ORIGINAL INVESTIGATION

Occurrence, Causes, and Outcome of Delirium in Patients With Advanced Cancer

A Prospective Study

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Context: Delirium impedes communication and contributes to symptom distress in patients with advanced cancer. There are few prospective data on the reversal of delirium in this population.

Objectives: To evaluate the occurrence, precipitating factors, and reversibility of delirium in patients with advanced cancer.

Design: Prospective serial assessment in a consecutive cohort of 113 patients with advanced cancer. Precipitating factors were examined using standardized criteria; 104 patients met eligibility criteria.

Setting: Acute palliative care unit in a university-affiliated teaching hospital.

Main Outcome Measures: Delirium occurrence and reversal rates, duration, and patient survival. Strengths of association of various precipitating factors with reversal were expressed as hazard ratios (HRs) in univariate and multivariate analyses.

Results: On admission, delirium was diagnosed in 44 patients (42%), and of the remaining 60, delirium developed in 27 (45%). Reversal of delirium occurred in 46 (49%) of 94 episodes in 71 patients. Terminal delirium occurred in 46 (88%) of the 52 deaths. In univariate analysis, psychoactive medications, predominantly opioids (HR, 8.85; 95% confidence interval [CI], 2.13-36.74), and dehydration (HR, 2.35; 95% CI, 1.20-4.62) were associated with reversibility. Hypoxic encephalopathy (HR, 0.39; 95% CI, 0.19-0.80) and metabolic factors (HR, 0.44; 95% CI, 0.21-0.91) were associated with nonreversibility. In mulitivariate analysis, psychoactive medications (HR, 6.65; 95% CI, 1.49-29.62), hypoxic encephalopathy (HR, 0.32; 95% CI, 0.15-0.70), and nonrespiratory infection (HR, 0.23; 95% CI, 0.08-0.64) had independent associations. Patients with delirium had poorer survival rates than controls ($P<.001$).

Conclusions: Delirium is a frequent, multifactorial complication in advanced cancer.Despite its terminal presentation in most patients, delirium is reversible in approximately 50% of episodes. Delirium precipitated by opioids and other psychoactive medications and dehydration is frequently reversible with change of opioid or dose reduction, discontinuation of unnecessary psychoactive medication, or hydration, respectively.

Arch Intern Med. 2000;160:786-794

DELIRIUM IS one of the most common neuropsychiatric complications in patients with advanced cancer.[1-6] The multiple synonyms used to describe this condition, eg, acute confusional state, terminal restlessness, or cognitive impairment, along with the variability in diagnostic criteria have hindered the conduct of research and the comparison of study findings.[7-10] Delirium has been underrecognized and underresearched in general medical patients and patients with cancer.[5,8,10] In patients with advanced cancer, delirium imposes an additional burden of symptom distress, as the consequent awareness and attentional deficits impede communication with their families and hinder participation in treatment decisions, counseling, and symptom assessment.[10-13] Delirium reversibility in advanced cancer has been the subject of much debate[5,6,13,14] but relatively limited research, mainly as retrospective studies[15-18] or case reports[19,20] and in the form of only a few prospective studies.[1,2,21-23] The cause of delirium in advanced cancer is often multifactorial,[5] but since 1990 there have been increasing literature reports on delirium and other neuropsychiatric side effects of opioids in patients with cancer.[24-26] Previous studies in patients with cancer have not incorporated a standardized or systematic approach to criteria for analysis of precipitating factors similar to that used

The affiliations of the authors appear in the acknowledgment section at the end of the article.

PATIENTS AND METHODS

STUDY POPULATION

This study was conducted in the tertiary level, acute palliative care unit (APCU) at Grey Nun's Hospital, a university-affiliated teaching hospital in Edmonton, Alberta. Patients with advanced cancer and a high level of symptom distress were referred to this unit from acute care hospitals, hospices, and home. Patient accrual occurred from February 1 through October 19, 1997. In-hospital follow-up ended in January 1998. Study inclusion criteria consisted of a histological diagnosis of cancer in consecutive patient admissions to the APCU. Patients were excluded if they were unable to speak English fluently or if they were unable to communicate because of direct or local effects of their cancer such as a tracheostomy. Patients with other psychiatric disorders were excluded if, in our opinion, the disorder interfered with the assessment of delirium. Patients with dementia were not excluded, but the rehabilitative focus of the APCU meant that patients with dementia were more likely to be admitted to one of our hospice units. Study entry occurred at admission to the APCU, and the end point was patient death or discharge.

Before study entry, verbal consent was obtained from cognitively intact patients or from family or proxy for cognitively impaired patients. Because there was no perceived risk for harm to patients, and because study interviews involved minimal deviation from standard clinical practice, written consent was not obtained. Patient and family wishes were respected at all times, and interviews were abbreviated appropriately in accord with their wishes or the clinical judgment of the investigator.

ROUTINE ASSESSMENTS AND INTERVENTIONS

A detailed history, results of a full physical examination, and Mini-Mental State Examination (MMSE)[29] were obtained from all patients on admission. The normality of MMSE scores was evaluated by age and educational level.[30] Patients underwent twice weekly cognitive screening with the MMSE and at any time if the onset of delirium was suspected clinically. Patients underwent clinical assessment twice daily during the weekdays and once daily at weekends by experienced attending palliative care physicians. All patients underwent chest radiography, urinalysis, complete blood cell count, and measurement of electrolyte, urea, creatinine, albumin, bilirubin, aspartate aminotransferase, alkaline phosphatase, and calcium levels on admission. Total daily opioid dose, expressed as subcutaneous morphine equivalent daily dose, was documented daily using ratios derived from the standard equianalgesic tables,[31] except in the case of methadone, where a ratio of 5:1[32] was used for subcutaneous morphine to oral methadone.

Patients with clinical evidence suggestive of toxic effects of opioids, eg, delirium, myoclonus, or tactile hallucinations, had an opioid dose reduction or change of opioid. Patients with clinical or laboratory evidence of dehydration were hydrated using hypodermoclysis. Patients with infection were treated with appropriate oral or intravenous antibiotics in accordance with patient and family wishes. Patients with hypercalcemia were treated with subcutaneous clondronate or intravenous pamidronate disodium.

All patients with a diagnosis of delirium commenced regular neuroleptic therapy. Midazolam hydrochloride infusion was used in the event of unsuccessful control of agitation with neuroleptic medication.

SEMISTRUCTURED INTERVIEW AND *DSM-IV* CRITERIA

On admission, patients who were cognitively impaired on results of MMSE testing or who showed clinical evidence of delirium underwent assessment by one of the study investigators (P.G.L., B.G., I.L.M., or J.L.P.) within 24 hours of admission. These patients had a semistructured interview that was designed to operationalize the respective *DSM-IV* criteria for delirium: (1) disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention; (2) change in cognition (eg, memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia; (3) development of the disturbance during a short period (usually hours to days) and tendency to fluctuate during the course of the day; and (4) evidence from the history, results of physical examination, or laboratory findings suggesting that the disturbance is caused by the direct physiological consequences of a general medical condition.

MEMORIAL DELIRIUM ASSESSMENT SCALE

Patients meeting *DSM-IV* criteria for delirium on admission underwent a standardized assessment of delirium severity using the physician-rated Memorial Delirium Assessment Scale (MDAS).[33] This is a validated 10-item instrument; each item is a feature of delirium and is scored from 0 to 3 depending on its intensity and frequency. The first 6 items of the MDAS (reduced level of awareness, disorientation, short-term memory impairment, impaired digit span, attention disorder, and disorganized thinking) were rated in relation to the clinical interview findings. Some MDAS item scoring was prorated in patients with severe hypoactive delirium. The remaining 4 MDAS items (perceptual disturbance, delusions, psychomotor activity, and sleep-wake cycle disturbance) were rated in relation to the interview findings and their presence during the previous 24 hours. Information obtained from nursing observational assessments in a standardized format, the Delirium Observational Checklist Scale (DOCS), was also used to facilitate MDAS ratings in relation to the last 4 items. All MDAS scores in this study reflected delirium severity in the preceding 24 hours.

DELIRIUM OBSERVATIONAL CHECKLIST SCALE

This ad hoc instrument was designed to deliver standardized information from nurses during their 8-hour working shifts. On 1 sheet, nurses marked a checklist regarding the presence of 54 delirium behaviors. These behaviors were grouped under the following 7 headings, each representing a recognized feature of delirium: delusional expression, perceptual disturbance, physical or verbal aggression, nonaggressive agitation, hypoactivity, attention disorder, and orientation and memory disorder. After

Continued on next page

completing the checklist, nurses then scored each of the 7 features in relation to observed intensity and frequency during their 8-hour shifts. Nurses were trained in the use of this instrument as part of an earlier pilot study (P.G.L., unpublished data, November 1996).

FREQUENCY OF SPECIFIC STUDY ASSESSMENTS

Within 72 hours of admission, patients meeting *DSM-IV* criteria for delirium underwent 2 semistructured interviews and MDAS ratings. After the initial 72 hours, patients who remained delirious underwent a semistructured interview and MDAS testing once every 72 hours thereafter, until delirium reversal or death. The DOCS nursing assessment was initiated by the nursing staff on the suspicion of early signs of delirium and also on the request of the investigating physicians.

CRITERIA FOR ANALYSIS OF PRECIPITATING FACTORS

We examined the organic precipitating factors for the development of delirium.[34] We modified the approach used by Francis et al[27] in their prospective study of elderly medical patients. After patient discharge or death, two of us (P.G.L. and B.G.) reviewed each patient's clinical, laboratory, and radiological data in association with the attending physician's discharge summary. Clarification was sought from the attending physicians in the event of any data discrepancies or disagreement on the rating of causes between investigators. Each potential precipitating factor for delirium was assessed in relation to the following general criteria: evidence of presence from specific clinical, laboratory, or radiological findings (criterion 1); temporal association with the course of delirium consistent with a potential precipitating role (criterion 2); and changes in the severity of delirium in association with similar changes in the precipitating factor (criterion 3). Criterion 3 was further defined as delirium improvement (at least a 25% reduction in MDAS score) or reversal corresponding to evidence of improvement or resolution of the precipitating factor. Alternatively, MDAS scores failed to decrease or even increased with clinical or other evidence of unsuccessful treatment or progression of the putative precipitating factor.

Criteria 1 and 3 were further defined for specific precipitating factors.

Psychoactive Medications

Patients received a psychoactive medication that is known to cause delirium (criterion 1), or delirium improvement or reversal occurred within 5 days of dose reduction (at least 20% reduction of daily dose of the medication), discontinuation of drug therapy, or change of opioid (criterion 3).

Dehydration

One or more of the following was included under criterion 1: creatinine level within the reference range's upper limit of 115 µmol/L (1.3 mg/dL) and urea nitrogen level of greater than 8 mmol/L in the absence of bleeding into the gastrointestinal tract; urea nitrogen level of greater than 8 mmol/L and/or creatinine level of greater than 115 µmol/L (1.3 mg/dL) and returning to reference range or showing at least a 30% decrease with hydration; sodium level of greater than 150 mmol/L and returning to reference range with hydration; and mild hyponatremia (sodium level, 130-125 mmol/L) that reversed to levels of greater than 130 mmol/L with hydration. For criterion 3, delirium improved or reversed within 3 days of commencing hydration with hypodermoclysis.

Intracranial Factor

Improvement in delirium within 5 days of initiating steroid therapy for brain tumor or within 4 weeks in the case of radiotherapy or chemotherapy for brain tumor was considered as clinically meaningful ranges for criterion 3.

Withdrawal of Alcohol or Other Drugs

Withdrawal of alcohol or other drugs is a known cause of delirium, and there is clinical evidence of autonomic hyperreactivity or seizure within 7 days of withdrawal (criterion 1). For criterion 3, treatment involves restarting the original drug therapy or substitution of an alternative drug from the same class.

Hypoxic Encephalopathy

Oximetry levels of less than 90% while receiving room air or requiring an oxygen flow of at least 2 L/min to maintain oxygen saturation levels of at least 90% was evidence of hypoxic encephalopathy (criterion 1).

Metabolic Factors

The following laboratory reference values were used for specific metabolic factors: persistent creatinine level of greater than 150 µmol/L (1.70 mg/dL) (renal insufficiency); glucose level of less than 4 mmol/L (72.0 mg/dL) (hypoglycemia); magnesium level of less than 0.7 mmol/L (1.75 mg/dL) (hypomagnesemia); and aspartate aminotransferase levels of greater than 40 U/L, or alanine aminotransferase levels of greater than 50 U/L, or bilirubin levels of greater than 20 000 µmol/L (1169.6 mg/dL) (hepatic impairment). Hypercalcemia was recorded if calcium levels (corrected for albumin level) were greater than 2.6 mmol/L (10.4 mg/dL) (criterion 1).

Hematologic Factors

Hemoglobin level of less than 10 g/L indicated anemia. For disseminated intravascular coagulation, the laboratory evidence consisted of low platelet levels, prolonged prothrombin and partial thromboplastin times, and D-dimer levels of greater than 0.5 mg/L (criterion 1).

in the study of elderly hospitalized general medical patients.[27]

The purpose of this study was to determine the following characteristics of delirium: the occurrence rate at admission and following admission; the outcome in terms of duration, reversibility, and survival; the precipitating etiologic factors; and the possible association of certain precipitating factors with reversibility or nonreversibility of delirium in patients with advanced cancer. To our knowledge, this is the first prospective study of delirium in this

Each precipitating factor was classified according to the degree to which it met criteria 1, 2, and 3. A probable classification was made when all 3 criteria were met, possible classification when 2 criteria were met, and a comorbidity classification when only 1 criterion was met.

TERMINAL DELIRIUM AND SURVIVAL ANALYSIS

For the purpose of our study, terminal delirium was defined as delirium in patients who underwent assessment and met the *DSM-IV* criteria for delirium at least 6 hours before death. Patient deaths occurring between the physician's evening and next-morning assessments were not classified as involving terminal delirium, unless the patient had been interviewed previously and met the *DSM-IV* criteria for delirium diagnosis.

For patients who died after discharge, data were obtained from their provincial cancer board registry concerning date of death. Follow-up in relation to patient survival after hospital discharge extended to October 19, 1998, one year after the entry of the last patient to the study.

STATISTICAL ANALYSIS

Statistical analysis was conducted using the SAS statistical package.[35] Categorical data relating to demographics for control subjects and delirious patients were compared using the χ^2 test. Mean number of causes of delirium and mean durations were compared using the *t* test. The distribution of precipitating factors associated with delirium reversibility or nonreversibility was examined using the χ^2 test. For the descriptive part of the analysis, the precipitating factors were examined separately; eg, 2 different psychoactive drugs were treated as 2 distinct precipitating factors. These factors were then further grouped and condensed into more general categories, including psychoactive medications, dehydration, nonrespiratory infection, hypoxic encephalopathy, metabolic factors, hematologic factors, and miscellaneous. Univariate and multivariate Cox proportional hazards[36] models were then used to evaluate the association between precipitating factors (grouped in broader categories) and reversal of delirium. In the Cox model, the duration of the delirium episode associated with a particular precipitating factor category was the dependent variable, reversed episodes were considered events, and nonreversed episodes were censored. Categories where precipitating factors occurred more than once per episode were treated as occurring only once for the purpose of analysis in the Cox proportional hazards model. Survival analysis curves for precipitating factors significantly associated with reversibility and nonreversibility were constructed using the Kaplan-Meier method.[37] Finally, actual survival of delirious and nondelirious groups from the time of admission was compared using the Kaplan-Meier method. Differences in Kaplan-Meier survival curves were tested using the log-rank test.

population to combine *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnostic criteria,[28] a validated severity-measuring instrument to monitor delirium severity serially, and a systematic approach to the analysis of precipitating factors of delirium.

Table 1. Admission Characteristics of Patients With an Episode of Delirium on Admission or During Their Hospital Stay Compared With Control Group

Characteristics	Group Delirium (n = 71)	Control Group (n = 33)	*P*
Age, mean ± SD, y	63.4 ± 10.8	58.9 ± 13.5	.06
Sex, No. of M/F	38:33	15:18	.44
Primary cancer diagnosis, No. (%)*			
Genitourinary	19 (27)	9 (27)	.89
Gastrointestinal tract	9 (13)	5 (15)	
Lung	21 (30)	9 (27)	
Hematological	4 (6)	1 (3)	
Head and neck	3 (4)	1 (3)	
Breast	8 (11)	6 (18)	
Unknown primary location	2 (3)	0	
Other	5 (7)	2 (6)	
Extent of cancer disease			
Local only	0	0	.34
Regional only	14 (20)	4 (12)	
Distant metastases	57 (80)	29 (88)	
Organ sites of cancer disease			
Brain primary or metastases	10 (14)	6 (18)	.71
Hepatic metastases	17 (24)	6 (18)	
Pulmonary primary or metastases	43 (60)	17 (52)	
Referral source			
Home	21 (30)	16 (48)	.28
Acute hospital	22 (31)	7 (21)	
Hospice	6 (8)	3 (9)	
Cancer center	22 (31)	7 (21)	
Length of cancer diagnosis			
≤3 mo	17 (24)	2 (6)	.25
3-6 mo	6 (8)	4 (12)	
6 mo to 1 y	12 (17)	5 (15)	
1-2 y	11 (15)	6 (18)	
>2 y	25 (35)	16 (48)	

**Because of rounding, percentages may not all total 100.*

RESULTS

CHARACTERISTICS OF STUDY POPULATION

Admission characteristics of the 104 eligible patients are summarized in **Table 1**. Of 113 acute consecutive patient admissions, 104 patients met the eligibility criteria for study entry. Nine patients were excluded for linguistic reasons (n = 4) and because of tracheostomies (n = 2), expressive dysphasia (n = 1), depressive psychosis (n = 1), and family wishes (n = 1). Thirty-three patients (control group) had no delirium on admission or during their hospital stay. Their admission characteristics were compared with 71 patients (delirium group) who had at least 1 episode of delirium on admission (prevalent delirium) or after admission (incidental delirium). The overall mean (± SD) age for the 104 study group patients was 62 ± 11.9 years, and dementia was diagnosed during admission in 4 patients (3.8%). Most study patients (64.4%) were admitted from hospital or hospice settings.

OUTCOME MEASURES

Rates of delirium occurrence and reversal, and delirium durations are summarized in **Table 2**. Delirium was pres-

Table 2. Summary of Delirium Characteristics in 71 Patients

Delirium Characteristics	Episodes Present at Admission (n = 44)	Episodes With Onset After Admission (n = 50)	*P*	Total No. (%) of Delirium Epsiodes (n = 94)
Occurrence rate, No. (%)				
First epsiodes	44 (100)	27 (54)	. . .*	**71** (76)
Repeated episodes	. . .	23 (46)	. . .	**23** (24)
Delirium reversed	22 (50)	24 (48)	.36†	**46** (49)
Delirium nonreversed	22 (50)	26 (52)		**48** (51)
Duration, median (range)				
Reversed delirium	3.5 (1-19)	3.5 (1-22)	>.99†	3.5 (1-22)
Nonreversed delirium	7 (1-40)	6 (1-47)	.74†	6.5 (1-47)
No. of precipitating factors, mean ± SD				
Reversed delirium	3.3 ± 1.3	2.8 ± 1.1	.18†	3.1 ± 1.2
Nonreversed delirium	3.6 ± 1.6	2.8 ± 1.3	.08†	3.1 ± 1.4
Reversibility of episodes, No./ Total No. (%)‡				
First episodes	22/44 (50)	18/27 (67)	.01§	**40/71** (56)
Repeated episodes	. . .	6/23 (26)		**6/23** (26)

**Not applicable.*
†*Characteristics in delirium on admission vs delirium with onset after admission.*
‡*Percentages refer to expressed proportions.*
§*Reversibility of first vs second or more episodes.*

ent in 44 (42.3%) of the 104 study patients on admission and reversed in 22 patients (50.0%). Of the 60 patients who were delirium free on admission, incidental delirium occurred in 27 (45.0%) and reversed in 18 (66.7%) of these. There was no significant difference between the reversibility rates of delirium on admission and that of incidental delirium (*P* = .17). Fifty episodes of incidental delirium combined with 44 episodes on admission resulted in an overall total of 94 episodes in 71 patients. Twenty-seven of the 50 episodes of incidental delirium occurred in patients who did not have delirium on admission, whereas 23 episodes followed a delirium on admission that reversed. Eighteen patients had a second episode, 1 patient had 3 episodes, and 1 patient had 4 episodes. The overall reversibility was 46 (49%) of 94 episodes. The reversibility of a repeated episode (second episode or more) was 6 (26%) of 23 episodes compared with 40 (56%) of 71 first episodes (*P* = .01). The overall median duration was 3.5 days (range, 1-22 days) for reversed delirium and 6 days (1-47 days) for nonreversed delirium.

Terminal delirium occurred in 46 (88%) of 52 patients who died in hospital. In the control group, 29 patients (88%) were discharged vs 23 patients (32%) in the delirium group (*P* = .007). From the 23 delirium group patients discharged, 21 had no delirium on discharge. The location of discharge for the 29 controls was home in 11

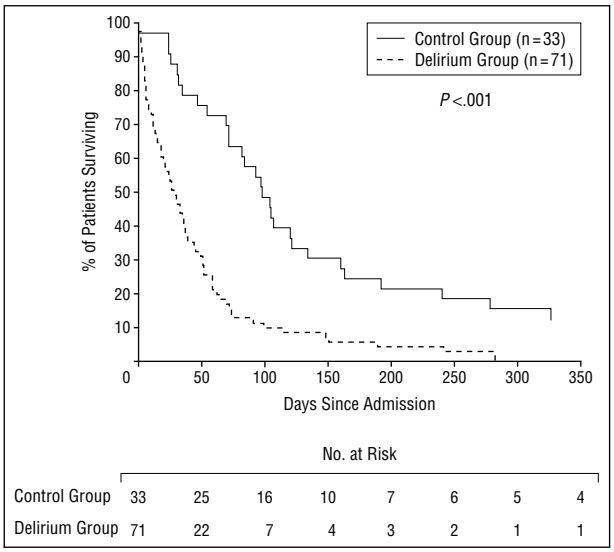

Figure 1. *Kaplan-Meier plot of patient survival in 104 study patients.*

(38%) and continuing care in 18 (62%), compared with home in 7 (30%) and continuing care in 16 (70%) of the 23 delirium group discharges (*P* = .88). The survival of all patients from the day of their hospital admission is represented in the Kaplan-Meier plot in **Figure 1**. Comparison of the delirium and control groups revealed a much shorter survival in the delirium group (*P*<.001).

ANALYSIS OF PRECIPITATING FACTORS AND THEIR ASSOCIATION WITH DELIRIUM REVERSIBILITY

Comparison of the number of precipitating factors per episode of delirium is summarized in Table 2. The median (range) number of precipitating factors per episode of delirium was 3 (1-6) for reversed and nonreversed delirium. The distribution of precipitating factors for the first episodes of reversed and nonreversed delirium is represented in **Table 3**. The application of standardized criteria resulted in a probable classification in 98 (77.8%) of 126 factors associated with reversed delirium and 60 (58.8%) of 102 factors associated with nonreversed delirium (*P* = .96). The 13 nonopioid drug factors associated with reversed delirium included methylphenidate hydrochloride and methotrimeprazine, each in 3 instances; anticholinergics in 2 instances; and selective serotonin reuptake inhibitors, theophylline, tricyclics, benzodiazepines, and haloperidol decanoate in 1 each. The 21 metabolic factors associated with nonreversible episodes consisted of hepatic impairment in 8 instances, refractory hypercalcemia in 5, and hyponatremia and renal insufficiency in 4 each. In reversed episodes, a higher proportion of precipitating factors was present in the case of opioids (*P* = .01), nonopioid psychoactive medications (*P* = .01), and dehydration (*P* = .007). In nonreversed episodes, a higher proportion of precipitating factors was present in the case of respiratory infection (*P* = .045), pulmonary cancer disease (*P* = .001), and metabolic factors (*P* = .01).

In the Cox proportional hazards model, the 12 precipitating factor categories in Table 3 were condensed to

Table 3. Distribution of Precipitating Factors for the First Episode of Delirium in 71 Patients*

Precipitating Factors	Reversed Episodes (n = 40)			Nonreversed Episodes (n = 31)			P†
	Probable	Possible	Total	Probable	Possible	Total	
Psychoactive medications							
Opioids	35	3	**38**	7	9	**16**	.01
Nonopioids	8	5	**13**	1	1	**2**	.01
Dehydration	18	8	**26**	2	6	**8**	.007
Nonrespiratory infection	10	2	**12**	3	6	**9**	.86
Alcohol or other drug withdrawal	2	2	**4**	0	0	**0**	.07
Intracranial cause	3	0	**3**	7	0	**7**	.10
No cause apparent	1	0	**1**	0	0	**0**	.37
Hypoxic encephalopathy							
Respiratory infection	10	1	**11**	15	3	**18**	.05
Pulmonary cancer disease	0	0	**0**	5	4	**9**	.001
Cardiogenic	2	0	**2**	4	0	**4**	.27
Metabolic	5	6	**11**	12	9	**21**	.01
Hematologic	4	1	**5**	4	4	**8**	.21
Totals	**98**	**28**	**126**	**60**	**42**	**102**	. . .

*Data are given as number of precipitating factors; ellipses, not applicable.
†Comparing totals for each precipitating factor in reversed vs nonreversed episodes.

Table 4. Summary of Univariate and Multivariate Analyses of Precipitating Factor Categories Associated With Reversibility of Delirium*

Categories†	No. (%) of Episodes		Univariate Analysis			Multivariate Analysis	
	Reversed (n = 40)	Nonreversed (n = 31)	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI
Psychoactive drugs	38 (95)	15 (48)	8.85	2.13-36.7	.003	6.65	1.49-29.6
Dehydration	26 (65)	8 (26)	2.35	1.20-4.62	.01	1.50	0.70-3.20
Miscellaneous other causes	7 (18)	7 (23)	0.69	0.30-1.59	.37	1.10	0.45-2.70
Nonrespiratory infection	10 (25)	8 (26)	0.56	0.26-1.18	.12	0.23	0.08-0.64
Hypoxic encephalopathy	11 (28)	22 (71)	0.39	0.19-0.80	.008	0.32	0.15-0.70
Metabolic	10 (25)	18 (58)	0.44	0.21-0.91	.02	0.46	0.21-1.02
Hematologic	5 (13)	7 (23)	0.58	0.22-1.51	.25	1.21	0.43-3.44

*CI indicates confidence interval.
†Some categories from Table 3 have been combined.

give 7 broader categories for univariate and multivariate analysis, as summarized in **Table 4**. In addition, the parameter of age greater than 65 years was also included in this model as a possible confounding variable but was not significant at univariate level with a hazard ratio (HR) of 0.67 (95% confidence interval [CI], 0.34-1.32) or at multivariate level with a hazard ratio (HR) of 0.98 (95% CI, 0.44-2.19). Psychoactive drugs ($P = .003$) and dehydration ($P = .01$) were significantly associated with reversibility at the univariate level, but only psychoactive drugs maintained independent association with reversibility in the multivariate analysis, which generated an HR of 6.65 (95% CI, 1.49-29.62). Hypoxic encephalopathy ($P = .008$) and metabolic factors ($P = .02$) were significantly associated with nonreversibility at univariate level, but of both factors, only hypoxic encephalopathy retained significance in multivariate analysis and generated an HR of 0.32 (95% CI, 0.15-0.70). In addition, although nonrespiratory infection was not significant at the univariate level, it emerged as a significant independent factor associated with nonreversibility in the multivariate analysis, which generated an HR of 0.23 (95% CI, 0.08-0.64). Survival curves for delirium reversibility as an event in relation to the precipitating factor categories of psychotropic medication and hydration are represented in **Figure 2**.

COMMENT

Our study of delirium in patients with advanced cancer involved a systematic prospective evaluation, combining *DSM-IV* diagnostic criteria with serial use of a validated delirium severity-measuring instrument and standardized criteria in the analysis of precipitating factors of delirium. Comparison with the other limited number of prospective studies in patients with advanced cancer is difficult, especially where more global terms such as cognitive impairment[2] were used, different diagnostic criteria were used,[21] delirium was studied in select cohorts with specific causes such as opioids,[23] or the sample size was very small.[1] Studies in elderly general medical patients usually exclude patients younger than 70 years,[27,38] whereas the mean age of our study group was 62 years, a factor that also limits comparison.

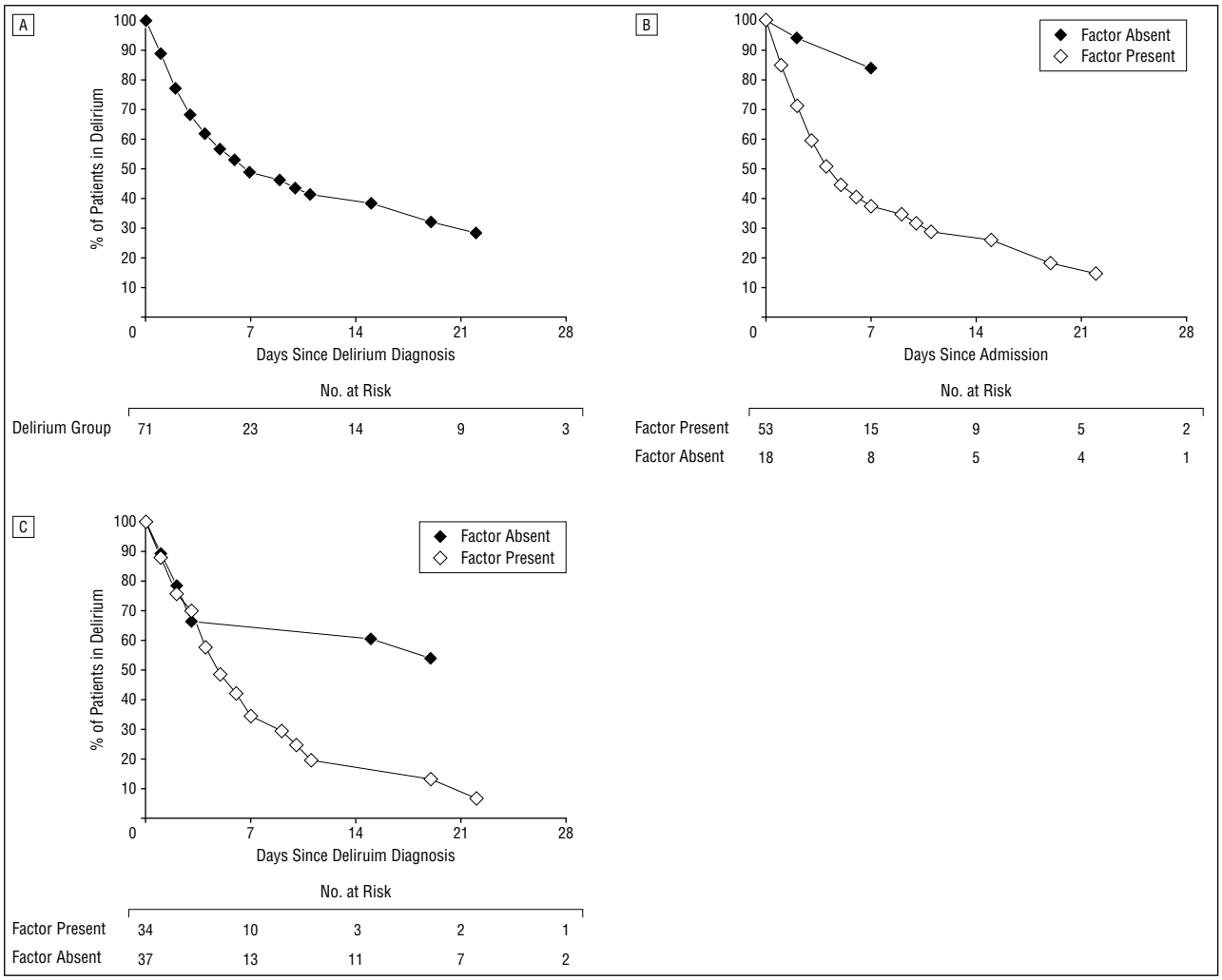

Figure 2. *Kaplan-Meier survival curves for time to reversal of delirium as an event in all patients (A) and in relation to precipitating factors associated with reversibility. Precipitating factors include psychoactive medication (B;* P*<.001), and dehydration (C;* P *= .01).*

Our study findings suggest a very high occurrence rate of delirium in patients with advanced cancer, ie, 42% in patients on admission, 45% for first onset after admission, and 88% in patients who died with advanced cancer. A lower occurrence rate of 28% in the first week of admission to a palliative care unit has been reported recently.[3] A small prospective longitudinal study of 13 patients with advanced cancer found terminal delirium occurring in 11 deaths (85%).[1] Bruera et al[2] found evidence of cognitive impairment in 83% of patients with advanced cancer, occurring on average 16 days before death. Pereira et al[15] found evidence of cognitive impairment in 44% of patients admitted to a palliative care unit. The high frequency of delirium in our study has marked implications in relation to impaired communication at a critical juncture in the patient's illness, particularly in relation to participation in family interaction, symptom assessment, and therapeutic decision making.

The overall reversibility rate of 49% in our study has not been reported previously in prospective studies, except in a select cohort of patients with toxic effects of opioids.[23] The reversibility of delirium on admission was similar to that for incidental delirium. Retrospective studies have reported cognitive improvement as evidenced by changes in MMSE scores in approximately 30% of patients with advanced cancer.[2,15] However, the extent of cognitive impairment alone does not necessarily reflect the overall severity of delirium. The reversibility rate of 49% is in contrast to the 88% occurrence rate for terminal delirium. This contrast subserves the "dichotomy in clinical perception" referred to by Portenoy,[6] where delirium can be considered an almost normal physiological mode of exit in one context and an eminently reversible pathologic process in another.

Our reversibility rate of 49% also highlights the need to examine the precipitating factors associated with delirium reversal. Although our study found a median number of 3 precipitating factors per episode of delirium, opioids and nonopioid psychoactive medications were clearly identified as precipitating factors independently associated with delirium reversibility, combining to give an HR of 6.65 (95% CI, 1.49-29.62). Although dehydration was significantly associated with delirium reversibility, its association was not independent in the multivariate analysis. This suggests that dehydration, although a recognized reversible precipitant of delirium,[39] tends to act in association with other reversible factors such as opioid toxicity. Although the role of hydration in patients with

advanced cancer is controversial,[40-42] many studies of delirium, mainly in elderly general medical patients, attest to its contributory role in the development of delirium.[43-45] The frequency of psychoactive medications (predominantly opioids) as a precipitating factor for delirium likely relates to the fact that all study participants were administered opioids at least at some stage during their hospital stay. The association of opioids with delirium reversibility confirms earlier study results[23,25] identifying opioid toxicity as a reversible cause of delirium. The factors associated with nonreversibility include pulmonary cancer disease, respiratory infection, nonrespiratory infection, and metabolic causes. Hypoxic encephalopathy, including respiratory cancer disease and respiratory infection, and nonrespiratory infection were independently associated with nonreversibility of delirium. Further analysis of potentially reversible factors in a predictive and validation model is warranted.

There was a very marked difference in survival between the delirium and control groups ($P<.001$). This is consistent with previous reports in patients with cancer[1] and also in the elderly general medical population.[46] It is not clear how much the delirium process itself, as opposed to its underlying causes, contributes to this difference in survival. Furthermore, given the decreased reversibility of repeated episodes in our study, repeated episodes of delirium with consequent neurotoxic effects might be an independent predictor of poor survival.

For the physician in clinical practice, our study findings highlight the need to diagnose delirium and to recognize both its multifactorial nature and its reversibility. Diagnosis of delirium is aided by cognitive screening with tools such as the MMSE, as used in this study. On recognizing the multifactorial nature of delirium, the physician needs to be particularly attentive to the identification of reversible factors such as opioid toxicity, adverse effects associated with other psychotropic medications, and dehydration. These factors in the population with advanced cancer can be treated with low-burden interventions such as opioid change or dose reduction, discontinuation or dose reduction of other psychotropic medications, and hydration with hypodermoclysis.

The strengths of our study include its prospective nature, the relatively close surveillance of patients, and the use of rigorous standardized study methods, particularly the use of a validated delirium severity-measuring instrument and standard criteria for delirium diagnosis and analysis of precipitating factors. Although our patients were referred from a wide variety of sources, the tertiary level APCU setting could limit the generalizability of some of our study findings by imposing a referral bias toward patients with a greater burden of symptom distress and therefore a higher risk for delirium. The relatively low number of patients with dementia could have introduced a positive bias toward delirium reversibility. However, this is likely to be balanced by the possibility that some of the patients with nonreversible delirium also had an underlying dementia that was not diagnosed previously. The high-intensity level of patient care, facilitated by high nurse-patient and physician-patient ratios, also could limit the extrapolation of our study findings to other settings such as hospices with a lower level of staffing. Delirium on admission and incidental delirium were combined in the analysis of precipitating factors. This procedure introduces a possible bias in that less knowledge is available regarding the causes and duration of delirium on admission as opposed to incidental delirium. However, comparison of delirium on admission and incidental delirium showed no difference in relation to duration, number of causes, distribution of causes, or reversibility rate. The frequency of delirium severity assessments was limited in this study in an effort not to impose undue burden on terminally ill patients. It is therefore possible that some cases of terminal delirium might not have been diagnosed. Fluctuations in the MDAS scoring could be explained by fluctuations in delirium per se as opposed to the effects of treatment of various causes. The necessary prorating of some of the MDAS scores also limits the interpretation of scores,[47] mainly in relation to nonreversed delirium. Our study was not designed to examine the role of environmental stresses that could have contributed to the development of delirium.[38,48]

CONCLUSIONS

Delirium is a frequent complication of advanced cancer, is associated with poorer survival, and is present in most patients before death. Delirium is multifactorial but warrants a search for underlying reversible causes. Causes that are highly associated with reversibility, such as psychoactive medications and dehydration, are potentially correctable with minimally invasive measures such as change of opioid, dose reduction, or discontinuation of other psychoactive medications, and hydration using hypodermoclysis. Further research is warranted to establish a predictive model for delirium reversibility that would also incorporate baseline vulnerability factors in patients with advanced cancer.

Accepted for publication June 29, 1999.

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This study was supported in part by funding from the Cantel-Overton Fellowship, University of Alberta, Edmonton (Dr Gagnon), and the Institut Jules Bordet, Unite Bruxelles, Brussels, Belgium (Dr Mancini).

Presented in part at the First International Conference on Research in Palliative Care, Methodologies and Outcomes, Bethesda, Md, May 8, 1998.

We wish primarily to thank the patients and their families for their participation. We gratefully acknowledge the contributions of the following: Sandy McKinnon, RN, and nursing staff, Paul Walker, MD, and Sharon Watanabe, MD, Grey Nun's Hospital, Edmonton, for their cooperation; Jane Ingham, MD, Lombardi Cancer Center, Georgetown University, Washington, DC, for her suggestions on study design; and William Breitbart, MD, Memorial Sloan-Kettering Cancer Center, New York, NY, for his assistance and advice regarding the Memorial Delirium Assessment Scale.

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