Delirium Superimposed on Dementia Predicts 12-Month Survival in Elderly Patients Discharged From a Postacute Rehabilitation Facility

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Background. Delirium superimposed on dementia (DSD) is highly prevalent and associated with high mortality among hospitalized elderly patients, yet little is known about the effect of DSD on midterm mortality. The purpose of this study was to assess 12-month survival in patients with DSD and matched groups with dementia alone, delirium alone, or neither delirium nor dementia.

Methods. Among 1278 consecutively admitted elderly participants (aged ≥ 65 years) to our Rehabilitation Unit between January 2002 and May 2005, four matched samples of 47 participants each (DSD, dementia alone, delirium alone, or neither delirium nor dementia) were selected. Matching was based on age, gender, and reason for admission. Postdischarge 12-month survival was assessed in the four groups with Kaplan–Meyer analysis and compared with Cox proportional hazard regression models adjusted for confounders.

Results. Survival was significantly lower for DSD patients than for the other three groups. After adjustment for comorbidity and Barthel Index score before admission, patients with DSD had significantly higher mortality (hazard ratio, 2.3; 95% confidence interval, 1.1–5.5; $p = .04$) than did patients with neither delirium nor dementia.

Conclusions. Demented patients who experienced delirium during hospitalization had a more than twofold increased risk of mortality in the 12 months following discharge than did patients with dementia alone, with delirium alone, or with neither dementia nor delirium.

ALTHOUGH delirium and dementia are highly interrelated, with dementia predisposing to delirium and delirium being a risk factor for further cognitive decline in demented patients (1,2), the pathogenesis and the consequences of delirium superimposed on dementia (DSD) remain relatively neglected areas of investigation (1). For example, although it is commonly accepted that DSD is highly prevalent—albeit frequently underrecognized—and associated with poor somatic and functional outcomes among elderly hospitalized patients (2–6), it is still unclear whether DSD is a risk factor for shortterm and midterm mortality. The few studies that examined 1-year survival in persons who developed DSD provided conflicting results (7,8) and failed to demonstrate whether DSD is an independent predictor of mortality (3,8,9). In particular, although studies have addressed the prognostic value of dementia and delirium alone, no previous studies assessed the joint effect of these two conditions, independent of relevant confounders, such as older age and surgical interventions.

The aim of this study is to assess 1-year mortality after discharge from a postacute rehabilitation setting in four groups of patients with DSD, dementia alone, delirium alone, or neither delirium nor dementia carefully matched for age and reason for admission (i.e., whether patients received rehabilitation due to surgery).

METHODS

Samples and Data Collection

The study sample was selected among all 1278 first admissions aged ≥ 65 years of our Rehabilitation and Aged Care Unit (RACU) from January 1, 2002 through May 31, 2005. Of these persons, 426 (33.3%) were admitted for postorthopedic surgery rehabilitation. Baseline data on demographic characteristics (age, gender, and living arrangement), health, and premorbid functional status were obtained on admission from the best available sources, including medical records, interviews with health care professionals or family members, and clinical examinations. The presence of specific diseases was ascertained according to standard criteria, and global assessment of health status was assessed by calculating the Charlson comorbidity score, a measure of comorbidity which is a strong predictor of mortality (10). Premorbid functional status was assessed using the Barthel Index (11) based on proxy reports and referenced to 1 month prior to admission (for nonsurgical

Table 1. Characteristics of Patients in Four Matched Study Groups

Characteristics	Neither Delirium Nor Dementia (N = 47)	Dementia Alone (N = 47)	Delirium Alone (N = 47)	Delirium and Dementia (N = 47)	p
Age, y	79.3 ± 6.4	79.6 ± 6.8	79.4 ± 6.8	80.1 ± 6.6	.94
Female sex	37 (78%)	37 (78%)	37 (78%)	37 (78%)	1.0
Postsurgical rehabilitation	22 (47%)	22 (47%)	22 (47%)	22 (47%)	1.0
Living alone before admission	27 (59%)	15 (32%)	16 (34%)	14 (30%)	.01
Barthel Index before admission (0–100)	89.0 ± 20.2	78.9 ± 26.0	83.0 ± 27.2	74.1 ± 24.5	.03
Charlson comorbidity score	1.6 ± 1.6	2.1 ± 1.5	2.6 ± 1.8	2.4 ± 2.0	.04
Medical conditions					
Cerebrovascular disease	10 (21%)	31 (66%)	23 (49%)	26 (55%)	< .0005
Congestive heart failure	5 (11%)	5 (11%)	8 (17%)	6 (13%)	.76
Respiratory diseases	4 (8%)	7 (15%)	11 (23%)	7 (15%)	.25
Uncomplicated diabetes	1 (1%)	—	1 (7%)	3 (2%)	.27
Peripheral vascular disease	3 (6%)	3 (6%)	2 (4%)	1 (2%)	.73
Cancer	—	—	1 (2%)	—	.39
Mini-Mental State Examination (0–30)*	26.2 ± 3.4	18.2 ± 6.2	22.5 ± 6.7	13.4 ± 6.0	< .0005
Drugs on admission, n	4.7 ± 2.6	5.1 ± 2.3	6.0 ± 3.0	5.7 ± 2.7	.12
Length of stay, d	22.8 ± 6.8	23.1 ± 6.8	27.8 ± 12.4	24.0 ± 10.6	.04

Notes: Values denote mean ± standard deviation (SD) or n (%); p denotes significance on analysis of variance (ANOVA) for continuous or Chi-square for categorical variables.

*Scores refer to the cognitive assessment at resolution of delirium; it was not available for four patients with delirium alone and for four patients with delirium superimposed on dementia, respectively, because they were still delirious at discharge.

patients) or prior to the acute event that led to surgery (for surgical patients). Delirium was ascertained by experienced geriatricians (GB and RT) using the Confusion Assessment Method (CAM) (12), in which delirium was defined as the presence of acute onset or fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. The Mini-Mental State Examination (MMSE) (13) was administered on admission to patients without delirium or at discharge when delirium was considered to be present on admission. Patients were categorized as demented if they had a diagnosis of dementia preceding RACU admission as assessed from medical records and proxy reports in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Third revision (DSM III-R) criteria (14). DSD was defined as occurrence of delirium (ascertained on admission or during RACU stay) in a patient with pre-existing dementia. Vital status of study participants over the 12 months following discharge was systematically assessed by telephone interviews with proxies. We obtained informed consent (or proxy consent for patients with cognitive impairment) from all patients. The protocol was approved by the Ethics Committee of Gerontological Sciences of the Geriatric Research Group, Italy.

Matching Procedure for the Selection of the Study Groups

There were 780 patients with neither dementia nor delirium, 316 with dementia alone, 63 with delirium alone, and 119 with DSD. A matching strategy was used to make the study groups comparable for baseline characteristics. In particular, DSD patients were matched 1:1 for age (within 3 years), sex, and reason for admission (rehabilitation following surgery vs following other events) with patients with dementia alone, delirium alone, and neither delirium nor dementia. Matching was successful for 47 DSD patients who are included in this study.

Statistical Analyses

Chi-square tests or analyses of variance (ANOVAs) were used to examine differences of demographic and clinical characteristics among the four groups. The effect of group membership to time of death was explored with Kaplan–Meyer analysis and formally tested with Cox proportional hazard regression models, after adjusting for potential confounders.

RESULTS

The characteristics of patients in the four groups are shown in Table 1. Overall, the study population included very old patients, prevalently women, mostly admitted to the RACU for nonsurgical reasons. The proportion of patients living alone at home was higher in those with neither delirium nor dementia and was comparable in the other three groups. Patients with neither delirium nor dementia tended also to be less functionally impaired before RACU admission and to have a lower burden of comorbidity in comparison to those with dementia alone, delirium alone, or DSD. From one-half to two-thirds of participants with dementia alone, delirium alone, or DSD were affected by cerebrovascular disease (CVD), whereas in only one-fifth of patients with neither delirium nor dementia, a CVD diagnosis was ascertained. The MMSE was available for all patients except for four with delirium and four with DSD (to whom formal administration of this test was not possible because they were still delirious at discharge). As expected, the DSD group had the lowest cognitive performances.

Survival was significantly lower for DSD patients than for the other three groups. In particular, in the 12 months following discharge there were 12/47 deaths in the DSD group (26%), only 5/47 (10%) for the dementia alone and for the delirium alone groups, and 4/47 (8%) for the neither delirium nor dementia group. In a Cox proportional hazard

model adjusted for comorbidity, Barthel Index before admission, and group membership (DSD, dementia alone, delirium alone, or neither delirium nor dementia) as the main predictors, DSD (hazard ratio [HR] 2.3; 95% confidence interval [CI], 1.1–5.5; $p = .04$ vs patients with neither delirium nor dementia) and Barthel Index before admission (HR, 0.98; 95% CI, .97–.99; $p = .02$) significantly predicted death over the 12-month follow-up (Figure 1). Delirium alone and dementia alone were associated with a nonsignificant increased risk of death (HR, 1.6; 95% CI, .3–6.9; $p = .48$; and HR, 1.3; 95% CI, .2–5.9; $p = .70$, respectively). When MMSE was also included in the Cox regression model, the risk of death associated with DSD was even higher (HR, 3.7; 95% CI, 1.5–9.0; $p = .003$). Overall, the results indicate greater risk of death for patients with co-occurring delirium and dementia relative to patients with neither.

DISCUSSION

This study shows that patients with dementia who experienced delirium during hospitalization had a more than twofold increased risk of mortality in the 12 months following discharge than did patients with dementia alone, delirium alone, or neither dementia nor delirium.

The mortality rate for patients with dementia in our study is similar to the rate reported in previous studies (15,16). However, the mortality rates for delirious and DSD patients was extremely high and deserves comment. Rahkonen and colleagues (17) found a similar mortality rate for persons with delirium in a population of healthy, community-living elders (10%), Francis and Kaapor (7) found a mortality rate of 34% at 2 years in patients with hip fracture, and McCusker and coworkers (8) reported a 42% 12-month mortality rate in persons discharged from an acute care hospital. In the study by Francis and Kaapor (7), baseline cognitive impairment was a strong predictor of death. On the contrary, McCusker and colleagues (8) found that DSD and dementia had no effect on mortality. The discrepancy between these studies is likely due to differences of patients' global health and the criteria used to ascertain delirium (18). It is interesting that, despite the large variability in crude mortality rates, the mortality risk associated with DSD in our study (HR, 2.3; 95% CI, 1.1–5.5; $p = .04$) is comparable to risks found in these earlier studies, suggesting that the effect of DSD on mortality may be relatively independent of patient population and global health.

It has been known for a long time that delirium alone and dementia alone are factors increasing the risk of death (8,16). One of the most obvious explanations for the observation of increased risk of death in patients with delirium alone is that delirium occurs in brains with incipient dementia (19,20) and the increased risk is due to dementia rather than delirium. The results of this study seem to indicate that this may not be the case, as the occurrence of delirium in patients with dementia confers a risk of death greater than that in patients with dementia alone. The pathophysiology underlying this effect is, however, not completely understood.

One can hypothesize that an adverse clinical event that precipitates delirium in a demented person could ignite
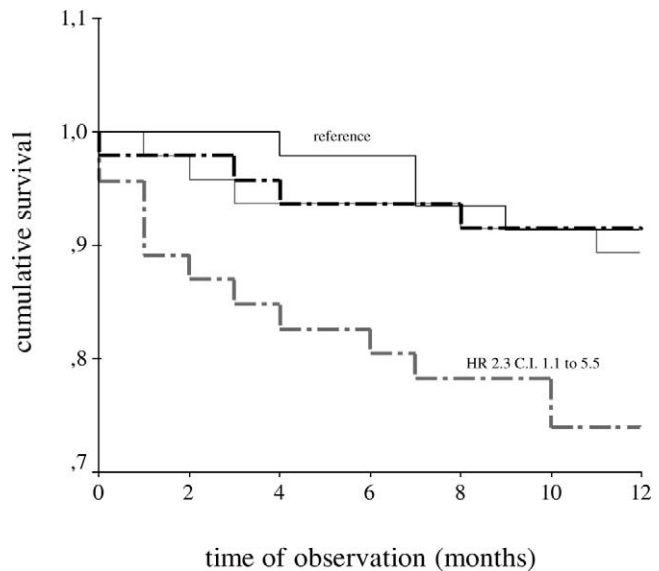

Figure 1. Survival of patients with neither delirium nor dementia, dementia alone, delirium alone, or delirium superimposed on dementia. Hazard ratio (HR) and 95% confidence interval (C.I.) were computed in Cox regression models where comorbidity and Barthel Index before admission were covariates, and patients with neither delirium nor dementia made up the reference group. *Black solid line* = no delirium, no dementia; *black dotted line* = dementia; *grey solid line* = delirium; *grey dotted line* = delirium superimposed on dementia.

a chain of adverse brain metabolic reactions involving the serotoninergic, cholinergic, gabaergic, and inflammatory pathways that tend to self-maintain delirium (20,21), thus prolonging its effect over time (22) and limiting the patient's ability to recover to premorbid functional status. When the clinical event that precipitates delirium is an acute illness, inflammatory signalling and neurotransmitter imbalance may be paralleled by dysregulations in hormonal axes and metabolic derangements that impair the biological homeostasis, leading to frailty and failure to thrive. In line with this hypothesis, it has been shown that delirium is significantly correlated with low muscle mass of the thigh (23), and that during acute inflammation-mediated metabolic stress, a redistribution of the body protein content occurs, with preferential depletion of skeletal muscle proteins (24). Delirium in demented patients should therefore be thought of as a marker of neurochemical and biological abnormalities occurring at both a cognitive and a physical level, and as the first step of a cascade of adverse reactions leading to increasing risk of disability and mortality.

This study has strengths and limitations. The individual matching of the patient groups allowed us to compare samples homogeneous for the two major factors that are well-known predictors of delirium and mortality (i.e., age, surgical intervention), as well as gender. Furthermore, experienced and extensively trained physicians ascertained the diagnoses of delirium and dementia using the state-of-the-art method and criteria that are generally considered the gold standard. Therefore, we are confident that the risk of dementia misclassification in patients with delirium (and vice versa) was very low. One limitation is the relatively small number of patients in the four study groups, which

may have reduced the statistical significance of the results. Another limitation is that the results of our study may not generalize to individuals from other clinical settings, such as acute general hospitals, because delirium prevalence may be significantly different. Finally, we assessed the presence but not the severity of highly prevalent clinical conditions (such as anemia, malnutrition, and advanced hepatic, cardiac, and kidney diseases); therefore, we cannot fully exclude that residual confounders affected our results.

The findings of this study support the need for developing interventions aimed at identifying patients with DSD, addressing the associated risk factors, and informing clinicians, nurses, and caregivers of the need to establish in these patients a continuity of care and surveillance. These interventions may be particularly important in trying to reduce mortality in patients with DSD.

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