

Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care

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Delirium is a common problem and cause of distress among patients with palliative care needs. The focus to date has been on managing the patient with agitated, hyperactive delirium, as these patients are very noticeable within the palliative care setting. This study in two parts shows that palliative care patients with agitated delirium are a minority of the total proportion of those with delirium. Part I: 100 acute admissions to a specialist palliative care unit were assessed and while 29% were found to have delirium, 86% of these had the hypoactive subtype of delirium. We also demonstrated a positive correlation between high ratings on a depression screening tool and delirium severity ratings. Part II: 8 specialist palliative care units took part in a point prevalence study of delirium over a 48-hour period. One hundred and nine patients were assessed and while 29.4% of these inpatients had delirium, 78% of them had the hypoactive subtype. Patients with hypoactive delirium may be much less noticeable or may be misdiagnosed as having depression or fatigue and the results of this study would advocate the routine use of delirium screening tools in all palliative care settings. *Palliative Medicine* 2006; **20**: 17–23

Key words: Delirium; depression; fatigue; hypoactive; palliative; screening

Introduction

Delirium or acute confusional state remains one of the most common neuropsychiatric problems among patients with end-stage disease^{1–3} and, as such, is a major source of distress for patients and their lay and professional carers. It can have a profound negative impact on both the length and quality of a palliative care patient's remaining time. Delirium can be terrifying for both the patient and their family⁴ and can also have an adverse effect on other patients in an inpatient setting. Patients with delirium are unable to make decisions about important aspects of their care and management. Delirium disrupts the therapeutic relationship between the patient and healthcare professional and also interferes dramatically with the identification and control of other physical and psychological symptoms.⁵ In the palliative care setting, where time is so precious, delirium is a tragic waste of time.

Delirium is characterized by a global disturbance in cerebral function affecting consciousness, attention, cognition and perception with a course that may fluctuate over a period of hours.^{6,7} Any individual palliative care patient may have numerous risk factors

for delirium (drugs, infection, metabolic imbalances, hypoxia, constipation, dementia, comorbidity, poor mobility, advanced disease etc).² There is some general consensus on how to treat patients with agitated or hyperactive delirium^{8,9} but the management of patients with hypoactive delirium has received much less attention.^{10,11} There is little recognition in generalist or specialist palliative care that the prevalence of delirium among palliative care patients is much higher than is generally perceived, partly because the majority of these patients present with a hypoactive subtype symptom profile which is much less likely to be diagnosed.⁸ While agitated patients attract medical and nursing attention with their distressing and disruptive behaviour, the symptoms of hypoactive delirium are easy to miss but may cause just as much distress for the patient and their family. Patients with hypoactive/hypoalert delirium have slowed psychomotor function, lethargy, confusion, sedation, reduced awareness of, and interaction with, their surroundings, and impaired ability to sustain attention.⁸ Mild symptoms may appear to casual observation as low mood or fatigue and unless these patients are formally screened for cognitive impairment their delirium may be misdiagnosed or missed altogether.¹² There are very few studies that have highlighted this aspect of delirium and as a result the general lack of awareness of hypoactive delirium is a major factor in the misdiagnosis and mistreatment of this common condition.¹³

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Objectives

This two-part study had five objectives:

1. Establish the prevalence of delirium among all admissions to a hospice inpatient unit and how that changes over a subsequent 7-day period.
2. Establish the point prevalence of delirium in existing inpatients of eight specialist palliative care units.
3. Clarify to what extent the hypoactive subtype of delirium contributes to the overall prevalence of the condition.
4. Show whether screening for delirium is practicable and acceptable for this patient population.
5. Assess the relationship between the diagnosis and severity of delirium and symptoms of fatigue and low mood.

Part I. Prevalence in acute admissions

Methods

Patient population. This prospective survey was conducted in the inpatient unit of St Columba's Hospice in Edinburgh. This unit takes referrals from local hospitals (including a major cancer centre) and from the local community through general practitioners and its own community specialist nursing service. Patients with end-stage disease are admitted for symptom control, rehabilitation, respite and terminal care. All consecutive admissions to the hospice were eligible for inclusion in the survey unless their Glasgow Coma Score (GCS) was less than 3. The assessments were continued until 100 patients had taken part in the survey. This number was a significant proportion and therefore representation of the annual admissions for that unit.

Verbal consent was obtained from patients where possible and from family or carers where the patient was unable to give consent. We were advised by a member of the local ethics committees that an application for formal ethical approval was not required as it was felt that the patient assessments did not deviate significantly from usual clinical practice and because there was no risk of harm to patients involved in the survey. It is recognized that, while this was the advice at the time, today's criteria for ethical approval would require a formal application to be made as simply asking patients to complete questionnaires that were not a standard part of the admission clerking is sufficient grounds for requiring formal ethical approval.

Data were analysed with appropriate statistical tests (ie, the *t*-test, the Fischer test, Wilcoxon, Spearman etc) using the Statistical Package for Social Science.

Assessments. Patient details and demographics were taken from the medical and nursing notes including age, sex, diagnosis, performance status (using the WHO performance scale) and where they had been admitted from (home or hospital). The presence or absence of cerebral pathology was noted from the medical history as was a history of pre-existing dementia, psychiatric disorder and whether a diagnosis of opioid toxicity (sedation, myoclonic jerks, hallucinations etc.) had been recorded in the patient's notes. A clinical diagnosis of infection and/or dehydration was also noted from the patient's medical records. The assessment was carried out approximately 24 hours after admission to allow time for the nurses and medical staff to observe the patient's level of function and interaction. This enabled the recognized features of delirium such as delusional ideas, hypo/hyperactivity, disturbance of the sleep-wake cycle, hallucinations, agitation or aggressive behaviour to emerge and be noted. The assessment was repeated 7 days after the initial assessment providing the patient was still an inpatient.

Confusion Assessment Method. The Confusion Assessment Method (CAM) is a set of nine operationalized criteria from the DSM-III-R that can be administered quickly by non-psychiatrists to diagnose delirium.¹⁴ It is sensitive, specific and has excellent inter-rater reliability. It also has a four-item algorithm, which was included in the survey assessment and has been validated in the palliative care population.³

Memorial Delirium Assessment Scale. The Memorial Delirium Assessment Scale (MDAS) is a ten-item measure of delirium severity (total score range is 0–30) that has been validated in advanced cancer and in AIDS patients.¹⁵ Although it is a measure of delirium severity and can be used to assess change in severity over time, it has not been validated as a diagnostic instrument. It is however helpful in allowing the discrimination of the two different subtypes of delirium in patients who have been diagnosed with delirium using the CAM.

Mini Mental State Examination. The Mini Mental State Examination (MMSE) has become one of the most frequently used tests in the evaluation of cognitive impairment and is commonly quoted as the gold standard against which other instruments are tested.¹⁶ A score of 23 or less is considered as the cut-off for cognitive impairment, however the MMSE makes no distinction between delirium and dementia as the basis for the cognitive impairment and is therefore not a diagnostic tool for delirium.

Fatigue Severity Scale. An assessment tool for fatigue was included to clarify whether subjective fatigue had any

correlation with the diagnosis or severity of hypoactive delirium. The Fatigue Severity Scale (FSS) was designed for use in the medically ill¹⁷ and has been validated in advanced cancer populations.^{18,19} The scale consists of nine statements and patients are asked to rate their agreement or disagreement on a seven-point Visual Analogue Scale.

Hospital Anxiety and Depression Scale. It is not possible to make the diagnosis of depression in patients with delirium. However, the affective features of hyperactive or hypoactive delirium may mimic anxiety or depression and therefore the Hospital Anxiety and Depression Scale (HADS) was included in the assessment.²⁰ The HADS was specifically designed for use in medically ill patients and, although it cannot be used to accurately diagnose depression in palliative care patients, it has been validated as one of the useful screening tools in this population.²¹ The scale comprises 14 questions each scoring 0–3 points and can easily be scored by non-psychiatric staff.

Results

There were 113 admissions to the inpatient unit during the assessment period and 100 of these were included in the survey. The reasons for exclusion are documented in Table 1.

Of these 100 patients 51 were female and 49 were male and the mean (\pm SD) age was 68.7 (\pm 15) years. Seventy-three patients were admitted to the unit from home and 37 were transferred from local hospitals. All patients were suffering from advanced malignancy apart from one who had end-stage cardiac failure and cerebrovascular disease. In terms of performance status (PS) on admission, 12 of the 100 patients were PS4, 49 were PS3, 33 were PS2 and 6 were PS1.

Out of 100 patients admitted to the inpatient unit, 29 were found to have delirium on admission and of these 25 had hypoactive delirium, with four patients having the mixed subtype and none having pure hyperactive or agitated delirium (see Table 2).

After seven days 73 patients were reassessed and the remaining 27 patients were excluded for reasons detailed

Table 1 Reasons for exclusion from study (total admissions 113)

Reasons for exclusion	
Included in survey $n=100$	Reassessed after 7 days $n=73$
GCS ^a <3 ($n=4$)	GCS <3 ($n=3$)
Died within 24 h ($n=4$)	Died ($n=12$)
Refused ($n=4$)	Discharged ($n=11$)
Missed ($n=1$)	Transferred to hospital ($n=1$)

^aGCS, Glasgow Coma Scale.

Table 2 Delirium prevalence

	Baseline ($n=100$)	1 week ($n=73$)
CAM ^a delirium diagnosis	29	19 (26%)
Subtype		
Hypoactive	25	13 (18%)
Hyperactive	0	4 (5%)
Mixed	4	2 (3%)

^aCAM, Confusion Assessment Method.

in Table 1. Out of the 73 patients who were reassessed after seven days of inpatient care, 19 (26%) had delirium. The subtype prevalence is detailed in Table 2 and Table 3 shows the details of what happened to patients with and without delirium over the first week of admission. There were five new cases of delirium after one week (three had hypoactive delirium and two had the mixed subtype) and of those who had delirium on admission only four (14%) had no evidence of delirium after one week. All of the patients who were found to have the hyperactive subtype of delirium after one week ($n=4$) had a diagnosis of delirium on admission (three had hypoactive delirium and one had a mixed subtype).

In the CAM –ve patients ($n=71$) the median MMSE score was 26 (interquartile range (IQR) = 4). Seventeen of the CAM –ve patients (23.9%) scored less than 24 on the MMSE. For the CAM +ve patients ($n=29$) the median MMSE score was 15 (IQR = 19) and 24 of these patients (89.7%) scored less than 24 on the MMSE.

Spearman's test was used to establish relationships between the MDAS (measuring delirium severity) and the other assessment scales used. The correlation coefficient is the Spearman's rho and the 95% confidence interval (CI) is given. The MDAS was found to have a significant correlation with the MMSE ($p < 0.001$; Spearman's rho = -0.786 ; 95% CI = $-0.697, -0.851$), the total HAD score ($P=0.009$; Spearman's rho = 0.285 ; 95% CI = $0.073, 0.472$) and the depression subscale of the HAD ($P=0.005$; Spearman's rho = 0.309 ; 95% CI = $0.100, 0.492$). There was no correlation with the anxiety subscale of the HAD ($P=0.068$; Spearman's rho = 0.201 ; 95% CI = $-0.015, 0.399$) or the FSS ($P=0.099$; Spearman's rho = 0.187 ; 95% CI = $-0.036, 0.392$).

Table 3 Outcome after one week

	Initial delirium diagnosis +ve ($n=29$)	Initial delirium diagnosis –ve ($n=71$)
Delirium	48% (14)	7% (5)
Normal	14% (4)	72% (51)
Died	31% (9)	4% (3)
Discharged	3.5% (1)	14% (10)
GCS <3 ^a	3.5% (1)	3% (2)

^aGCS, Glasgow Coma Scale.

Fisher's exact test was used to assess the relationship between delirium (CAM +ve) and other variables. A diagnosis of delirium was shown to be significantly related to a performance status of 3 or 4 ($P < 0.001$), cerebral disease ($P = 0.003$), infection ($P = 0.017$), dehydration ($P = 0.0009$) and opioid toxicity ($P = 0.001$). No relationship was identified between a positive diagnosis of delirium and psychiatric history, hypoxia, constipation or drugs other than opioids.

Logistic regression showed that the best predictive model of CAM positive comprised cerebral disease and a clinical diagnosis of opioid toxicity. Cerebral disease and infection were independent of the other predictor variables. Performance status of 3 or 4, dehydration and opioid toxicity were all associated with one another and to avoid problems of multicollinearity only one of them was selected for the model. Of these three variables, opioid toxicity was the strongest predictor when combined with cerebral disease and infection. When opioid toxicity, cerebral disease and infection were combined, infection was no longer a significant predictor. This left cerebral disease and opioid toxicity to form the equation predicting the log odds of CAM positive (log odds of CAM positive = $-2.435 + 2.457$ cerebral disease + 3.073 opioid toxicity). This provided an odds ratio for cerebral disease of 11.66 ($P < 0.001$; 95% CI = 3.11, 43.69) and for opioid toxicity of 21.61 ($P < 0.001$; 95% CI 6.00, 77.78). Therefore, cerebral disease increases the probability of a patient being CAM positive by a factor of 11.66, while opioid toxicity increases the probability of being CAM positive by a factor of 21.61. There were insufficient numbers in each cell to explore any interaction effects.

Part II. Point prevalence in existing inpatients

Methods

Patient population. This point prevalence survey took place simultaneously in eight Specialist Palliative Care Inpatient Units in Central and East Scotland. These units comprised six hospices, one hospice ward within a district general hospital and one palliative care service within a district general hospital. All inpatients during the same 48-hour period in each of these units were eligible for inclusion provided that:

1. Their conscious level was such that their GCS was greater than or equal to 3.
2. They had been admitted at least 24 hours prior to assessment.
3. Verbal consent was obtained from the patients where possible. When the patient was unable to give consent this was sought from the family or carers. Each of the Local Ethics Committees was approached but we were advised that formal ethical approval was not required for the same reasons as quoted above.

Assessments. Each site was visited by the study investigator (JS) to train one or two members of staff on the use of the screening tools. The assessments were then carried out over the same 48-hour period in all sites.

Patient demographics were taken from medical and nursing notes including age, diagnosis, performance status (using the WHO performance scale), date of admission and where patients had been admitted from (home or hospital). Information was also recorded regarding cerebral disease, psychiatric history and possible delirium risk factors such as the presence of infection, hypoxia, constipation, dehydration, hypercalcaemia, opioid toxicity or other metabolic or drug abnormalities.

A general measure of cognitive function was carried out (MMSE) followed by a diagnostic tool for delirium (CAM) and a measure of delirium severity and subtype (MDAS).

Results

There were a total of 126 inpatients in all of the units during the 48-hour period of assessment. One hundred and nine patients (87%) were included in the survey and reasons for exclusion were detailed as follows: GCS <3, $n = 8$; refused, $n = 3$; communication difficulties, $n = 2$; barely responsive, $n = 2$; condition very poor, $n = 1$; and out of the hospice, $n = 1$. Table 4 shows the demographic details of the patients included in the survey subdivided by individual palliative care unit. Thirty-two patients (29.4%) were found to have a diagnosis of delirium (CAM +ve) (Table 5). Of these patients with delirium 25 (78%) were shown to have the hypoactive subtype, while only two (6%) had a hyperactive subtype and five (16%) showed a mixed picture.

Table 4 Demographic details

	Specialist palliative care inpatient units							
	1	2	3	4	5	6	7	8
Number of patients (n)	20	27	7	12	7	5	17	14
Mean age (years)	65.6	66.6	63.9	65.9	63.7	75	65.8	82.8
Mean length of stay (days)	13.8	39.5	19.6	7.0	20.7	20.8	17.8	26.8
Mean perf. status (0–4)	2.8	2.8	3.8	3.3	2.6	1.6	2.5	3.4
Delirium diagnosed (n)	7 (35%)	8 (30%)	3 (43%)	3 (25%)	1 (14%)	1 (20%)	5 (29%)	4 (29%)

Table 5 Delirium prevalence and subtype

	Total patients (<i>n</i> = 109)	Proportion of total patients	Proportion of CAM +ve patients
CAM +ve (delirium diagnosed)	32	29.4%	100%
Subtype			
Hypoactive	25	23%	78%
Hyperactive	2	1.8%	6%
Mixed	5	4.6%	16%

Using Fisher's exact test the relationship between delirium (CAM +ve) and other variables was analysed. A diagnosis of delirium was shown to be significantly related to opioid toxicity ($P=0.001$), constipation ($P=0.008$) and dehydration ($P=0.014$).

Discussion

The finding that 29% of acute admissions and 29.4% of existing inpatients of SPCUs had delirium is in line with the experience of the limited number of studies that have investigated this symptom in palliative medicine.²²⁻²⁴ The fact that 86% ($n=25$) of the acute admissions with delirium and 78% of the existing inpatients with delirium showed symptoms of the hypoactive subtype is of great clinical importance. This finding may explain why delirium so often goes unnoticed and undiagnosed in the palliative care setting as these patients' symptoms may superficially appear as simply being withdrawn or having low mood or fatigue.

Previous studies have suggested a link between fatigue and delirium²⁵ and in view of the prevalence of hypoactive delirium it is perhaps surprising that there was no significant correlation between the MDAS and the FSS. The investigators felt that this was more of a reflection of the fact that many patients seemed to have difficulty using the scale and found the wording of some of the questions hard to comprehend.

Depression cannot be diagnosed where delirium is present. Although the HADS ratings were not valid as indicators of depression in the patients who had delirium, the correlation of the MDAS severity rating scale for delirium with the depression subscale of the HADS is an important finding. It confirms that the symptoms of delirium may mimic those of depression and therefore patients who score highly on screening tests for depression may in fact have hypoactive delirium. This has very important clinical and research implications in the palliative care setting as it suggests that any assessment of depression must include an assessment for delirium. Research studies looking at depression in palliative care patients must also include a diagnostic tool for delirium to avoid misclassification.

The authors acknowledge the methodological limitations of these studies in that using the CAM-operationalized criteria to diagnose delirium mean that there will inevitably be patients with acutely impaired cognition who do not meet the CAM criteria for diagnosis (subsyndromic delirium) and will therefore go undetected. It is also acknowledged that a medical history of dementia or psychiatric illness will not comprehensively detect those patients with pre-existing chronic background cognitive impairment that has not yet been recognized or diagnosed.

Management of delirium should include consideration of potentially reversible causes⁹ and this study highlighted opioid toxicity, infections, dehydration and constipation as factors that correlated with a diagnosis of delirium in the palliative care inpatient population. The treatable nature of these factors further emphasizes the need for early detection of delirium so that attempts can be made to reverse the underlying causes.

Drug treatment of the delirium itself usually focuses on use of neuroleptic medication such as haloperidol,²⁶ the more sedative levomepromazine or one of the newer neuroleptics such as risperidone or olanzapine.^{6,8,27} However one study has suggested that hypoactive delirium predicts a poor response to olanzapine.²⁸ Adjuvant anxiolytics can also be symptomatically helpful⁶ but use of benzodiazepines alone should be avoided in the management of delirium (unless related to alcohol withdrawal) as they can paradoxically worsen the confusion.^{8,26,29} There has been very little research into the best treatment of hypoactive delirium perhaps because previously there has been little recognition of the fact that it is the most common subtype of delirium in palliative care patients. It is easy to justify the use of neuroleptics and sedative agents where patients are agitated, distressed and disruptive but patients with hypoactive delirium may simply be slow or sleepy and not appear to be outwardly distressed. The use of neuroleptics to treat their delirium is less clear-cut in this situation. There have been case reports suggesting that psychostimulants such as methylphenidate may reverse hypoactive delirium^{10,11,30} but larger studies are needed before this can be advocated for routine use.

Conclusion

These results further the cause for advocates of screening in the debate over whether patients with end-stage disease should or can be routinely screened for delirium. We have confirmed that delirium is a significant contributing factor in the morbidity of patients in inpatient specialist palliative care. We have also shown that these patients mainly exhibit features of the hypoactive subtype of delirium and are therefore very likely to be missed or misdiagnosed as depressed or fatigued in the absence of a formal cognitive assessment. These findings also emphasize the importance of having a cognitive assessment as part of any research study looking at depression in palliative care patients. Moreover we have shown that it is possible to use screening tools for delirium very successfully in this patient population.

Acknowledgements

With special thanks to Denis Martin, Dr Diana Wilson, Dr Alison Gordon, Dr Fred Benton and all of the medical staff, nursing staff and patients of St Columba's Hospice, Edinburgh; Marie Curie Hospice, Edinburgh; Ward 16, Queen Margaret Hospital, Dunfermline; Victoria Hospice, Kirkcaldy; Macmillan Palliative Care Team, Borders General Hospital; Roxburghe House, Aberdeen; St Andrews Hospice, Airdrie; Strathcarron Hospice, Stirlingshire.

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