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Original Article

Increased Symptom Expression among Patients with Delirium Admitted to an Acute Palliative Care Unit

Maxine de la Cruz, MD,[1] Sriram Yennu, MD,[1] Diane Liu,[2] Jimin Wu,[2] Akhila Reddy, MD,[1] and Eduardo Bruera, MD[1]

Abstract

Introduction: Delirium is the most common neuropsychiatric condition in very ill patients and those at the end of life. Previous case reports found that delirium-induced disinhibition may lead to overexpression of symptoms. It negatively affects communication between patients, family members, and the medical team and can sometimes lead to inappropriate interventions. Better understanding would result in improved care. Our aim was to determine the effect of delirium on the reporting of symptom severity in patients with advanced cancer.
Methods: We reviewed 329 consecutive patients admitted to the acute palliative care unit (APCU) without a diagnosis of delirium from January to December 2011. Demographics, Memorial Delirium Assessment Scale, Eastern Cooperative Oncology Group (ECOG) Performance status, and Edmonton Symptom Assessment Scale (ESAS) on two time points were collected. The first time point was on admission and the second time point for group A was day one (+two days) of delirium. For group B, the second time point was within two to four days before discharge from the APCU. Patients who developed delirium and those who did not develop delirium during the entire course of admission were compared using chi-squared test and Wilcoxon rank-sum test. Paired *t*-test was used to assess if the change of ESAS from baseline to follow-up was associated with delirium.
Results: Ninety-six of 329 (29%) patients developed delirium during their admission to the APCU. The median time to delirium was two days. There was no difference in the length of stay in the APCU for both groups. Patients who did not have delirium expressed improvement in all their symptoms, while those who developed delirium during hospitalization showed no improvement in physical symptoms and worsening in depression, anxiety, appetite, and well-being.
Conclusion: Patients with delirium reported no improvement or worsening symptoms compared to patients without delirium. Screening for delirium is important in patients who continue to report worsening symptoms despite appropriate management.

Keywords: advanced cancer; delirium symptom; symptom expression

Introduction

Delirium is the most common neuropsychiatric condition in very ill and debilitated patients and those patients at the end of life.[1–4] The underlying etiology is often multifactorial in a vulnerable and frail patient.[3,5,6] Delirium results in significant distress not only to the patient but also to his or her family and health caregivers.[7,8] Misinterpretation of symptoms is common and may lead to inappropriate interventions.[9–12] Psychological distress has been reported in family and health caregivers as patients' reported needs are often difficult to appropriately assess and manage.

Previous studies suggest that in patients with delirium, disinhibition often occurs and patient's self-report of symptoms may be inaccurate.[9] Prior case studies in patients with undiagnosed delirium may be subjected to inappropriate management because of misinterpretation of symptoms.[9] In a recent study by our group, 33% of patients with missed delirium had ''pain'' as the most frequent reason for consultation.[12] In such patients, opioid rotation rather than opioid escalation would be a more appropriate management. There have been limited published studies in the literature that suggest that delirium affects patient reporting of symptoms.[9] It is therefore important for clinicians to know how delirium

[1]Department of Palliative Rehabilitation and Integrative Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas.
[2]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas.
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affects reporting of symptoms to tailor the management of such patients correctly.

The purpose of this study was to determine whether the presence of delirium affects patient's reporting of specific cancer-related symptoms.

Methods

This is an *ad hoc* analysis in previous published study,[4] in which we reviewed 609 consecutive patients admitted to the acute palliative care unit (APCU) at a major academic cancer center during the period of January 1–December 31, 2011. The study was approved by the Institutional Review Board of the University of Texas MD Anderson Cancer Center.

To be eligible for this study, we included only those patients who did not have a diagnosis of delirium at the time of admission. Delirium was defined as those patients with a score of ≥7/30 in the Memorial Delirium Assessment Scale (MDAS), and those with a diagnosis of delirium as per DSM IV criteria and documented as delirium in the patients' medical record. A total of 329 patients were included in the study. Demographic information, including gender, age, race, cancer diagnosis, ECOG Performance status, source of admission, delirium etiology, treatment, and discharge disposition, was collected. The MDAS[13] score was also collected.

Statistical analysis

We analyzed two groups, those patients who developed delirium after admission to the APCU and those patients who did not develop delirium by their discharge from the APCU. The Edmonton Symptom Assessment Scale (ESAS)[14] was collected for both groups at baseline (admission to the APCU) and at follow-up. For patients with delirium, follow-up ESAS was collected within three days of developing delirium. For patients without delirium, follow-up ESAS was collected + three days before discharge from the APCU. Wilcoxon signed rank test was applied to assess whether the change of ESAS from baseline to follow-up was significantly different from. The Wilcoxon rank-sum test was used to test the difference in age, days of stay, and baseline and change of ESAS measures between patients who developed delirium and those who did not develop delirium. Association between categorical variables was examined by the chi-squared test.

Results

A total of 329/609 (54%) patients were admitted to the APCU with no diagnosis of delirium. Ninety-six of 329 (29%) developed delirium during the course of their admission to the APCU. Baseline characteristics of the two groups are shown in Table 1. Patients who developed delirium with poorer ECOG scores [ECOG 2 4% vs. 12%, ECOG 3 30% vs. 54%, and ECOG 4 66% vs. 32% ($p = < 0.0001$)] were more likely to die compared to those who did not develop delirium during their admission to the APCU (32% vs. 9%, $p = < 0.0001$). ESAS pain at baseline was worse in those patients without delirium (median 7 vs. 5, $p = 0.0040$), and dyspnea was reported to be worse in those with delirium (median 5 vs. 3, $p = 0.0115$). All other characteristics were not found to be statistically different.

Median time to development of delirium is two days. Also, the most common delirium subtype is mixed 34/72 (47%); 24 patients did not have a subtype recorded. Haloperidol remains the most common drug used to control symptoms of delirium 55/96 (57%). For those patients who developed delirium during admission, only 17/96 (17%) had resolution of delirium.

Table 1. Comparison of Demographics and Clinical Characteristics of Patients Who Developed Delirium and Those Who Did Not Have Delirium throughout Admission

Covariate	*Levels*	*Total, n (%)*	*Patients without delirium throughout admission, n (%)*	*Patients who developed delirium, n (%)*	p
All patients		329 (100)	233 (70.8)	96 (29.2)	
Gender	Female	180 (54.7)	125 (53.6)	55 (57.3)	0.5461
Age	Mean ± SD		54.82 ± 13.8	57.43 ± 13.6	0.1068
Race	Asian	23 (7.1)	17 (7.4)	6 (6.5)	0.9737
	Black	50 (15.5)	35 (15.3)	15 (16.1)	
	Hispanic	46 (14.3)	34 (14.8)	12 (12.9)	
	White	202 (62.7)	142 (62)	60 (64.5)	
	Other	1 (0.3)	1 (0.4)	0 (0)	
	Unknown	7			
ECOG	1	2 (0.6)	2 (0.9)	0 (0)	<0.0001
	2	33 (10)	29 (12.4)	4 (4.2)	
	3	156 (47.4)	127 (54.5)	29 (30.2)	
	4	138 (41.9)	75 (32.2)	63 (65.6)	
Cancer diagnosis	Hematologic	31 (9.4)	17 (7.3)	14 (14.6)	0.0644
	Solid tumors	262 (79.6)	216 (92.7)	82 (85.4)	
Discharge disposition	Death	80 (24.3)	20 (8.6)	60 (62.5)	<0.0001
	Home	88 (26.7)	85 (36.5)	3 (3.1)	
	Hospice	161 (48.9)	128 (54.9)	33 (34.4)	
Days of stay	Mean ± SD		6.94 ± 3.81	7.23 ± 5.06	0.7739

SD, standard deviation.

Table 2. Baseline ESAS Values for Patients Who Developed Delirium and Those Who Did Not Have Delirium throughout Admission

Covariate	*Patients without delirium throughout admission mean ± SD*	*Patients who developed delirium mean ± SD*	p
Pain	6.11 ± 3.09	5.02 ± 3.15	0.0040
Fatigue	6.48 ± 2.75	6.13 ± 3.00	0.4616
Nausea	2.61 ± 3.23	1.90 ± 2.87	0.0703
Depression	3.00 ± 3.14	2.72 ± 3.24	0.3677
Anxiety	3.80 ± 3.37	4.42 ± 3.14	0.1798
Drowsiness	3.32 ± 3.14	3.40 ± 3.12	0.9266
Appetite	5.62 ± 3.39	5.67 ± 3.52	0.7949
Well-being	5.82 ± 2.58	5.32 ± 2.55	0.2687
Dyspnea	3.45 ± 3.38	4.63 ± 3.40	0.0115
Sleep	4.85 ± 3.34	4.52 ± 3.37	0.5167

ESAS, Edmonton Symptom Assessment Scale.

Table 2 shows the baseline ESAS symptom values. Table 3 shows the comparison for the intensity of change in ESAS values within each group and between the two groups. Patients with no delirium showed an improvement in their ESAS scores for pain, fatigue, depression, anxiety, drowsiness, appetite, well-being, and sleep. For those patients with delirium, ESAS symptom scores were worse for depression, anxiety, appetite, well-being, and sleep. When comparing the change in the ESAS scores between the groups, all variables were noted to be statistically significant.

Discussion

Our study has shown that patients with delirium report overall worse symptom distress in the different components of the ESAS when compared to those who did not develop delirium. In patients who did not develop delirium, optimal adjustment of medications along with an interdisciplinary approach to patient care showed a decrease in reported symptom intensity, which is consistent with other studies.[15–17] Our findings suggest that delirium should be suspected particularly in patients with severe and refractory symptom expression. Some symptoms, including pain, were expressed more severely; these patients are at a higher risk of opioid dose escalation or additional use of other adjuvants that may aggravate delirium. These patients may also be candidates for a formal delirium assessment.

In those patients who are self-evident to have delirium such as those who were unable to express their symptoms but clearly confused and or agitated, and those who are unresponsive, misinterpretation of symptoms is not a major factor. It is those who are able to express their symptoms, although inappropriately, who are most likely to be misinterpreted by a clinician. Our group published data on patients seen by our palliative consult service showing that about a third of patients referred had a diagnosis of delirium and about 60% of these patients had delirium that was missed by the primary referring team.[12] This is of important clinical consequence especially since missed delirium can lead to more invasive and inappropriate management.

The exact mechanism of increased symptom expression among patients with delirium is not known. The final common neural pathway in delirium is thought to be associated with low cholinergic and excess dopaminergic state.[18,19] Other neurotransmitters such as GABA and serotonin affect the activity of both the cholinergic and dopaminergic pathways, contributing to the development of the symptoms of delirium.[20] High symptom expression of almost every symptom is consistent with the pathophysiology of delirium that involves reducing the GABA inhibitory activity thereby allowing disinhibited expression of distress, and patients may also appear more anxious or agitated.[21]

Delirium is a common occurrence in patients who are frail, vulnerable, very ill, and debilitated.[22] The finding of worsening symptom expression in patients with delirium suggests that perhaps other tools in conjunction with patient-reported scales such as the ESAS may be useful. Further investigation is needed to better understand the best evaluation modalities that can be used in patients with delirium to appropriately address and manage their symptoms. Incorporating other information that may be available such as those reported by family and other health professionals caring for the patient may be necessary to get a more accurate picture of the patient's symptom distress.

There are several study limitations that may be better addressed perhaps in a prospective observational study. Some

Table 3. Comparison of the Change in ESAS Values from Follow-Up to Baseline between Patients Who Developed Delirium and Those Who Did Not Have Delirium throughout Admission

	Patients without delirium throughout admission			*Patients who developed delirium*			
Covariate	*Median (range)*	*Mean ± SD*	p[a]	*Median (range)*	*Mean ± SD*	p[a]	p[b]
Pain	−3 (−10 to 5)	−3.01 ± 2.92	<0.0001	0 (−10 to 10)	0.37 ± 3.75	0.4	<0.0001
Fatigue	−2 (−10 to 7)	−1.94 ± 3.45	<0.0001	0 (−5 to 9)	0.79 ± 3.28	0.2637	0.0002
Nausea	0 (−10 to 6)	2.61 ± 3.23	<0.0001	0 (−10 to 6)	1.90 ± 2.87	0.8128	0.0338
Depression	−1 (−10 to 6)	3.00 ± 3.14	0.0007	1.5 (−5 to 6)	2.72 ± 3.24	0.0273	0.0007
Anxiety	−1 (−10 to 9)	3.80 ± 3.37	0.0015	1 (−4 to 10)	4.42 ± 3.14	0.0235	0.0017
Drowsiness	−1 (−9 to 10)	3.32 ± 3.14	0.0007	0 (−6 to 7)	3.40 ± 3.12	0.3308	0.0288
Appetite	−2 (−9 to 7)	5.62 ± 3.39	<0.0001	1.5 (−5 to 10)	5.67 ± 3.52	0.0041	<0.0001
Well-being	−1 (−8 to 7)	5.82 ± 2.58	0.0001	1 (−3 to 8)	5.32 ± 2.55	0.0469	0.0016
Dyspnea	0 (−10 to 7)	3.45 ± 3.38	<0.0001	0 (−8 to 6)	4.63 ± 3.40	0.6308	0.0255
Sleep	−2 (−10 to 6)	4.85 ± 3.34	<0.0001	1 (−8 to 9)	4.52 ± 3.37	0.4393	0.0012

[a]*p* was from Wilcoxon signed-rank test, assessing the changes within groups.
[b]*p* was from Wilcoxon rank-sum test, assessing the changes between groups.

information that is relevant to symptom expression discussions cannot be addressed due the retrospective design. Longitudinal assessment of ESAS with more frequent time points would have been more helpful to describe patterns of reporting in patients with delirium. It is also challenging to properly assess symptoms as patients with delirium may find it problematic to quantify symptom intensity using a numerical scale. Perhaps a more simplistic method is more appropriate such as those used in pediatric populations or those with dementia.[23–25] It is also important to note that these ESAS records do not indicate whether it was the patient, caregiver, or member of the medical team who ascribed the symptom intensity.

Conclusion

The study shows that patients with delirium report higher distress in depression, anxiety, appetite, well-being, and sleep compared to those who did not develop delirium. Screening patients with severe and refractory symptom expression for delirium may be warranted in patients at increased risk.

Author Disclosure Statement

No competing financial interests exist.

References

1. Breitbart W: Psycho-oncology: Depression, anxiety, delirium. Semin Oncol 1994;21:754–769.
2. Breitbart W, Alici Y: Agitation and delirium at the end of life: ''We couldn't manage him''. JAMA 2008;300:2898–2910, E1.
3. Casarett DJ, Inouye SK: Diagnosis and management of delirium near the end of life. Ann Intern Med 2001;135:32–40.
4. de la Cruz M, et al.: The frequency, characteristics, and outcomes among cancer patients with delirium admitted to an acute palliative care unit. Oncologist 2015;20:1425–1431.
5. Centeno C, Sanz A, Bruera E, et al.: Delirium in advanced cancer patients. Palliat Med 2004;18:184–194.
6. Breitbart W, Strout D: Delirium in the terminally ill. Clin Geriatr Med 2000;16:357–372.
7. Breitbart W, Gibson C, Tremblay A: The delirium experience: Delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics 2002;43:183–194.
8. Bruera E, et al.: Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. Cancer 2009;115:2004–2012.
9. Delgado-Guay MO, Yennurajalingam S, Bruera E: Delirium with severe symptom expression related to hypercalcemia in a patient with advanced cancer: An interdisciplinary approach to treatment. J Pain Symptom Manage 2008;36:442–449.
10. Lawlor PG, et al.: Occurrence, causes, and outcome of delirium in patients with advanced cancer: A prospective study. Arch Intern Med 2000;160:786–794.
11. Fainsinger R, et al.: Symptom control during the last week of life on a palliative care unit. J Palliat Care 1991;7:5–11.
12. de la Cruz M, et al.: The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. Support Care Cancer 2015;23:2427–2433.
13. Fadul N, et al.: Evaluation of the memorial delirium assessment scale (MDAS) for the screening of delirium by means of simulated cases by palliative care health professionals. Support Care Cancer 2007;15:1271–1276.
14. Bruera E, et al.: The Edmonton Symptom Assessment System (ESAS): A simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6–9.
15. Mori M et al.: Unrelieved pain and suffering in patients with advanced cancer. Am J Hosp Palliat Care 2012;29: 236–240.
16. Reddy A, Hui D, Bruera E.: A successful palliative care intervention for cancer pain refractory to intrathecal analgesia. J Pain Symptom Manage 2012;44:124–130.
17. Delgado-Guay M, et al.: Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. Support Care Cancer 2009;17:573–579.
18. Hshieh TT, et al.: Cholinergic deficiency hypothesis in delirium: A synthesis of current evidence. J Gerontol A Biol Sci Med Sci 2008;63:764–772.
19. Inouye SK, Ferrucci L: Elucidating the pathophysiology of delirium and the interrelationship of delirium and dementia. J Gerontol A Biol Sci Med Sci 2006;61:1277–1280.
20. Marcantonio ER, et al.: Serum biomarkers for delirium. J Gerontol A Biol Sci Med Sci 2006;61:1281–1286.
21. Maldonado JR: Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 2013;21:1190–1222.
22. Inouye SK: Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord 1999;10:393–400.
23. Lichtner V, et al.: The assessment and management of pain in patients with dementia in hospital settings: A multi-case exploratory study from a decision making perspective. BMC Health Serv Res 2016;16:427.
24. Lichtner V, et al.: Pain assessment for people with dementia: A systematic review of systematic reviews of pain assessment tools. BMC Geriatr 2014;14:138.
25. Tsze DS, et al.: Validation of self-report pain scales in children. Pediatrics 2013;132:e971–e979.

Address correspondence to:
Maxine de la Cruz, MD
Department of Palliative Rehabilitation
and Integrative Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX 77030

E-mail: mdelacruz@mdanderson.org