



Symptom expression in advanced cancer patients admitted to hospice or home care with and without delirium

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Abstract

The aim of this study is to investigate the relationship between delirium and symptom expression in advanced cancer patients admitted to palliative care services. This is a secondary analysis of a consecutive sample of advanced cancer patients who were admitted to home care and hospices, and prospectively assessed for a period of 10 months. The Edmonton Symptom Assessment Scale (ESAS) and the MDAS (Memorial Delirium Assessment Scale) were measured at admission (T_0) and after seven days of home care or hospice care (T_7). Of the eight hundred and forty-eight patients screened in the period, 585 were not considered in the analysis for various reasons. The mean age was 72.1 years (SD 13.7), and 146 patients were males (55.5%). The mean Karnofsky status recorded at T_0 is 34.1 (SD = 6.69). The mean duration palliative care assistance is 38.4 days (SD = 48, range 2–220). Of 263 patients who had a MDAS available at T_0 , 110 patients (41.8%) had a diagnosis of delirium. Of them, 167 patients had complete data regarding MDAS measurement, either at T_0 and T_7 . A larger number of patients (n 167, 63.5%) had delirium after a week of palliative care. Patients with delirium are likely to be older, to have a lower Karnofsky level at T_0 , and to be home care patients. At T_0 , weakness, nausea, drowsiness, lack of appetite, and well-being are associated with delirium. At T_7 , weakness, poor appetite, and poor well-being are significantly associated with delirium. 27% of patients who had a normal cognitive status at T_0 developed delirium at T_7 . In patients with delirium, an improvement in the cognitive status corresponds to a significant improvement in weakness, depression, and appetite. Conversely, the occurrence of delirium in patients who had a normal cognitive status at admission significantly increases the level depression, while the level of weakness and appetite decrease. Symptom expression is amplified in patients with delirium admitted to home care or hospices, while patients without delirium can be more responsive to palliative treatments with a significant decrease in intensity of ESAS items

Keywords Advanced cancer · Delirium · Memorial Delirium Assessment Scale · Edmonton Symptom Assessment Scale · Palliative care

Introduction

Delirium is a serious condition due to multifactorial mechanisms frequently observed in advanced cancer patients. Delirium produces significant distress to the patient, relatives, and health caregivers. Delirium adversely has an impact upon functional decline, increases the length of hospital stay and medical costs, and is associated with a shortened survival [1–3]. Indeed, delirium is also the most

frequent symptom requiring a palliative sedation either at home or in hospice [4–7].

This complex disorder occurring in advanced cancer patients has been variably reported in the literature, the prevalence ranging between 13% and 88%, with a particular frequency at the end of life. In a previous study performed in 847 patients recruited either at home care or in hospice, about 42% of patients had delirium at admission [8]. The number of patients with delirium increased 1 week after admission despite a palliative care intention, different from what occurs in an acute palliative care unit (APSCU), where a significant number of patients improve their cognitive function, possibly due to a more aggressive intervention in patients with a longer survival expectation [9].

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Altered cognitive function may lead to misinterpretation of symptom assessment that may lead to inappropriate interventions. Regrettably, this neuropsychiatric disorder is often unrecognized or insufficiently diagnosed, and poorly managed by clinicians, even in the hospital [3, 10, 11]. Delirium may impair recognition of physical symptoms rendering suboptimal symptom management [12, 13]. A retrospective study shows that patients who developed delirium during hospital admission, report a higher level of symptoms, particularly pain [14].

Data regarding the relationship between delirium and psychological and physical symptoms in advanced cancer patients taken care of at home or in hospice is lacking. Given the paucity of existing data in these settings, in the past decade, the HOCAI (Home Care, Italy) group has been established to gather information on advanced cancer patients that include almost all palliative care services in most countries, particularly Italy.

The purpose of this study is to assess whether the presence of delirium may affect the expression of physical and psychological symptoms reported by advanced cancer patients admitted to palliative care services, including home care and hospice, and whether such a relation changes after 1 week of palliative care.

Materials and methods

This is a secondary analysis of data collected during a previous study assessing delirium prevalence in patients admitted to palliative care services [8]. A sample of advanced cancer patients who were consecutively admitted to seven home care and hospices in Italy, was prospectively assessed from January to December 2018. Inclusion criteria were age > 18 years and no anticancer treatment. Exclusion criteria were the inability to be assessed due to cognitive failure or language problems, and consequently to give an informed consent, or anticancer therapies. To reproduce the real world of home care and hospice care, no specific protocol was used for the management of delirium. Management of delirium was based on local policies, according to the available means in such settings.

Data collection

Patients' demographics, including age, gender, primary diagnosis, and Karnofsky status, were collected. The Edmonton Symptom Assessment Scale (ESAS) was used to assess the physical and psychological symptoms at admission and 1 week after a palliative care treatment [15]. ESAS is a self-reported tool assessing the intensity of most common psychological and physical symptoms. ESAS uses a 0 (no symptom) to 10 (worst intensity) point numeric rating

scale to examine the intensity of each symptom over the past 24 h. This tool is valid and reliable for assessing the global symptom burden and is sensible to changes produced by a treatment [16]. The Memorial Delirium Assessment Scale (MDAS) was used to assess the cognitive status of patients and measured at admission (T_0), and after 7 days (T_7). The sample was divided in two groups, with and without delirium, according to a MDAS score threshold of 7. MDAS is frequently used in palliative care to quantify the intensity of delirium. MDAS includes different items assessing the level of consciousness, disorientation, short-term memory, digit span, attention, disorganized thinking, perceptual disturbances, delusions, psychomotor activity, and sleep–wake cycle disturbances [17, 18].

Statistical analysis

Descriptive sample statistics of the patients observed have been reported. The MDAS continuous response has been characterized using a threshold of seven defining two response groups. Mean values and standard deviations have been provided at the observation onset and after 1 week. Overall difference of multivariate mean symptoms in the MDAS groups, at the baseline and at the end, has been tested performing Hotelling T^2 test. The T test assessed individual symptom difference providing the corresponding 95% confidence interval estimation. The frequency of delirium status changes during the follow-up has been calculated. The hypothesis that delirium status changes affects the mean symptoms' difference vector has been explored using a MANOVA test ($W_{\text{Wilks}} = 0.76, p < 0.05$). Estimates of symptoms' variations given the delirium condition changes have been provided. The analysis has been carried out using the statistical software STATA (version 14).

Results

Of the eight hundred and forty-eight patients screened in the period taken into consideration, 585 were not considered in the analysis for various reasons, the most frequent of them being poor collaboration due to inability to record ESAS (48.9%). Of the 263 patients who participated into the study, 66 patients dropped out because they had just one evaluation at T_0 . The inability to have an evaluation after a week was due to death ($n = 33$), patients' requests ($n = 5$), or other reasons ($n = 28$). The mean age was 72.1 years (SD 13.7), and 146 patients were males (55.5%). The mean Karnofsky status recorded at T_0 is 34.1 (SD = 6.69). The mean duration palliative care assistance is 38.4 days (SD = 48, range 2–220).

Of the 263 patients who had a MDAS available at T_0 , 110 patients (41.8%) had a diagnosis of delirium. Of them, 167

Table 1 Characteristics of patients with and without delirium

	Without delirium, <i>n</i> (%)	With delirium, <i>n</i> (%)	<i>p</i>
Age (years, mean, SD)	69.9 (14.7)	75.1 (11.7)	0.00
Gender (F/M)	74/79	41/67	0.09
Karnofsky (mean, SD)	35.1 (7.06)	32.7 (5.9)	0.00
MDAS (mean, SD)	2.52 (2.07)	13.23 (6.02)	0.00
Primary tumor (multivariate comparison ^a)			
Lung	42 (27.3%)	17 (15.7%)	0.14
Breast	8 (5.2%)	4 (3.7%)	
Gynecological	14 (9.1%)	2 (1.8%)	
Gastrointestinal	30 (19.6%)	26 (24.1%)	
Prostate	10 (6.5%)	7 (6.5%)	
Pancreas	17 (11.1%)	14 (13.05%)	
Urological	14 (9.1%)	12 (11.1%)	
Head–neck	4 (2.6%)	10 (9.3%)	
Hematologic disease	8 (5.2%)	8 (5.2%)	
Other	6 (3.9%)	16 (14.8%)	
Setting			
Hospice	115 (75.2%)	62 (57.4%)	0.00
Home care	38 (24.8%)	46 (42.6%)	

*Hotelling T^2 comparison**Table 2** Comparison of ESAS items in patients with and without delirium at T_0

	Without delirium (153 patients)	With delirium (110 patients)	<i>p</i>
Pain (mean (SD))	1.53 (2.25)	1.72 (2.91)	0.56
Weakness	5.78 (2.97)	6.57 (2.83)	0.03
Nausea	0.50 (1.57)	1.04 (2.31)	0.02
Depression	3.44 (3.41)	3.63 (2.99)	0.65
Anxiety	2.99 (3.36)	1.72 (2.95)	0.00
Drowsiness	3.63 (2.94)	4.81 (3.36)	0.00
Dyspnea	2.54 (3.13)	2.03 (2.75)	0.17
Appetite	4.31 (3.37)	5.29 (3.34)	0.02
Well-being	3.86 (2.94)	4.98 (2.80)	0.00
ESAS tot	31.49 (14.03)	27.61 (12.62)	0.01

Table 3 Comparison of ESAS items in patients with and without delirium at T_7

	Without delirium (96 patients)	With delirium (167 patients)	<i>p</i>
Pain (mean (SD))	1.33 (2.25)	0.59 (1.65)	0.01
Weakness	4.23 (3.20)	6.24 (2.81)	0.00
Nausea	0.81 (2.22)	0.70 (1.73)	0.71
Depression	2.81 (3.46)	3.38 (3.45)	0.25
Anxiety	2.85 (3.17)	2.21 (3.14)	0.17
Drowsiness	3.39 (3.33)	3.92 (3.29)	0.28
Dyspnea	2.10 (2.98)	2.24 (2.70)	0.74
Appetite	3.06 (3.35)	4.47 (3.27)	0.02
Well-being	3.25 (2.94)	4.46 (3.47)	0.01
ESAS tot	25.85 (14.79)	26.07 (15.79)	0.53

patients had complete data regarding MDAS measurement, either at T_0 and T_7 . A larger number of patients (n 167, 63.5%) had delirium at T_7 . The characteristics of patients are reported in Table 1. Patients with delirium at T_0 are likely to be older and male, to have a lower Karnofsky level at admission, and to be home care patients.

The values of ESAS items in patients with delirium and without delirium recorded at admission (T_0) are presented in Table 2. Values of weakness, nausea, anxiety, drowsiness, poor appetite and poor well-being are significantly higher in patients with delirium.

In Table 3, the mean intensity of ESAS symptoms recorded at T_7 in patients with and without delirium is

reported. Values of weakness, poor appetite, and poor well-being are significantly higher in patients with delirium, while pain intensity is lower in patients with delirium.

Fourteen patients (5.3%) who had delirium at T_0 , had a MDAS < 7 at T_7 (disappearance of delirium); 71 patients (27%) who had a normal cognitive status at admission developed delirium at T_7 , while 178 patients did not have a change in their status. Of these, 96 patients (36.5%) had delirium both at T_0 and T_7 , and 82 patients (31.2%) did not have delirium both at T_0 and T_7 .

Changes of symptom intensity in patients, according to the passage from a status of delirium and vice versa are presented in Table 4. In patients with delirium, an improvement

Table 4 Variation of ESAS items from *T0* to *T7* in different groups of patients from *T0* to *T7*

	From delirium to no delirium (14 patients)	From no delirium to delirium (71 patients)	Unchanged delirium (178 patients)	Unchanged no delirium	<i>p</i>
Δ Pain (mean [CI])	−0.14 [−1.75; 1.47]	−0.06 [−0.44; 0.32]	−0.68 [−1.33; −0.02]	−0.32 [−0.99; 0.36]	>0.05
Δ Weakness	−2.42 [−4.09; −0.77]	−0.8 [−1.92; 0.32]	0.39 [−0.40; 1.19]	−0.93 [−1.7; −0.15]	0.00
Δ Nausea	0.71 [−0.59; 2.02]	0.46 [−0.17; 1.08]	−0.39 [−1.05; 0.27]	0.46 [0.03; 0.89]	>0.05
Δ Depression	−2.57 [−4.76; −0.38]	1.26 [−0.23; 2.74]	−0.61 [−1.64; 0.42]	−0.44 [−1.13; 0.25]	0.00
Δ Anxiety	−0.43 [−2.15; 1.29]	0.28 [−0.62; 1.20]	0.18 [−0.74; 1.10]	−0.02 [−0.68; 0.64]	>0.05
Δ Drowsiness	−1.28 [−3.14; 0.57]	0.46 [−0.60; 1.51]	0.18 [−0.84; 1.20]	−0.12 [−0.84; 0.60]	>0.05
Δ Dyspnea	0.28 [−2.17; 2.74]	0.28 [−0.30; 0.87]	0.53 [−1.19; 1.27]	−0.51 [−1.22; 0.19]	>0.05
Δ Appetite	−3.14 [−5.94; −0.34]	0.86 [0.30; 1.41]	−0.78 [−1.60; 0.03]	−0.80 [−1.45; −0.16]	0.00
Δ Well-being	−1.57 [−5.94; −0.34]	0.91 [−0.18; 2.01]	−0.32 [−1.09; 0.45]	−0.93 [−1.65; −0.21]	>0.05

in the cognitive status corresponded to a significant improvement of weakness, depression, and appetite (column 1). Conversely, the occurrence of delirium at *T7* in patients who had a normal cognitive status at *T0* significantly increased the level of depression and poor appetite, while the level of weakness decreased (column 2). Changes in weakness, depression, and appetite also occurred in patients who did not change their cognitive status (column 3 and 4).

Discussion

This study shows that a large number of patients admitted to palliative care services have alterations of the cognitive status, particularly when they are older, male, have a lower Karnofsky status, and are being cared for at home. Despite palliative care intervention, the number of patients with delirium, according to the MDAS cut-off commonly employed to make a diagnosis of delirium, increased after 1 week. Patients with delirium reported overall worse symptom burden when compared to those who did not have delirium. After 1 week of palliative care treatment, delirium is significantly associated with weakness, poor appetite, and poor well-being. Unexpectedly, intensity of pain was lower in patients with delirium. This study also shows that a minority of patients present a reversible delirium, while more patients worsen after 1 week of palliative care intervention, although the majority of patients, about 60%, did not have a change in their cognitive status. Finally, an improvement in cognitive status is associated with an improvement of symptom burden such as weakness, depression, and appetite, while patients whose status worsened reported a worsening of depression and appetite. Indeed, changes in weakness, depression, and appetite also occur in patients who do not have a change in their cognitive status.

The interpretation of these data is difficult. For instance, there is a relationship between delirium and expression of a cluster of symptoms, such as weakness, nausea, drowsiness,

lack of appetite, and poor well-being, most of them associated with a short survival. Of interest, delirium is a risk factor for shorter survival [19]. Regrettably, survival in patients admitted to palliative care services in Italy is short, about 30 days, suggesting a late referral to palliative care [20, 21]. On the other hand, many patients were unable to participate in this study, because of severe conditions impeding any simple evaluation. This is consistent with data gathered from previous experiences with the HOCAI study group, in which delirium is the most frequent symptom reported at the end of life requiring palliative sedation [4, 7]. Thus, the findings of this study in very advanced cancer patients may reveal a natural association rather than a consequential relationship between delirium and some symptoms, which concomitantly converge towards the end of life.

Data regarding the influence of delirium on symptom expression in patients admitted to home or hospice care are lacking. There is some information from studies performed in palliative care units, where presumably life expectancy is longer, and reversibility of delirium is more likely, possibly because of a more comprehensive assessment and intensive symptom management. In a study performed in a palliative care unit, delirium could be reduced by optimal adjustment of medication with careful assessment and available therapies, but its persistence in non-responders is associated with an increase in symptom expression. Moreover, patients who develop delirium after admission have a lower rate of delirium reversal and poorer survival [22]. In a retrospective study performed in a palliative care unit, patients who develop delirium during admission report a higher level of depression, anxiety, poor appetite, diminished well-being, and poor sleep. A decrease in delirium is associated with an improvement in reported symptom intensity [14]. In particular, pain is constantly overexpressed, different from what is observed in the present study, in which delirium is not found to be associated with high levels of pain intensity. It is likely that optimization of medications in such units in an early

stage of disease, may allow a more relevant decrease in reported symptom intensity, suggesting that delirium may be an impediment to achieve the goal of symptom control. In patients admitted to home care or hospices, delirium might more frequently be due to the general derangement in the last weeks of life, rather than to reversible causes, for example, opioids used for pain management [4, 7]. Regardless of the low possibility of reversing delirium, cognitive status should be assessed even in lower intensity medical environments, such as hospice or home care. On the other hand, it has been found that even in about 60% of hospital consultations, delirium is missed by the primary referring team [3]. The exact mechanism of symptom overexpression in patients with delirium is not known. The low cholinergic and excess dopaminergic states are common neural pathways in delirium. Other neurotransmitters, including GABA and serotonin, may affect the activity of these pathways. It is likely that the pathophysiology of delirium is associated with a reduced GABA inhibitory activity, which results in a disinhibitory expression of distress [23],

There are some study limitations. This study was performed in an advanced cancer population. Non-cancer patients, who are likely to develop delirium, were not included. There was a lack of a basic cognitive assessment at baseline, for example, with mini-mental state examination. People with mild cognitive impairment could have been able to respond to questions and sign an informed consent at T0, but would have been more prone to delirium compared to cognitive intact subjects. Data concerning relevant clinical issues related to delirium (e.g., drugs, brain lesions, previous treatments such as brain radiotherapy), were not assessed.

Severely ill patients were not included in this study due to the difficulties in assessing them, as shown by the number of patients able to participate (about 30%) from a large cohort. Many patients had serious conditions not allowing a minimal assessment, and it is likely that most of them had high levels of MDAS. This is an inevitable and unresolved problem in such a population, also confirming, regrettably, the late referral to palliative care services in Italy. Another limitation of the study is represented by the lack of standard protocols for the management of delirium. Palliative care treatment was based on individual basis to find the best solution in a specific clinical condition, rather than using a specific protocol in the different palliative care services. This, however, may better reflect the real world of almost all palliative care services available in Italy, being the standard of care available for very advanced cancer patients. Moreover, the intent of this paper was not to evaluate a specific treatment, which would have required a different design. On the other hand, data were prospectively and longitudinally collected with two time points, at admission and after a palliative care

intervention, using an interval which is meaningfully considered a sufficient time for having a clinical response.

Conclusion

The study shows that a large number of patients, who are able to communicate, admitted to palliative care services, present with delirium. Despite a palliative care intervention, the number of patients with alterations in cognitive status increases after 1 week. Delirium is associated with an increase in intensity of a cluster of symptoms that are typically associated with a short survival. Indeed, in the few patients who do not have delirium at admission and after a palliative intervention, symptom improvement is better. Screening for delirium in advanced cancer patients with severe symptom intensity is highly recommended in palliative care settings including hospice and home care.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statements on human and animal rights Ethical approval was obtained by local Institutional Review Board at each site.

Informed consent Informed consent was obtained from all patients.

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