcome of mortality), analysis of covariance (ANCOVA) or linear regression (depending on the whether the independent variable was categorical or continuous) was performed controlling for age, gender and GDS score.

Results

Of 256 eligible patients, dual consent was obtained from 154 patient and 154 family research subjects (308 consents). The refusal rate was 39% (*n*=102). Fourteen subjects were consented and enrolled but later dropped out due to family/proxy concerns regarding the patient's ability to participate in interviews. Thus, the final sample included 139 patients.

Descriptive statistics for baseline measures are given in Table 1. Briefly, the average age of subjects was 83 year (SD=7), 41% were male, 57% were single, divorced or widowed, and the average number of years of education was 12 years (SD=3). Thirty-three percent were dehydrated on admission and 33% had fallen within two weeks prior to admission. Thirty-four percent had an infection at baseline and 36% had some sensory impairment.

The overall incidence of delirium was 32% (44/139) and the range of days to incident delirium was 1 to 8 days. During the baseline period (Table 1), subjects with delirium were older, more likely to be male, had lower Katz Impairment scores, higher GDS score, lower MMSE scores on admission, and higher Blessed scores than subjects without delirium. Slightly more persons with delirium had a prior fall, although the RR was not statistically significant. Length of stay measured at discharge was significantly higher for those with delirium (mean=9.1) than those without delirium (mean=5.7) ($p<0.0001$). Subjects with delirium were more likely to have died at one month than those without delirium. ($p=0.0153$).

In addition, we analyzed the adjusted relative risk estimates for the final model of incident delirium. Significant risk factors or risk factors with RR estimates at least 1.5 (or less than 0.66 if protective, from Table 1) that were examined in a more comprehensive multiple proportional hazards model included age, gender, having had a fall in the last two weeks, number of impaired ADLs (based on Katz), GDS scores, MMSE scores at baseline, and Blessed scores at baseline. The final proportional hazards included gender and GDS score.

Males were nearly 1.8 times as likely to develop delirium than females and for every one unit increase in the GDS, subjects were 1.5 times more likely to develop delirium.

Finally, Table 2 gives the results of examining outcomes related to incident delirium measures. For mortality, there were no statistically significant predictors of death after controlling for age, gender or GDS. For length of stay, subjects with incident delirium had significantly longer lengths of stay, as incident delirium severity increased by one unit the length of stay increased by 0.4 days, and as the number of inpatient days with delirium increased by one-day the length of stay increased by 1.8 days. For change in the impaired KATZ ADLS from admission to follow-up, as incident delirium severity increased by one unit the change in impaired KATZ ADLs increased by 0.05 units.

DISCUSSION

The most compelling finding from this study is the high incidence of delirium in hospitalized older adults with dementia and the association with poor clinical outcomes in those who develop delirium superimposed on dementia. DSD is difficult to detect and prevent; persons with DSD are at risk for poor quality of life. Those with delirium had a 25% short term mortality rate (p=0.0153), substantially increased length of stay (9.1 versus 5.1 days with an OR 1.8) and poorer physical function at discharge and follow-up. At one month follow-up, subjects with delirium had greater functional decline and lower GDS scores than those without delirium.

The incidence of delirium in this study was high (32%). Being delirious any time was associated with death and poor function. Delirium was also associated with the stage of the persons' baseline dementia, advanced age, lower MMSE scores, and falling before admission.

Previous studies have found delirium associated with increased mortality. Three studies found that, within one year of a delirium episode, a significant number of persons died or were institutionalized.[24–26] Other research has reported death within one year of documented delirium episodes and a threefold increased rate of death in the ICU.[24,27–32] This study is one of only a few to focus on increased mortality with DSD and to focus uniquely on *hospitalized* patients with delirium and dementia.

The main risk factors for delirium in this study were male sex and severity of dementia. Our results, combined with those from other recent studies by Voyer and colleagues,[8,33,34] point to the critical importance of screening for dementia in hospitalized older adults as dementia severity is a significant indicator of delirium severity. For instance, Voyer and colleagues[34] reported that persons with mild dementia were likely to experience a mild delirium while those with a more severe level of dementia were more likely to experience moderate to severe delirium. Our findings show that those who experienced episodes of delirium represented a highly vulnerable population with advanced dementia, sensory impairment, more falls and dehydration at admission, and higher Blessed scores. A recent study by Saczynski and colleagues[35] found 40% of patients who had experienced postoperative delirium did not return to their baseline at 6 months. Clearly, preventing delirium should be a critical priority to prevent such deterioration in the highly vulnerable population of hospitalized patients with dementia.

Patients in this study were on a mean of over 11 medications. One third of dementia patients in our study had also experienced a fall and dehydration at baseline. Other studies have found a relationship between cognitive decline, falling and medications.[36] Many of these

patients came into the hospital with potentially modifiable and preventable community or ambulatory care conditions of polypharmacy, falling, sensory impairment, and dehydration.

Importantly, in our study, length of stay was significantly higher (9.1 versus 5.7) for those with delirium compared to those without delirium. This finding is alarming when examining the economic impact of preventing delirium. Previous studies have found the cost of delirious episodes rivals those for diabetes and heart disease and that decreasing length of stay by just one day would save over $20 million dollars per year.[4,37]

In summary, this study is one of the first to report a high incidence of DSD and poorer outcomes for persons who experience delirium compared to those with dementia alone. This is one of only a few studies examining unique risk factors and delirium severity for DSD in the acute care setting. Findings from the current study report potential risk factors for development of incident delirium and highlight the challenge of preventing DSD before and during hospitalization. The generalizability of this study may be limited by the use of a non-diverse study population drawn from a single hospital in the northeast U.S., though the use of a community hospital increases the relevance to real world practice settings. Determination of baseline cognitive status and the differentiation of delirium and dementia are difficult, but validated, state-of-the-art methods were used which have been applied in previous studies.

This study provides fundamental methodological improvements over previous work, and advances the science by providing valuable data on the natural history, correlates, and outcomes of DSD. The strengths of this study include the prospective cohort design, the daily assessment for delirium based on a 24-hour period, methods for determining cognitive status at baseline in this difficult population, and utilizing strict blinding of the well-trained outcome assessors.

This study lays the groundwork for future studies to improve care for persons with dementia who present to acute care and to plan prevention programs for delirium *before t*hey are admitted to the hospital. We must be able to translate best practice for DSD into the acute care and community settings to prevent or minimize effects of delirium in persons with dementia. Interventions to increase early detection of delirium by hospital staff have the potential to decrease the severity and duration of delirium and to prevent unnecessary suffering and costs from the complications of delirium and preventable readmissions to the hospital. Thus, this study holds substantial clinical and economic implications for this population in the acute care setting, and will direct future studies leading to changes in real world practice settings for persons with dementia.

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The PI, Dr. Fick had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1

Characteristics (with relative risk estimates) and outcomes of patients with and without delirium.

Factor	Total N=139		Relative Risk	95% CI**	p-value
	Delirium N=44, 31.7%	No Delirium N=95, 68.3%			
DEMOGRAPHIC COVARIATES					
Age, mean (SD) *	85.9 (5.9)	82.4 (7.0)	1.07	1.02 – 1.12	0.0051
Male Gender, n (%)	23 (52.3)	33 (34.7)	1.83	1.01 – 3.31	0.0456
Single/Divorced/Widowed, n (%)	23 (52.3)	56 (60.2)	0.81	0.45 – 1.47	0.4882
Education in Years, mean (SD)	12.6 (3.2)	12.1 (3.0)	1.06	0.95 – 1.17	0.3146
CLINICAL COVARIATES					
Dehydration, n (%)	12 (30.8)	30 (33.7)	0.88	0.45 – 1.74	0.7152
Fall in last two weeks, n (%)	14 (41.2)	21 (29.6)	1.73*	0.87 – 3.43	0.1186
Infection, n (%)	13 (40.6)	21 (30.9)	1.42	0.70 – 2.88	0.3328
Sensory Impairment, n (%)	16 (36.4)	33 (34.7)	1.04	0.56 – 1.91	0.9132
Lawton Score, mean (SD)	1.6 (1.3)	2.3 (2.0)	0.84	0.70 – 1.01	0.0592
Katz Impaired, mean (SD)	2.3 (2.0)	3.4 (2.1)	0.82	0.71 – 0.95	0.0072
Charlson Score, mean (SD)	2.5 (1.8)	2.3 (1.4)	1.06	0.86 – 1.30	0.6013
BUN, mean (SD)	28.2 (17.6)	25.6 (15.3)	1.01	0.99 – 1.03	0.4175
Creatinine (mean, SD)	1.6 (1.3)	2.4 (6.8)	0.99	0.90 – 1.08	0.7356
Cornell Depression Score, mean (SD)	1.6 (0.8)	1.2 (0.9)	1.35	0.99 – 1.83	0.0553
Global Deterioration Score, mean (SD)	4.7 (1.2)	3.9 (1.3)	1.45*	1.14 – 1.86	0.0027
Pain Score, mean (SD)	2.1 (3.0)	2.0 (2.9)	1.01	0.91 – 1.12	0.8540
Total Number of Regular Medications, mean (SD)	11.5 (4.6)	11.0 (5.0)	1.00	0.94 – 1.67	0.9771
Total Number of Beers Medications, mean (SD)	0.3 (0.7)	0.4 (0.7)	0.76	0.46 – 1.27	0.2933
COGNITIVE IMPAIRMENT COVARIATES					
MMSE Score, mean (SD)	12.7 (6.8)	17.1 (6.6)	0.94	0.90 – 0.98	0.0019
Blessed Score, mean (SD)	9.5 (3.5)	7.7 (2.9)	1.14	1.04 – 1.24	0.0038
MEASURES OF DELIRIUM – COVARIATES FOR FOLLOW-UP OUTCOMES					
Maximum Incident Delirium Severity, mean (SD)	15.4 (5.6)	8.7 (6.1)			<0.0001
Inpatient Days with Positive CAM, mean (SD)	2.0 (1.1)	0.2 (1.4)			<0.0001
FOLLOW-UP OUTCOMES					
Mortality, n (%)	11 (25.0)	9 (9.5)			0.0153
Length of Stay, mean (SD)	9.1 (4.4)	5.7 (4.1)			<0.0001
Change in Lawton IADL from Admission to Follow-up, mean (SD)	0.4 (1.5)	0.2 (1.8)			0.5094
Change in Katz Impaired ADL from Admission to Follow-up, mean (SD)	0.3 (1.7)	0.4 (1.6)			0.6919

* Standard deviation,

** Confidence interval

Table 2

Logistic, ANCOVA or Linear Regression Models of Incident Delirium Measures on Mortality, Length of Stay, Change in IADLs and Change in ADLS

Variable	Level	Adjusted* Estimate of Association	p-value
OUTCOME MORTALITY			
Incident Delirium**, **OR (95% CI)**	Yes	2.33 (0.82 – 6.61)	0.1130
	No	1.00	
Maximum Incident Delirium Severity**, **OR (95% CI)**		1.05 (0.96 – 1.14)	0.2719
Number of Inpatient Days with Positive Delirium**, **OR (95% CI)**		1.15 (0.89 – 1.49)	0.2871
OUTCOME LOS			
Incident Delirium***, **means (SE)**	Yes	9.2 (0.7)	<0.0001
	No	5.6 (0.5)	
Maximum Incident Delirium Severity****, **slope (SE)**		0.43 (0.06)	<0.0001
Number of Inpatient Days with Positive Delirium****, **slope (SE)**		1.80 (0.21)	<0.0001
OUTCOME – CHANGE IN LAWTON IADLS FROM ADMISSION TO FOLLOWUP			
Incident Delirium***, **means (SE)**	Yes	0.51 (0.33)	0.3787
	No	0.15 (0.20)	
Maximum Incident Delirium Severity****, **slope (SE)**		−0.003 (0.03)	0.9260
Number of Inpatient Days with Positive Delirium****, **slope (SE)**		0.16 (0.11)	0.1497
OUTCOME – CHANGE IN KATZ IMPAIRED ADLS FROM ADMISSION TO FOLLOWUP			
Incident Delirium***, **means (SE)**	Yes	0.19 (0.26)	0.5086
	No	0.40 (0.17)	
Maximum Incident Delirium Severity****, **slope (SE)**		0.05 (0.03)	0.0437
Number of Inpatient Days with Positive Delirium****, **slope (SE)**		0.13 (0.09)	0.1717

Activities of daily living (ADL), Instrumental activities of daily living (IADL)

* Adjusted for age, gender and GDS score

** Logistic Regression

*** One-way ANOVA

**** Simple linear regression