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Etiologies of Delirium and Their Relationship to Reversibility and Motor Subtype in Cancer Patients

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Background: Delirium is one of the most commonly encountered complications in patients with cancer. The etiology of delirium in cancer is often multi-factorial, and few reports have examined the causes of delirium. This study investigated the causes of delirium and their association with reversibility and motor subtypes of delirium in cancer patients.
Methods: The subjects were inpatients with cancer who had been referred to our Department of Psychiatry and diagnosed with delirium by psychiatrists. The causes of delirium were determined using standard operationalized criteria. The association between delirium reversibility and each clinical factor was examined in detail and longitudinally.
Results: Data were available from a total of 100 patients. Among them, 58% had hyperactive delirium and 14% had hypoactive delirium. Delirium improved in 56% of the patients after 1 week of standard treatment. The most frequent causes of delirium were opioids (29%), inflammation (27%), dehydration and/or sodium level abnormalities (15%). While two or more causes were identified in 40% or more of the cases, the cause of delirium was not identified in 20% of the patients. Neither reversibility nor motor subtypes of delirium was associated with any specific etiological factor.
Conclusions: When treating delirium, prevalences of the causes of delirium, as identified in this study, should be kept in mind. Further research is required to investigate what specific treatments may facilitate the prompt recovery from delirium among cancer patients.

Key words: delirium – etiologies – cancer – general ward – reversibility – consultation-liaison

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INTRODUCTION

Delirium is an acute and transient disturbance of cortical functioning that manifests as deficits in cognition, attention, consciousness and recent memory. Presenting symptoms and signs usually include insomnia with a disturbance or reversal of the sleep/awake cycle, psychomotor agitation or retardation and sometimes perceptual abnormalities such as illusions or hallucinations.

Delirium is one of the most commonly encountered complications in patients with cancer. It occurs in 25–40% of hospitalized patients and may be seen in up to 80% of patients in the terminal stage of their disease (1–6). Patients with delirium tend to require longer hospital stays and have higher mortality rates (2,7,8). In patients with cancer, delirium imposes an additional burden, as the consequent deficits in awareness and attention impede communication with their families and hinder participation in treatment decisions, counseling and symptom assessment (9–11).

One of the most important strategies for the management of delirium is the early identification of the potential cause of delirium and subsequent treatment. However, the causes of delirium are various, and their clinical identification is difficult. Very few studies have investigated the causes of delirium among cancer patients. In addition, to the best of our knowledge, few studies have examined the relation between the causes of delirium and reversibility. Lawlor et al. (2) investigated the cause of delirium among advanced cancer patients who had been admitted to an acute palliative care unit. They reported that the most common cause of delirium was opioids (76%) and psychoactive medications (21%). Furthermore, opioids and dehydration were associated with delirium reversibility, whereas hypoxic encephalopathy and metabolic factors were associated with the non-reversibility of

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delirium. Morita et al. (4) also investigated the pathologies and clinical features of terminal cancer patients with delirium who had been admitted to hospice care. They identified metabolic failure (e.g. hepatic failure, prerenal azotemia and hyperosomolality: 29%, 21% and 21%, respectively) and medication (25%) as the most common causes of delirium in this population. Furthermore, they suggested that delirium caused by medication and hypercalcemia is more likely to improve significantly with treatment. In addition, Gaudreau et al. (12,13) reported in a prospective cohort study that opioid exposure significantly increased the risk of delirium (odds ratio of 1.7) in hospitalized cancer patients.

In clinical oncology settings, the management of patients with delirium is often done through psychiatric consultation at the general wards. However, no studies have investigated the causes of delirium in psychiatric consultation settings. Because these previous studies described above were conducted in palliative care settings, the generalizability of their findings may be limited. For example, the active treatment is scarcely done there. In addition, the method used to identify the etiology of delirium was not clear, and operational diagnostic criteria such as the DSM were not applied in one study (14).

The clinical manifestations of delirium vary widely but may be classified as hyperactive, hypoactive or mixed subtypes, depending on the symptomatology, especially the level of psychomotor activity and alertness. Hyperactive patients are agitated, restless and very distracted, and they respond to stimuli with discrimination. These patients may even be physically combative. Hypoactive patients are quiet, inactive and lethargic, with an overall reduction in their responses to stimuli (15–18). Several studies have suggested that hyperactive, hypoactive and mixed delirium subgroups may differ according to etiology, pathophysiology, detection rates, delirium treatment experience and duration of episodes and outcome (19–22). As far as we know, few studies have addressed the association between the cause of delirium and the clinical subtype in cancer patients.

The purposes of this study were to determine the precipitating etiologic factors of delirium and the reversibility of delirium originating from each different cause in a psychiatric consultation setting. We also investigated the association between each precipitating factor and the clinical subtypes.

PATIENTS AND METHODS

Study Population

This study was conducted at Nagoya City University Hospital, an 808-bed teaching and tertiary care facility of the Nagoya City University Medical School in Aichi, Japan. The subjects included in this study were consecutive adult cancer patients who were referred to the Department of Psychiatry in a consultation-liaison setting between August 2005 and December 2007. All the patients had been hospitalized in general medical wards other than the psychiatric or pediatric wards.

The eligibility criteria were an age of 18 years or over, a confirmed diagnosis of cancer and fulfillment of the criteria for delirium according to the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) (23) as determined by a trained psychiatrist. The exclusion criteria were a post-operative period of within a fortnight, recent withdrawal from a respirator, underlying obvious dementia and the presence of intracranial disease such as brain metastasis or a cerebral vascular accident. Because this study aimed to examine the relationship between the cause of delirium and the responsiveness to treatment, cases whose delirium was thought to be associated with the above-mentioned exclusion criteria were excluded.

Since this research was performed using data collected during routine clinical practice, informed consent and Institutional Review Board approval were not obtained.

Procedure

First, we evaluated the global condition of patients, the severity and motor subtypes of delirium and its precipitating factors at baseline (when the delirium was first diagnosed). At the same time, we also asked patients' physicians, nurses or caregivers about the overall physical functioning of the patients to evaluate patients' performance status. A structured evaluation was performed, and we evaluated the time–dosage relation between delirium and factors at the time of delirium deterioration. These evaluations were performed by two trained psychiatrists (R.S. and T.O.) Then, standard therapy for delirium (24) was performed. Two main approaches were utilized: symptomatic therapy using antipsychotics such as haloperidol or risperidone (25–31), and reporting the potential cause of delirium to the attending physician and requesting medical treatment, if possible. A follow-up investigation was conducted 1 week later, at which time the severity of the delirium and delirium-related factors were evaluated.

Precipitating Factors and Criteria for Cause Identification

To investigate the biological precipitating factors for the development of delirium, we utilized an *a priori* list of precipitating factors developed using literature references and examined all the listed items using a data entry sheet that we developed.

Each potential precipitating factor for delirium was assessed with regard to the following three criteria (2,7,32). Criterion 1 was the evidence of its presence based on specific clinical and laboratory data. Criterion 2 was a temporal association with the course of delirium consistent with a precipitating factor. Criterion 3 was the improvement of delirium or its non-improvement corresponding to evidence of amelioration or continuation, respectively, of the precipitating factor. When the factor met all three criteria, it was judged to be the most probable precipitating factor of

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delirium and was defined as the 'cause' of delirium in this study. When only criteria 1 and 2 were recognized, that is, when delirium with a possible precipitating factor was encountered, the cause of the delirium was qualified as a 'possible factor'.

The following potential precipitating factors and their definitions were utilized in this study.

Psychoactive Medications and Other Drugs (e.g. Opioids, Benzodiazepines, Steroids, Anti-Cholinergic Agents, H2-blockers and Antiepileptic Agents)

Patients received a new psychoactive medication or an increased dosage of a medication known to cause delirium. The use of opioids, benzodiazepines and steroids was examined in each patient, since these drugs are frequently utilized.

Dehydration or Sodium Level Abnormality

A creatinine level higher than 1.3 or a urea nitrogen level of >20 mg/dL in the absence of bleeding into the gastrointestinal tract with hydration. Sodium levels of >150 mmol/L and <130 mmol/L were defined as hypernatremia and hyponatoremia, respectively.

Structural Brain Lesion

Evidence of CNS problems detected during the episode of delirium was obtained by checking for the occurrence of stroke or the presence of brain tumors, although patients with delirium superimposed on obvious dementia or confirmed intracranial lesions had been excluded from the study.

Alcohol or Other Substance Abuse

Withdrawal from alcohol or other drugs is a known cause of delirium, producing clinical evidence of autonomic hyperreactivity or seizure within 7 days of withdrawal.

Hypoxia

Oximetry levels of $<90\%$ while receiving room air or requiring an oxygen flow of at least 2 L/min to maintain oxygen saturation levels of at least 90% were regarded as evidence of hypoxic encephalopathy.

Metabolic Factors Like Liver or Renal Failure, Hypoglycemia

The following laboratory reference values were used for specific metabolic factors: aspartate aminotransferase levels of >40 U/L, alanine aminotransferase levels of >50 U/L, bilirubin levels of >1.1 mg/dL (hepatic impairment), a persistent creatinine level of >1.7 mg/dL (renal insufficiency) and a glucose level of <72 mg/dL (hypoglycemia).

Hypercalcemia

Hypercalcemia was recorded if the calcium levels (corrected for the albumin level) were >10.4 mg/dL.

Anemia

A hemoglobin level of <10 g/L was regarded as indicating anemia.

Clotting Abnormality

Laboratory evidence consisting of low platelet levels, prolonged prothrombin and partial thromboplastin times, and D-dimer levels of >0.5 mg/L.

Inflammation

Laboratory evidence consisting of a high white blood cell count or an elevated C-reactive protein level >0.4 mg/dL.

Reversibility of Delirium

Patient response to treatment for delirium was assessed using the DELIRIUM RATING SCALE REVISED 98 (DRS-R-98) (33) 1 week after the baseline assessment. The DRS-R-98 is a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items. The severity scale has a possible range of 0–39 and the diagnostic scale has a range of 0–7. Although the DRS-R-98 is more suitable for diagnostic aims, the quantification of symptom severity using this scale is widely accepted in clinical settings. Using a DRS-R-98 severity score of 15/16 points as the cutoff for distinguishing delirium from other psychiatric disorders, a sensitivity of 92% and a specificity of 93% were obtained. According to this cutoff, a 'reversible case' was defined as a patient whose severity score had dropped to 15 or less at the time of the follow-up examination.

Motor Subtypes of Delirium

The motor subtypes of delirium (15–18) were evaluated using available data from clinical interviews, a review of the case records and information obtained from the medical staff. Clinical information used to determine the subtypes was gathered with regard to the mental status of the patient over several days and nights. The clinical subtypes were evaluated using the phenomenological subtypes initially described by Liptzin and Levkoff in 1992 (34). Using this standard, patients were classified as 'hyperactive' subtype if they had 3 or more of 16 items (such as hypervigilance, restlessness), patients were classified as 'hypoactive' subtype if they had 4 or more of 7 items (such as unawareness, decreased alertness) and patients were classified as 'mixed' subtype if they met the criteria for both hyperactive and hypoactive subtypes.

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Statistical Analysis

When investigating the relation between cause and reversibility, we regarded the existence of each 'possible factor' as an independent variable and the reversibility of delirium as the dependent variable. We could not take 'cause of delirium' as independent variable in this analysis because its definition included judgment of reversibility (see the criteria used to identify the cause of delirium). When investigating the relation between the cause and the motor subtypes, we regarded the existence of each investigated factor as an independent variable and the subtype of delirium as the dependent variable. Patients with mixed-type delirium were excluded from these analyses to compare the two distinct delirium conditions.

In both analyses, the association between each possible independent and dependent factor was tested using an appropriate univariate analysis to determine the potential factors. Associated factors ($P < 0.10$) were retained. Then, we used a multivariate analysis to investigate these factors. Similarly, a univariate analysis was conducted using demographic data, such as age, sex, stage of cancer (we divided it into I–III and IV or recurrence, and treated it as category data) and performance status (PS) (we divided it into 0–2 and 3–4, and treated it as category data), and significant variables ($P < 0.1$) were entered into a stepwise multivariate logistic regression analysis to adjust potential confounding factors. A χ^2 test or Fisher exact test was used for the univariate analysis of categorical data. The relation between the number of causes and the reversibility of delirium was analyzed using a Mann–Whitney *U*-test. A Kaplan–Meier analysis was used to calculate the survival period from the beginning of psychiatric consultation until death. A two-tailed *P* value of <0.05 was regarded as significant in all of the statistical analyses. The statistical analysis was conducted using the SPSS ver.11.5 Japanese version for Windows.

RESULTS

Patient Characteristics

Among the 112 delirious patients who met the inclusion criteria, 12 patients were excluded from the analysis (10 cases died soon after entry and 2 moved within 1 week of entry). The characteristics of the remaining 100 patients are summarized in Table 1. The mean patient age was 68 years (SD = 12 years), and 69% of the patients were male. About three-quarters of the patients had metastatic or recurrent cancer. More than three-quarters of the subjects had serious physical impairments (PS = 3–4). The median survival time after the diagnosis of delirium was 39 days (inter-quartile range = 124 days). Fifty-eight percent, 26% and 14% of the patients had hyperactive, mixed and hypoactive delirium subtypes, respectively.

Table 1. Demographic data ($N = 100$)

	N	%
Age (years)	Mean 68 (SD = 12), median 70	
Male	69	69
Clinical stage		
I	3	3
II	1	1
III	8	8
IV (metastasis)	48	48
Recurrence	27	27
Other	13	13
Performance status (ECOG)		
1	7	7
2	15	15
3	46	46
4	32	32
Primary cancer site		
Lung	24	24
Esophagus	15	15
Malignant lymphoma	10	10
Stomach	9	9
Colon	8	8
Survival time (days)	Median 39 (IQR = 124)	
DRS-R-98 severity score (points)	Mean 20 (SD = 6)	
Subtype of delirium		
Hyperactive delirium	58	58
Hypoactive delirium	14	14
Mixed type delirium	26	26
Others (unspecified)	2	2

DRS-R-98, Delirium Rating Scale-Revised-98; ECOG, Eastern Cooperative Oncology Group; IQR, inter-quartile range; SD, standard deviation.

Prevalence of Precipitating Factors

The most common cause of delirium was opioids (29%) (Table 2). The use of benzodiazepines and steroids was also identified in 14% and 9% of the subjects, respectively, and the use of psychoactive drugs accounted for ~50% of all causes of delirium. Inflammation reaction, dehydration and sodium abnormality, and metabolism abnormality were recognized in 27%, 15% and 15% of the cases, respectively. Hypercalcemia, anemia, hypoxemia and a clotting abnormality were also observed in <10% of the patients.

Association between the Reversibility of Delirium and the Presence of Each Precipitating Factor

The delirium of 56 patients (56%) who underwent standard treatment improved within 1 week after the baseline examination (Table 2). Delirium caused by opioids was significantly

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Table 2. Causes of delirium and reversibility ($N = 100$)

Precipitating factors	Identified cause		Including possible factors[a]		Reversed ($N = 56$)		Non-reversed ($N = 44$)		OR (95% CI)	*P* value
	N	%	*N*	%	*N*	%	*N*	%		
Opioids	29	29	36	36	15	27	21	48	2.5 (1.1–5.3)	0.03
Inflammation	27	27	43	43	29	36	23	52	2.0 (0.9–4.4)	0.10
Dehydration and sodium abnormality	15	15	24	24	12	21	12	27	1.4 (0.55–3.5)	0.50
Metabolism abnormality	15	15	22	23	9	16	13	30	2.2 (0.84–5.7)	0.10
Benzodiazepines	14	14	19	19	11	20	8	18	0.90 (0.33–2.5)	0.85
Steroids	9	9	14	14	8	14	6	14	0.95 (0.30–3.0)	0.93
Hypercalcemia	8	8	13	13	7	13	6	14	1.1 (.34–3.6)	0.87
Anemia	7	7	15	15	6	11	9	21	2.1 (0.70–6.6)	0.18
Hypoxemia	6	6	8	8	3	5	5	11	2.3 (0.51–10)	0.30
Clotting abnormality	6	6	10	10	3	5	7	16	3.3 (0.81–14)	0.10
No cause apparent	20	20	—	—	17	30	3	15	0.17 (0.05–0.62)	0.005

[a]Divided into two groups of reversible and non-reversible and then analyzed by independent variable 'possible factors'.
OR, odds ratio; 95% CI, 95% confidence interval.

Table 3. Number of precipitating factors and reversibility ($N = 100$)

Number of causes	All cases		Reversed ($P < 0.001$)[a] ($N = 56$)		Non-reversed ($P < 0.001$)[a] ($N = 44$)	
	N	%	*N*	%	*N*	%
Unidentified[b]	20	20	17	85	3	15
1	38	38	26	68	12	32
2	23	23	9	39	14	61
3	14	14	3	21	11	79
4	5	5	1	20	4	80

[a]Mann–Whitney *U*-test.
[b]Unidentified data were analyzed as missing data.

more unlikely to respond to treatment than delirium caused by other factors, as shown using a univariate analysis ($P = 0.03$). However, this significant difference disappeared after adjustments for PS, clinical stage and demographic data were made using a multivariate analysis. The results indicated that only poor physical functioning was a significant predictor of a poor prognosis for delirium.

Number of Causes and Reversibility of Delirium

The reversibility of delirium was significantly influenced by the number of causes (Table 3).

Association between Motor Subtypes of Delirium and the Presence of Each Precipitating Factor

No significant relations between motor subtypes of delirium and causes of delirium were seen (Table 4).

DISCUSSION

This is the first study to investigate the causes of delirium and their associations with reversibility and motor subtype in cancer patients who were admitted to a general ward. Medicines, such as opioids, and inflammation were the most common causes of delirium. None of the investigated factors showed a significant association with reversibility or clinical subtype.

Medicines, including opioids, were the most frequently identified causes of delirium in cancer patients hospitalized in general wards, consistent with the findings of previous studies performed in different clinical oncology settings. Since pain is a prevalent symptom and opioids are widely used to alleviate pain in cancer patients, opioid-induced delirium is probably the most common cause of delirium in an oncology setting. Infection, dehydration and sodium level abnormality were the next most common causes of delirium.

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Table 4. Relation between causes of delirium and clinical subtype

	Hyperactive ($N = 58$)		Hypoactive ($N = 14$)		*P* value
	N	%	*N*	%	
Opioids	13	22	6	43	0.16
Inflammation	16	28	2	14	0.49
Dehydration and sodium abnormality	9	16	1	7	0.68
Metabolism abnormality	8	14	1	7	0.68
Benzodiazepines	11	19	2	14	1.00
Steroids	4	7	1	7	1.00
Hypercalcemia	3	5	1	7	1.00
Anemia	4	7	1	7	1.00
Hypoxemia	5	9	0	0	0.58
Clotting abnormality	2	3	2	14	0.17

Fisher's exact test was performed using the hyperactive and hypoactive conditions.

These factors have also been previously reported as potentially important causes of delirium in cancer patients. Thus, the current study, as well as previous studies, demonstrates that opioids, infection, dehydration and mineral imbalances are common causes of delirium in cancer patients, regardless of the clinical setting. In this regard, opioid-induced delirium (76%) was commonly observed in a study by Lawlor et al. (2) (see the Introduction section). On the other hand, we cannot claim, based on the present findings, that these factors, when present, will commonly cause delirium.

The cause of delirium could not be identified in ~20% of the cases. Although we utilized a structured assessment of the causes of delirium in the current study, a more comprehensive evaluation may be necessary. Because some recent studies have suggested other possible causes of delirium, such as vitamin B1 deficiency (35), in cancer patients, our method might have failed to recognize the causes of delirium comprehensively. Antagonistically, high rate of unknown cause was may reflect the quite stringent criteria for attribution of cause in the methods. Some delirium might occur in cancer patients as a result of the accumulation of multiple mild abnormalities or potential factors. Furthermore, 1 week follow might not be long enough to see a reversal in delirium. On the other hand, multiple causes were identified in ~40% of the cases. According to data obtained in palliative care settings, Lawlor et al. and Morita et al. reported that the causes of delirium could not be identified in 1% and 7% of the cases, respectively. And, they also reported that the median number of identified factors were 3 and 2, respectively. These findings suggest that the causes of delirium observed in a general medical ward setting may vary to a greater extent than those in a palliative care setting, and medical staff members should pay attention to a broader range of possible causes.

The current study did not find an association between specific delirium-precipitating factors and delirium reversibility, and only physical functioning independently influenced the reversibility of delirium. Insomuch as patients receiving opioids in general wards may have a more critical physical condition, the influence of opioids on delirium may have been indirect. On the other hand, some previous studies conducted in palliative care settings have reported that delirium induced by medicines, such as opioids, is more likely to be reversible than delirium induced by other causes (2,4,16,17). Several possible explanations for the observed difference exist. First of all, the treatment interventions after the cause of the delirium had been identified may have differed. Namely, we only notified each patient's physician of the precipitating factors of delirium; whether any intervention was subsequently provided depended on the physician's practice. On the other hand, previous studies in palliative care settings applied more active and structured interventions, such as opioid rotation. The fact that delirium could not be improved in patients with multiple identified causes of delirium may indicate that delirium resulting from multiple causes is more difficult to recover from. In addition, more opioid-induced delirium occurred in a PCU setting study, suggesting that if opioids are widely used, the reversibility of delirium may increase.

The delirium which had many causes was hard to recover in this study. It may be because in the delirium developing from complicated causes, namely the delirium with many causes, it was difficult to treat its precipitating factors. In addition, the patients with delirium developing from complicated causes had such bad physical conditions that the condition was hardly reversible.

No specific delirium-precipitating factors were associated with the motor subtypes of delirium in the present study. Morita et al. (4) only just reported that hyperactive symptoms were significantly associated with drug-induced delirium, whereas dehydration-related pathologies were significantly associated with hypoactivity in a palliative care setting. Thus, the findings regarding the association between the cause of delirium and the motor subtype are inconsistent. In addition, the motor subtype of delirium may result from other factors (e.g. complicated clinical factors, biological factors, the patient's condition and the interaction of factors), rather than the causes that were investigated. Furthermore, the definition of delirium subtypes is problematic, and the operational definitions of the subtypes vary among study (36). To clarify the association between causal factors and the delirium subtype, further studies that overcome these issues are needed. On the other hand, the sample in this study had a high percentage of hyperactive cases contrasts with other studies of cancer patients. The exclusion of cases with dementia may also have reduced the frequency of hypoactive delirium. In addition, the reversibility of delirium was higher than other studies, again possibly related to high frequency of hyperactive delirium where prognosis seemed better.

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The current study has several advantages. One advantage was the investigational setting, as our study was performed in a general ward. Thus, our findings may be easier to generalize than those obtained in palliative care settings. Additionally, with regard to identifying the cause of the delirium, the time–dosage relation was judged more strictly than in other studies. Furthermore, clear subtype criteria that were independent of severity-of-illness evaluations and evaluations of cognitive function were used for the subtype evaluation.

This study also has several limitations. First, the referred patient sample may have been influenced by a physician bias. In particular, hypoactive delirium can be easily overlooked by physicians, and this may have led to a selection bias among the subjects. Second, the sample size is relatively small which may account for the lack of positive findings. In particular, the relation between the cause of delirium and the delirium subtype may have been distorted as there were very few cases of hypoactive delirium; consequently, significant features may have been overlooked. Furthermore, in our study, the treatment protocol was not standardized and approaches to delirium depended on the physician's practice or interest. This may have biased the assessment of its reversibility.

In conclusion, medication-induced delirium, especially opioid-induced delirium, is commonly observed in cancer patients hospitalized in general wards. Although opioids are a very important medication for cancer patients, their use must be carefully observed when medical examinations are performed in psychiatric consultation service. In addition, the causes of delirium were not association with delirium reversibility or the motor subtype of delirium. Additional research and biological classification are needed in the future.

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Conflict of interest statement

None declared.

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