The Long-term Prognosis of Delirium

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Nine published studies of the outcomes of delirium with at least six months of follow-up were reviewed. The results indicate that: 1) the symptoms of delirium are more persistent than previously thought; up to 15% of those without dementia and 49% of those with dementia continued to have core symptoms of delirium 12 months after the initial diagnosis; 2) a diagnosis of delirium is an independent predictor of increased mortality for up to three years after diagnosis and; 3) a diagnosis of delirium predicts continued poorer cognitive and physical functioning for up to 12 months after diagnosis.

Key words: *delirium, prognosis, dementia, functioning, cognitive status.*

Introduction

Although delirium has been described as a transient syndrome characterized by disordered attention, thinking and perception, as well as other symptoms, recent research has documented the heterogeneity of the clinical course of delirium and high rates of persistence of delirium symptoms for up to 12 months.[1-5] Furthermore, delirium appearsto be an important indicator of various adverse outcomes for up to three years after diagnosis. The purpose of this article is to review the results of published literature on the long-term prognosis of delirium and its prognostic factors.

Methods

This review was based on studies of the outcomes of delirium with at least six months of follow-up. Studies were excluded if they did not diagnose delirium using accepted criteria or did not present results of follow-up at least six months from diagnosis. From these studies, the author extracted information on methodological characteristics and on results related to the following outcomes: mortality, cognitive impairment, functional status, persistence of symptoms and prognostic factors.

Results

Nine studies that met the inclusion criteria were identified, with a total of 13 publications.[3-15] The studies were conducted in various settings, including medical,[9,10,12-14] surgical,[6,7] mixed medical-surgical,[3,11] psychiatric,[8] inpatient and emergency department services. Exclusion criteria differed among the studies. Criteria for delirium were based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), version III,[4,6-11] III-R5,[13-15] or IV.[12] Duration of follow-up ranged from six months to as long as a median of 32.5 months after diagnosis.[12] Most studies included both prevalent cases (diagnosed at initial assessment) and incident cases (diagnosed during hospitalization); two studies were limited to incident cases.[6,11] Although the earlier studies were limited to follow-up of patients with delirium,[6-8] the more recent studies included a control or comparison cohort comprised of either all patients screened for delirium who did not meet diagnostic criteria,[3,9-11] or a sample of the latter with frequency matching or with oversampling in patients with older age and cognitive impairment.[13-15] This aimed to equalize the distributions of these factors in the delirium and control groups.

These studies have had to cope with various methodological challenges, particularly how to disentangle the effect of delirium from the confounding effects of factors closely associated with delirium (e.g., dementia, functional impairment, severity of illness, comorbidity) that are strong predictors of poor outcomes in their own right.

Mortality

Two studies with up to two years of follow-up reported no significant increase in post-discharge mortality (Table 1).[4,10] However, three studies demonstrated a substantial increase in mortality due to delirium for up to several years after diagnosis, even after adjustment for dementia, functional impairment, severity of illness, comorbidity, institutional residence and other important confounders.[12,14,15] In one of these studies, the effect of delirium was particularlystrong among patients without dementia;[14] among those with dementia, there was a weak, nonsignificant effect of delirium on mortality.

Cognitive Status

The studies have used various measures of cognitive impairment, including the Mini-Mental State Exam (MMSE),[8,10,13] a clinical diagnosis of dementia,[12] and independence in instrumental activities of daily living (IADL), a measure closely associated with severity of dementia (Table 2).[13] Among the studies using the MMSE, admission mean values indicated great variation in the level of impairment, ranging from 9.7–27.0 (normal score 24.0 or higher). In one study, MMSE levels increased slightly from admission to 12 months follow-up among delirious patients with and without dementia; among controls there was little change over time.[13] However, patients with delirium maintained lower MMSE scores over time compared to controls. In the second study using the MMSE, after a two year follow-up patients with delirium had greater cognitive decline compared to their best in-hospital MMSE score than the controls.[10] The difference between these two studies can perhaps be explained by the use of the best in-hospital MMSE score in the latter study ver-

Table 1
Outcomes of Investigations of Association Between Delirium and Mortality

Authors	Time	Mortality Rate		Measure of Effect (95% confidence interval)	Comments
		Delirium	Controls		
Berggren (1987)[6]	12 mo	8.0%	–	–	
Francis (1992)[10]	24 mo	39.0%*	23.0%*	HR 1.4 (0.8–2.5)	Post-discharge survival, adjusted for cognitive impairment, cancer and baseline ADL
Gustafson (1988)[7]	6 mo	20.0%	–	–	
Kakuma (2003)[15]	18 mo	20.0%	3.9%	HR 7.24 (1.62–32.35)	Effect attenuated with longer follow-up
Koponen (1989)[8]	12 mo	37.0%	–	–	
McCusker (2002)[14]	12 mo	41.6% (63.3%)*	14.4% (17.4%)*	HR 2.11 (1.18–3.77)	Adjusted for comorbidity, physiological and clinical severity, dementia, etc. Weaker effect of delirium among demented patients.
O'Keeffe (1997)[4]	In-hospital 6 mo	16.0% 31.0%	5.0% 15.0%	OR 2.6 (0.7–6.2) OR 1.4 (0.7–2.8)	Adjusted for age, illness severity, comorbidity, disability, dementia
Rockwood (1999)[12]	3 years	79%	43%	HR 1.71 (1.02–2.87)	Adjusted for comorbidity, dementia, frailty, age, sex, marital status, living conditions

OR: odds ratio; HR: hazard ratio; ADL: activities of daily living.
*Kaplan-Meier estimates

sus the MMSE score obtained at admission in the former. In a third study of patients with the lowest initial MMSE scores, there was little change over time in mean MMSE scores of delirious patients.[8]

The strongest evidence of an increased incidence of dementia among delirious patients comes from the study with the longest follow-up (median 32.5 months).[12] Although the estimate of effect in this study was high, the confidence interval was wide, reflecting the small sample of patients assessed (15, of whom nine developed dementia). In contrast, another study that used IADL scores found that dementia but not delirium was associated with worse IADL scores at follow-up.[13]

Functional Status

In the two studies that examined the effect of delirium on functional status independently of mortality, delirium was associated with poorer functional status at follow-up among those with and without dementia,[13] and in community and nursing home samples (Table 3).[11]

Persistence of Symptoms

Two studies have investigated the long-term persistence of symptoms among patients with delirium. The first study described the clinical course of delirium both during and after hospitalization in a cohort of 125 hospitalized patients 65 years and older. These patients were admitted from community and long-term care settings with delirium that met DSM-III criteria: 34 with delirium at admission (prevalent cases) and 91 with new-onset delirium during their stay (incident cases).[3] At the time of discharge, 44% of patients no longer met DSM-III criteria, 31% initially recovered but relapsed before discharge, and 27% of patients continued to meet DSM-III criteria throughout their hospitalization. Only 4% of cases experienced complete resolution of their symptoms before discharge from the hospital. Among patients available for assessment at follow-up six months after discharge, 13% continued to meet DSM-III criteria for delirium, 69% had symptoms not meeting diagnostic criteria, and 18% had complete resolution of their symptoms.

The second study examined the persistence of delirium symptoms separately in delirious patients with and without dementia.[5] In both groups, the symptoms of delirium persisted at follow-up, with a loss of about one symptom, on average, compared to baseline. The mean numbers of symptoms of delirium at diagnosis and at 12-month follow-up, respectively, were 4.5 and 3.5 in the subgroup of patients with

Table 2
Investigations of Associations Between Delirium and Cognitive Outcomes

Authors	Outcome Measure	Time	Results		Measure of Effect (95% confidence interval)	Comments
			Delirium	Control		
Francis (1992)[10]	MMSE (mean)	Baseline* 2 years	27.0 ± 2.4 23.7 ± 5.1	27.0 ± 3.3 26.4 ± 4.2	Greater decline among delirium cases (p=0.02)	
Koponen (1989)[8]	MMSE (mean)	Admission 12 months	9.7 ± 6.6 9.5 ± 7.1	–	–	Sample size dropped from 70 at admission to 33 at 12 months. Greater decline among patients with dementia.
McCusker (2001)[13]	MMSE (mean)	Without dementia: (n=24) (n=33) admission 18.9 ± 5.7 24.2 ± 3.9 12 months 21.8 ± 5.5 25.4 ± 3.5 With dementia: (n=93) (n=37) admission 14.3 ± 6.9 19.6 ± 5.8 12 months 16.5 ± 8.1 20.7 ± 5.7			-3.4 (-6.2, -0.6)** -5.0 (-7.2, -2.8)**	Adjusted for age, sex, marital status, education, residence, comorbidity and severity of illness
	IADL (mean)	Without dementia: (n=26) (n=35) pre-morbid 10.7 ± 2.3 9.3 ± 2.9 12 months 8.3 ± 3.8 8.0 ± 3.2 With dementia: (n=95) (n=40) pre-morbid 6.2 ± 3.4 6.7 ± 3.4 12 months 4.2 ± 3.6 4.8 ± 2.9			-0.6 (-2.1, 0.9)** -0.7 (-1.9, 0.4)**	Adjusted for age, sex, marital status, education, residence, comorbidity and severity of illness
Rockwood (1999)[12]	Dementia (%)	3 years	18.1%/yr	5.6%/yr	RR 5.97 (1.83–19.54)	Adjusted for age, sex, comorbidity

*Highest level during hospitalization.
**Effect of delirium on the outcome at follow-up; a negative sign indicates that delirium patients had lower mean scores than non-delirious controls during the 12-month follow-up period.
RR: relative risk; MMSE: Mini-Mental State Exam; IADL: independent activities of daily living.

dementia and 3.4 and 2.2 among those without dementia. Inattention, disorientation and impaired memory were the most persistent symptoms. Among those without dementia, 11.1%, 8.8% and 14.8% met criteria for delirium at discharge, six- or 12-month follow-ups, respectively. These proportions were substantially higher among patients with dementia: 39%, 38.5% and 48.9%, respectively.

Prognostic Factors

One of the studies investigated prognostic factors among delirious patients, including characteristics of the delirium, such as clinical course, incident versus prevalent delirium and severity of symptoms. Among patients with delirium, the following factors predicted higher mortality: greater comorbidity, clinical and physiological severity of illness, absence of dementia and male sex. Greater severity of delirium predicted mortality only among non-demented patients.[14] Several measures of the in-hospital course of delirium were constructed. The episode of delirium lasted longer among patients with dementia compared to those without dementia. Among members of the delirium cohort who were discharged alive from hospital, in multivariate analyses premorbid and admission level of function, nursing home residence and slower recovery during the initial hospitalization were associated with worse cognitive and functional outcomes but not with mortality, after adjustment for dementia, severity of illness and other factors.[5]

Discussion

During the last decade, our knowledge of the prognosis of delirium has increased substantially. The presentation of delirium is heterogeneous; transience appears to be a feature of only a minority of cases and a diagnosis of delirium carries an increased risk for several adverse long-term outcomes. The studies reviewed here vary in their methodology, and have dealt with confounding factors that are closely associated with delirium (e.g., dementia, functional impairment, sever-

Table 3

Investigations of Associations Between Delirium and Functional Outcomes

Authors	Outcome Measures	Time	Results		Measure of Effect (95% confidence interval)	Comments
			Delirium	Control		
Francis (1992)[10]	Alive and living independently	2 years	35%	64%	RR 2.56 (1.10, 5.91)	Subjects were independent in all except one ADL at baseline; adjusted for cancer, age, marital status
Koponen (1989)[8]	GBS scale of ADL (range 0–165, lower score = better function)	Discharge 12 months	53 ± 25 69 ± 38	– –	–	
McCusker (2001)[13]	Barthel Index (range 0–100, higher score = better function)	Without dementia: admission 12 months With dementia: admission 12 months	(n=27) 53.4 ± 29.9 80.6 ± 28.2 (n=95) 41.2 ± 27.9 59.0 ± 33.1	(n=35) 62.7 ± 26.2 87.1 ± 13.2 (n=41) 55.9 ± 23.4 71.6 ± 28.5	-13.9 (-28.4, 0.6)* -16.5 (-27.4,-5.5)*	Adjusted for age, sex, marital status, education, residence, comorbidity, severity of illness
Murray (1993)[11]	ADL (0–7, lower score = better function)	Community sample: admission 6 months Nursing home sample: admission 6 months	(n=31) 3.45 ± 2.31 4.42 ± 2.16 (n=34) 4.03 ± 1.68 4.97 ± 1.80	(n=130) 1.13 ± 1.59 1.50 ± 1.93 (n=35) 3.74 ± 2.19 3.83 ± 2.31	Delirium predicted loss of function over time (p<0.009)	Adjusted for age, sex, previous cognitive impairment, comorbidity

*Effect of delirium on the outcome at follow-up; a negative sign indicates that delirium patients had lower mean scores than non-delirious controls during the 12-month follow-up period.
RR: relative risk; GBS: Gottfries-Brane-Steen; ADL: activities of daily living.

ity of illness, comorbidity) with varying degrees of success. The estimates of risk derived from studies with less adequate adjustment for these factors may therefore be biased.

It is noteworthy that none of the studies were performed outside acute care hospital settings, except for one study in a psychiatric hospital. Many of the delirium cases in the studies were prevalent at admission; only retrospective data are available on the pre-admission course. Studies in non-acute care settings are needed to fully understand the course and prognosis of delirium.

Three conclusions are based on consistent findings in at least two of the studies reviewed here:

Persistence of symptoms. The symptoms of delirium are more persistent than previously thought: up to 15% of those without dementia and 49% of those with dementia continued to have core symptoms of delirium 12 months after the initial diagnosis.

Mortality. A diagnosis of delirium predicts increased mortality for up to three years after diagnosis. This effect appears to be independent of the severity of medical illness, comorbid disorders and other factors. Non-demented patients may be more susceptible than those with dementia to increased mortality.

Cognitive and functional outcomes. A diagnosis of delirium predicts continued poor cognitive and physical functioning for up to 12 months after diagnosis.

Three tentative conclusions are based, at present, on only one study. First, delirium may be a predictor of the incidence of dementia. Second, a diagnosis of delirium (and the severity of delirium symptoms) may increase the risk of mortality more strongly in patients without than in those with dementia at baseline. Third, among patients with a diagnosis of delirium, a slower recovery from the initial episode may increase the risk of prolonged functional and cognitive impairment.

There remain many questions about the prognosis of delirium. First, the heterogeneity of the clinical presentation requires further investigation to determine the most meaningful classification of delirium symptoms for prognostic purposes. Second, the relationship of delirium to dementia needs clarification. Is delirium an early stage in the natural history of dementia, or is it a particular type of dementia? Some cases of delirium

may, for example, also have Lewy Body Dementia, which shares many of the diagnostic features of delirium (e.g., visual hallucinations, fluctuating performance).[16]

Clinical Implications

Delirium should be considered a significant, serious problem either in its own right and/or as a marker of serious risk, both among patients with and without dementia. To date, the prevention of delirium appears to hold more promise than treatment, although further investigation is clearly needed.[17-19] Nevertheless, it is important to detect patients with delirium for two reasons: to identify potentially treatable medical problems that could lead to increased mortality, and to plan for the additional health and social resources that will be needed for the care of these patients. The need for careful planning is particularly in order for those patients who do not recover quickly from the initial episode of delirium. ◆

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