Delirium and severe illness: Etiologies, severity of delirium and phenomenological differences

SOENKE BOETTGER, M.D.,[1] JOSEF JENEWEIN, M.D.,[1] AND
WILLIAM BREITBART, M.D.[2]

[1]Department of Psychiatry and Psychotherapy, University Hospital Zurich, Zurich, Switzerland
[2]Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, New York

ABSTRACT

Objective: Our aim was to examine the characteristics of delirium in the severely medically ill cancer population on the basis of sociodemographic and medical variables, delirium severity, and phenomenology, as well as severity of medical illness.

Method: All subjects in the database were recruited from psychiatric referrals at Memorial Sloan Kettering Cancer Center (MSKCC). Sociodemographic and medical variables, as well as the Karnofsky Performance Status (KPS) scale and Memorial Delirium Assessment Scale (MDAS) scores were recorded at baseline. Subsequently, these variables were analyzed with respect to the severity of the medical illness.

Results: Out of 111 patients, 67 qualified as severely medically ill. KPS scores were 19.7 and 30.7 in less severe illness. There were no significant differences with respect to age, history of dementia, and MDAS scores. Although the severity of delirium did not differ, an increased frequency and severity of consciousness disturbance, disorientation, and inability to maintain and shift attention did exist. With respect to etiologies contributing to delirium, hypoxia and infection were commonly associated with severe illness. In contrast, corticosteroid administration was more often associated with less severe illness. There were no differences with respect to opiate administration, dehydration, and CNS disease, including brain metastasis.

Significance of Results: Delirium in the severely medically ill cancer population has been characterized by an increased disturbance of consciousness, disorientation, and an inability to maintain and shift attention. However, the severity of illness did not predict severity of delirium. Furthermore, hypoxia and infection were etiologies more commonly associated with delirium in severe illness, whereas the administration of corticosteroids was associated with less severe illness.

KEYWORDS: Delirium, Severity of medical illness, Phenomenology, Etiologies

INTRODUCTION

Delirium is a neuropsychiatric disorder characterized by disturbances of consciousness, cognition, and perception. The syndrome has an abrupt onset, fluctuating course, and a contributing physiological etiology. Further characteristic symptoms include affective changes and psychomotor abnormalities, as well as sleep–wake cycle disturbances (Trzepacz et al., 1999).

The occurrence rate of delirium depends on the age of the patient and the severity of the illness (Francis et al., 1990; Voyer et al., 2007). In the general hospital setting, the occurrence of delirium in medically ill patients ranges between 15 and 30%, in the hospitalized elderly between 10 and 40% (Bucht et al., 1999; Lipowski, 1989), and in cancer patients from 57 to 85%. Among terminally ill patients, the incidence of delirium can reach 85% (Bond et al., 2006; Breitbart & Strout, 2000; Massie

Address correspondence and reprint requests to: Soenke Boettger, University Hospital Zurich, Ramistrasse 100, CH-8091 Zurich, Switzerland. E-Mail: soenke.boettger@usz.ch

et al., 1983). In particular in the elderly, the prevalence and incidence of delirium remain high. Some 14 to 24% of elderly patients may be delirious at the time of admission, and 6 to 56% will go on to develop delirium during their course of hospitalization. Furthermore, delirium is associated with poor functional outcome, increased morbidity and mortality, and prolonged hospitalization (Inouye, 1998).

Several risk factors for delirium have been identified. These include advanced age, cognitive impairment, low albumin level, bone metastases, and the presence of hematological malignancy (Ljubisavljevic & Kelly, 2003). Medications have been identified as another risk factor contributing to delirium—including benzodiazepines, corticosteroids, and opioids (Gaudreau et al., 2005). The reversibility and irreversibility of delirium have constituted another topic of investigation. Opioids and dehydration have been associated with reversible delirium, while hypoxic encephalopathy and infection have been identified as factors contributing to irreversible delirium (Lawlor et al., 2000*a*).

In patients with advanced cancer, delirium is usually a multifactorial syndrome. Among this population, opiates factor into almost 60% of episodes and represent the most frequent etiology (Centeno et al., 2004). In terminal cancer, opiates have been associated with incidence of delirium. In 50% of delirium cases, however, significant symptom improvement can be achieved, deeming delirium as a serious and frequent complication in terminal cancer with an outcome not as poor as previously believed (Gagnon et al., 2000).

Although a number of studies have sought to investigate the factors contributing to delirium, the characteristics of delirium in the severely medically ill cancer population remain understudied. Etiological factors in this population have been partly investigated, but the characteristics of delirium in this population remain unknown.

To date, there have been no studies of delirium severity and phenomenology among patients with severe medical illness. A secondary analysis of existing data was performed with respect to severely medically ill patients in order to identify the factors related to delirium associated with this population.

METHODS

Subjects

Subjects in our trial included patients referred for delirium management to the Memorial Sloan Kettering Cancer Center (MSKCC) psychiatry service from July of 2004 to June of 2006. Sloan Kettering is a 470-bed, private hospital specializing in the treatment of cancer, averaging more than 20,000 admissions per year. The consultation-liaison psychiatry service performs on average more than 2,000 consultations yearly.

All patients included in our study were managed for delirium and met the criteria for a diagnosis of delirium according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM−IV−TR) (American Psychiatric Association, 2000). The exclusion criteria included an inability to comply with delirium assessment and objections to assessment or management of delirium with antipsychotics on the part of the patient or their family.

Consent was obtained from all capable patients who participated in the study. In patients with a limited capacity to provide consent due to delirium, the primary caregiver provided verbal consent alongside the patient's assent to intervention.

All data were obtained from the routine care of patients, recorded in an MSKCC psychiatry service clinical database approved by the institutional review board, and a waiver was obtained for the data analysis.

Measurements

The following information was collected for the baseline assessment: age, sex, cancer diagnosis, stage of cancer (localized, metastatic, or terminal), psychiatric diagnoses including a history of dementia, presence of brain metastases, and delirium etiology. The level of functioning was assessed with the Karnofsky Performance Status (KPS) scale, indicating physical performance ability (Karnofsky & Burchenal, 1949). This scale was developed particularly for the cancer population, and scores range from 10 to 100. Scores less than 50 indicate an inability to care for oneself, requiring hospital care; a score of 40 indicates a disability with a need for assistance; a score of 30 indicates a severe disability requiring hospital admission; a score of 20 indicates a need for hospital admission and active treatment of a very sick patient; and a score of 10 indicates a moribund state.

Delirium severity was measured with the MDAS, a 10-item, 4-point clinician-rated scale (possible range 0−30) (Breitbart et al., 1997). MDAS items range from 0 (absent), to 1 (mild), 2 (moderate), and 3 (severe) in presentation. This instrument provides a clear description of the severity and presence of symptoms. Scale items assess disturbance in arousal and level of consciousness as well as several areas of cognitive functioning, in psychomotor activity, and in the sleep−wake cycle. An MDAS score above 10 identifies the presence of delirium (Lawlor et al., 2000*b*).

Statistical Analysis

Analyses were performed with the Statistical Package for the Social Sciences (SPSS, v. 20) for Windows.

For the purpose of our analysis, severity of medical illness was defined as a dichotomous variable with two levels: KPS < 30, representing the severely medically ill cancer population, and KPS ≥ 30, representing the less severely ill. Descriptive statistics were computed in order to assess sociodemographic and medical variables, and MDAS scores and subscores. In respect to delirium severity, mean MDAS scores were employed, and with respect to prevalence of single delirium symptoms, moderate and severe symptomatology.

Data on the interval scale such as age were computed with a t test, data on the ordinal or categorical scale (such as delirium severity or prevalence of etiologies) with the Mann–Whitney U test for pairwise comparison of independent samples, and data on the categorical scale with Pearson's chi-square test (χ^2). Post hoc, for all implemented tests, Cronbach's α was adjusted using the Bonferroni method. The significance level of α was set at $p < 0.05$.

RESULTS

Baseline Characteristics

Some 67 of 111 patients had a KPS score less than 30 (60.4%) and had severe medical illness, in contrast to 44 patients with a KPS score greater than 30 (39.6%) with less severe illness.

There were no differences in age, in presence of dementia or brain metastasis, or in stage of illness between severe and less severe (see Table 1). With respect to cancer diagnoses, the prevalence of brain cancer and gastrointestinal cancer differed between severe and less severe illness. Brain cancer was more frequently found in the less severely ill, whereas gastrointestinal cancer was more often found in the severely ill. There were no differences in prevalence of hypoactive versus hyperactive delirium; hypoactive delirium occurred in 49.3% in severe illness and 38.6% in less severe illness. Hyperactive delirium, in contrast, occurred in 50.7 and 61.4%, respectively.

Delirium Severity and Phenomenology

The MDAS scores at baseline were not different (Table 1). The severely ill had a baseline MDAS score of 18.8 and the less severely ill 17.4. However, there were differences in severity of disturbances of consciousness, orientation, and ability to maintain and shift attention (Table 2). In the severely ill cancer population, disturbance of consciousness was more pronounced (2.04 vs. 1.77), as were disorientation (2.19 vs. 1.89) and inability to shift and maintain attention (2.07 vs. 1.80). No differences were noted in

the cognitive domain, perceptual disturbances and delusions, psychomotor abnormality, or sleep–wake cycle disturbances.

In addition to the different degrees of symptomatological severity, differences in frequency of moderate and severe symptoms existed between both groups. Some 94% of the severely ill had a disturbance of consciousness compared to 77% of the less severely ill. Disorientation was present in 87% compared to 66%, respectively. In contrast to the severity of symptoms represented by mean MDAS scores, the difference with respect to ability to maintain and shift attention did not reach statistical significance ($p = 0.052$)

Etiologies Contributing to Delirium

The etiological factors contributing to delirium in severe medical illness were hypoxia and infection. In severe medical illness, hypoxia was present in 44.8% compared to 25.0% in less severe illness; infection was present in 34.3 and 9.1%, respectively. In contrast, the administration of corticosteroids was associated with higher KPS scores, indicating less severe illness or a protective effect of corticosteroid administration. Almost two thirds of the less severely ill (61.4%) received corticosteroids in contrast to one third (37.4%) of the severely ill. Other etiological factors did not reveal differences between severities of illness. The administration of opiates, the presence of CNS disease, dehydration, and the administration of other medications were comparable.

Severity if Illness and Functional Status

The severity of illness and level of functioning were different between groups as set by the design. The mean KPS scores in severe medical illness were 19.7 and 30.7.

DISCUSSION

In this sample of 111 patients with delirium, the overall delirium severity among severely medically ill cancer patients was not significantly different from less ill patients. However, impairment within the individual domains of consciousness, orientation, and ability to shift and maintain attention was more severe. The etiological factors contributing to more severe medical illness were hypoxia and infection. In contrast, the administration of corticosteroids was more frequently observed in less severely ill patients.

Surprisingly, severe medical illness was not associated with a higher MDAS score, suggesting that severity of medical illness does not necessarily predict severity of delirium. However, severity of medical illness was associated with an increased frequency,

Table 1. *Sociodemographic and medical characteristics of patients with severe illness*

	Severe Illness ($n = 67$)	Less Severe Illness ($n = 44$)	Statistics
Age	65.9 (23−86, $SD = 13.4$)	65.0 (23−89, $SD = 14.1$)	−0.326 (40), $p = 0.745$[a]
Gender (in %)			0.09 (4), $p = 0.834$[b]
Male	59.7	56.8	
Female	40.3	43.2	
Ethnicity (in %)			3.79 (4), $p = 0.486$[b]
White	90.9	79.1	
African American	9.1	14.9	
Hispanic	−	3	
Asian	−	1.5	
Other	−	1.5	
Diagnoses (in %)			
Lung	20.9	22.7	0.05 (1), $p = 1$[b]
Brain	4.5	20.5	7.03 (1), $p = 0.012$[b]
Gastrointestinal	31.3	11.4	5.91 (1), $p = 0.021$[b]
Genitourinary	7.5	11.4	0.49 (1), $p = 0.514$[b]
Sarcoma	6.0	9.1	0.39 (1), $p = 0.710$[b]
Head and neck	6.0	6.8	0.03 (1), $p = 1$[b]
Gynecological	11.9	4.5	1.77 (1), $p = 0.31$[b]
Endocrine	−	6,8	−
Lymphoma	−	2.3	−
Skin	4.5	−	−
Hematological	3.0	−	−
Other	4.5	4.6	0.05 (1), $p = 1$[b]
Stage (in %)			1.68 (2), $p = 0.463$[b]
Localized	30.3	41.9	
Advanced	50	44.2	
Terminal	19.7	14	
Brain metastasis (in %)	10.4	6.8	0.47 (1), $p = 0.737$[b]
Etiologies (in %)			
Opiates	88.1%	88.6%	0.01 (1), $p = 1$[b]
Corticosteroids	37.3%	61.4%	6.17 (1), p = 0.01[b]
Infection	34.3%	9.1%	9.19 (1), $p < 0.001$[b]
Hypoxia	44.8%	25.0%	4.46 (1), $p = 0.045$[b]
Presence of CNS disease	10.4%	15.4%	0.72 (1), $p = 0.012$[b]
Dehydration	6.0%	4.5%	0.11 (1), $p = 1$[b]
Other medications	85.1%	84.1%	0.02 (1), $p = 1$[b]
Sum of etiologies	5.0 (3−8, $SD = 9$)	5.0 (3−7, $SD = 1.1$)	1,458, $p = 0.906$[c]
MDAS score total	18.8 (12−30, $SD = 4.4$)	17.4 (11−28, $SD = 4.8$)	1,200, $p = 0.099$[c]
KPS score	19.7 (10−20, $SD = 1.7$)	30.7 (30−40, $SD = 2.5$)	2,278, $p < 0.001$[c]

MDAS = Memorial Delirium Assessment Scale; KPS = Karnofsky Performance Status scale.
[a]t test, [b]Pearson's chi-square test (χ^2), [c]Mann−Whitney U test.

severity, and level of disturbances of consciousness and disorientation. With respect to attentional impairment, only the difference in severity reached statistical significance. Thus, these findings represent new insights into the phenomenology of delirium in severe medical illness.

Previously, hypoxia and infection were identified as causes of irreversible delirium (Lawlor et al., 2000*a*). Due to the length of the observation period, no definite statement about reversibility could be made in our study, but, similarly, hypoxia and infection more frequently contributed to more severe medical illness. Although corticosteroids themselves represent a risk factor for delirium (Ljubisavljevic & Kelly, 2003), corticosteroids were more often associated with less severe illness in our study, and it appeared that corticosteroids may have a beneficial, protective effect on severity of illness.

The relevance of opiate administration contributing to delirium was higher than previously indicated. Compared to approximately 60% of opiate administration factoring in delirium episodes in patients with advanced cancer (Centeno et al., 2004), opiate administration factored into almost 90% of delirium episodes within our sample. This may partially be due to the particular population of medically ill cancer patients and frequent opiate administration in this population. There were no differences evident in opiate administration between the severely and less severely medically ill.

Table 2. *Severity of MDAS items and presence of moderate and severe symptoms*

	Severe Illness (n = 67)	Less Severe Illness (n = 44)	Statistics	Severe Illness (n = 67)	Less Severe Illness (n = 44)	Statistics
Disturbance of consciousness	2.04 (1–3, SD = 0.41)	1.77 (1–2, SD = 0.43)	1,108, p = 0[a]	94%	77%	6.77 (1), p = 0.017[b]
Disorientation	2.19 (1–3, SD = 0.66)	1.89 (1–3, SD = 0.75)	1,140, p = 0.029[a]	87%	66%	6.69 (1), p = 0.017[b]
Short-term memory	2.28 (1–3, SD = 0.71)	2.16 (1–3, SD = 0.68)	1,322, p = 0.319[a]	85%	84%	0.02 (1), p = 1[b]
Concentration	2.43 (1–3, SD = 0.63)	2.23 (1–3, SD = 0.68)	1,233, p = 0.113[a]	93%	86%	1.13 (1), p = 0.339[b]
Ability to maintain/shift attention	2.07 (1–3, SD = 0.72)	1.80 (1–3, SD = 0.73)	1,170, p = 0.057[a]	78%	61%	3.42 (1), p = 0.087[b]
Thought disorder	1.52 (0–3, SD = 0.79)	1.43 (0–3, SD = 0.67)	1,412, p = 0.687[a]	40%	39%	0.03 (1), p = 1[b]
Perceptual disturbance	1.15 (0–3, SD = 1.09)	1.02 (0–3, SD = 1.09)	1,372, p = 0.524[a]	37%	36%	0.10 (1), p = 1[b]
Delusions	0.91 (0–3, SD = 1.11)	1.16 (0–3, SD = 1.16)	1,281, p = 0.219[a]	30%	34%	0.22 (1), p = 0.680[b]
Psychomotor abnormality	2.19 (1–3, SD = 0.50)	2.07 (1–3, SD = 0.45)	1,300, p = 0.201[a]	96%	93%	0.29 (1), p = 0.680[b]
Sleep–wake cycle disturbance	2.01 (1–3, SD = 0.51)	1.91 (1–3, SD = 0.52)	1,320, p = 0.211[a]	91%	82%	2.05 (1), p = 0.241[b]

SD (standard deviation). [a]Mann–Whitney *U* test. [b]Pearson's chi-square test (χ^2).

Interestingly, gastrointestinal cancer was more often encountered in the severely ill and brain cancer more often encountered in the less severely ill. In addition, gastrointestinal cancer was more frequently advanced (73.1%) than brain cancer (8.3%), which in context with more systemic illness might provide a rationale for the higher prevalence in severe illness.

Both age and previous history of dementia were previously identified as risk factors for delirium (Ljubisavljevic & Kelly, 2003); however, they were not demonstrated to affect severity of illness and were not associated with severity of medical illness in our sample.

These findings reproduced earlier results, such as the association of hypoxia and infection as indicators of illness severity and possible irreversibility of delirium, in addition to providing new findings regarding the quality of delirium in the severely medically ill population. The level of disturbance in consciousness, disorientation, and attentional impairment were more severe and, in part, more frequent in the severely medically ill population. Both disorientation and inattention have been identified as more stable symptoms over the course of delirium (Levkoff et al., 1994; McCusker et al., 2003); however, the association of severity of symptoms with severity of medical illness has previously not been demonstrated.

Although our study has strengths, including the prospective collection of data and the systematic evaluation and documentation of delirium and contributing etiologies, certain limitations have to be noted. The design of our study was cross-sectional, so that the evolution of symptoms over time in respect to delirium severity could not be determined. Longitudinal studies have suggested psychomotor abnormalities, sleep–wake cycle disturbances in the early course of delirium (Fann et al., 2005), disorientation, inattention, impaired memory, and sleep disturbances as the most persistent symptoms through the course of delirium (Levkoff et al., 1994; McCusker et al., 2003). Within our sample, patients with cognitive deficits were not excluded. Brain metastases were present in 24%, and 18% had a history of dementia. However, excluding patients with cognitive deficits from the sample did not alter our results. This was not surprising, as dementia has not been deemed to alter delirium phenomenology (Trzepacz et al., 1998). The etiology of delirium in this sample population of cancer patients was multifactorial and included medications with psychotropic effects. Furthermore, all subjects had cancer diagnoses, and the generalizability of these results to the non-cancer population may be limited. Further studies are required to understand the impact of etiological factors on presentation of delirium.

In summary, delirium in the severely medically ill cancer population may be characterized by an increased disturbance of consciousness, disorientation, and an inability to maintain and shift attention. Severity of medical illness was not found to be associated with severity of delirium. The etiologies found to be associated with delirium in severe medical illness were hypoxia and infection.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest to declare.

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