Original Article

Catatonia Rating Scales in Patients with Persistent Vegetative State

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Abstract

Objective: Persistent vegetative state (PVS) has similar clinical presentations with catatonia. Both PVS and catatonia can be evaluated using clinical observation and rating scales. We intended to study how catatonia rating scales perform in assessing PVS patients as compared to the standard PVS scale. **Methods:** Thirty residents from two nursing homes for PVS patients were evaluated with Coma Recovery Scale-Revised (CRS-R) and two catatonia rating scales (Bush–Francis Catatonia Rating Scale [BFCRS] and KANNER scale). Ten residents recovering from PVS were selected as controls, and twenty residents still meeting the criteria of PVS were selected as PVS group. Three evaluations were assessed over 6 months. We compared and analyzed the scores of each visit. The components of BFCRS and KANNER scales were also analyzed to create a simpler version for PVS patients. **Results:** BFCRS and KANNER scales, as well as their simplified versions, had significant correlations with CRS-R ($p < 0.001$ for all). This could imply that catatonia rating scales could also be used in evaluating PVS patients. Upon closer examinations of scale components, all the three scales shared components such as consciousness levels and eye movements, but BFCRS and KANNER have evaluations on rigidity and negativism, which CRS-R does not had. **Conclusion:** Our data suggest that PVS and catatonia share an underlying pathological mechanism. Evaluations of muscle tension, an important component of catatonia rating scales, might offer a more thorough assessment of PVS patients. Further study of using catatonia rating scales in PVS patients is warranted.

Key words: Coma Recovery Scale, consciousness levels, eye movements, rigidity

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Introduction

After acute brain injury, patients can enter into a comatose state. To evaluate degrees of wakefulness and awareness, clinicians traditionally distinguish between various types of disorders of consciousness levels. After having corrected the underlying traumatic or nontraumatic medical emergencies, most comatose patients lacking wakefulness and awareness do improve and become more awake [1]. But some of them enter a state where they can become awake, but unfortunately remain unaware. This state of unresponsiveness is traditionally called vegetative state.

Vegetative patients can retain an irregular but cyclic state of circadian sleeping and waking, but cannot show any behaviorally detectable expression of awareness or recognition of external stimuli. They have only a few remaining life instincts and require intensive and around-the-clock care from medical staff or family members [2, 3]. For the vegetative state [4], the American Academy of Neurology has set up strict criteria. If the patient remains in this state for three months due to nontraumatic injury or >12 months due to a traumatic injury, the chance of waking up and living independently is very small, which is called persistent vegetative state (PVS) [3, 5]. If the patient does not wake up for more than a year, the condition can be considered a permanent vegetative state [6, 7]. When patients show

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fluctuating but reproducible behavioral signs of awareness but remain being unable to functionally communicate or use objects, they can be considered to be in a minimally conscious state (MCS). The Glasgow Coma Scale (GCS) is the most commonly used scale for assessing patient consciousness. Despite being one of the most frequently used tools to evaluate consciousness levels, GCS has its limitations, especially when applied to patients without possible verbal output, such as those with intubations or tracheostomy. Coma Recovery Scale-Revised (CRS-R) was developed in 2004 [8]. Its basic architecture is similar to GCS, but there are some additional items such as visual fixation and object manipulation. The scale is now the gold standard to distinguish PVS from MCS and even in conscious patients [9]. CRS-R is used to evaluate six aspects of PVS (auditory, visual, motor, oromotor/verbal, communications, and arousal), and patients can be diagnosed as MCS when they show at least one of the 11 items (consistent movement to command, reproducible movement to command, object recognition, object localization: reaching, visual pursuit, fixation, automatic motor response, object manipulation, localization to noxious stimulation, intelligible verbalization, and nonfunctional: intentional). A patient may no longer be considered vegetative if the patient can perform at least one of the two items– functional communication and object use.

Catatonia is a unique clinical phenomenon characterized by motor, vocal, and behavioral abnormalities such as stupor, negativism, mutism, and stereotyped behaviors. Many catatonia symptoms, such as stupor, mutism, posturing, and negativism, appear to overlap with the common presentations of PVS. While catatonia was previously attributed to a subtype of schizophrenia, studies of last few decades showed that catatonia can be an independent diagnosis [10-12]. But it can also be associated with a wide range of psychiatric and medical etiologies, such as schizophrenia, mood disorders, general medical conditions (GMCs) [13], substance withdrawal [14-17], or even illicit substances such as cathiones [18] and synthetic marijuana [19]. The timely relief of catatonia can allow clinicians to communicate with the patients and begin to treat the associated etiologies, if present. The evaluation of clinical symptoms of catatonia also mostly relies on clinical observation and use of rating scales, much like the evaluation of PVS. The Bush-Francis Catatonia Rating Scale (BFCRS) is the most widely used scale in both research and clinical practice [20, 21]. Studies showed that scores of rating scales can also be used to predict response to catatonia treatments [22]. For example, patients with catatonia who have responded to intramuscular injection of lorazepam have a remarkably lower BFCRS score than those requiring more management [23]. The KANNER scale is a relatively new scale compared to BFCRS, but according to the authors, this scale was designed to better detect changes after treatments, which has paramount clinical importance in documenting the changes after management [24].

To evaluate PVS patients with CRS-R, in this study, we intended to investigate how the two catatonia rating scales perform in assessing PVS patients.

Methods

Participants

From January 2018 to October 2018, 30 nursing home residents from two nursing homes for PVS patients were evaluated using CRS-R, BFCRS, and KANNER scales. Ten residents recovering from PVS were selected as controls, and twenty residents still meeting the criteria of PVS were selected as PVS group. CRS-R was done by a senior nursing supervisor and a senior neurologist. The BFCRS and KANNER scales were assessed by two senior psychiatrists. Three visits were planned, separated by two months between each visit. The nursing home staff helped collect the clinical data and medical history. Informed consent was acquired from the patients' family members. The study design was approved by the institutional review board of Chang-Gung Memorial Hospital, with the need of obtaining informed consent from patients' family members (protocol number = 201601148B0C601 and date of approval = November 8, 2017).

Rating scales

CRS-R is composed of 6 subscales – 0–4 points for auditory function, 0–5 points for visual function, 0–6 points for motor function, 0–3 points for verbal function, 0–2 points for communication function, and 0–3 points for arousal degree [8].

The BFCRS has 23 items with a score of 0–3 for each item [20-22]. To shorten the evaluation process in future, this study also tested shorter versions, including only items with more discriminating power.

The KANNER scale is named after Leo Kanner (1894–1981) who described the neuromotor and neurodevelopmental features of autism, which are also features of catatonia (Katatonia in German) [24]. The KANNER scale has 18 items, with 0–8 points for each item. To shorten the evaluation process in future, this study also tested shorter versions, including only items with more discriminating power.

Translation of Catatonia Rating Scales

The BFCRS (including instructions and items) was translated into traditional Chinese/Mandarin under the supervision of a senior psychiatrist (TL Huang) [22]. Professional terminologies, such as "mitgehen," remained in English. The translation process was approved by the developer of original BFCRS (A Francis) [22].

The KANNER scale (including confirmatory tests, test procedures, test examples, screening sheet, and items) was translated into traditional Chinese/Mandarin under the supervision of a senior psychiatrist (TL Huang) [23]. The translation process was approved by the developer of the original KANNER scale (BT Carroll) [24]. The original English version was kept together with the Chinese translation.

Statistical analysis

All results were represented as mean ± standard deviation. The differences between PVS group and controls were compared using Mann–Whitney U-test. Pearson's correlation was to detect correlations between variables.

All the study data were computed using Statistical Package for Social Science software version 19 for Windows (SPSS, Inc., Chicago, Illinois, USA). The differences between groups were considered significant if $p < 0.05$.

Results

The recruited nursing home residents included 17 males (56.7%) and 13 females (43.3%), with an average age of 50.69 ± 24.80 years. The causes of PVS were mainly diseases ($n = 18$), with an average onset age of 46.03 ± 13.16 years and an average duration of 8.92 ± 4.91 years (Table 1).

The CRS-R scores of the three visits are summarized in Table 2. The BFCRS scores of the three visits are summarized in Table 3. Some of the more distinguished items of BFCRS were identified and grouped into shorter versions for easier evaluation of PVS in future. The BFCRS-s4 included four items (2, immobility/stupor; 4, staring; 11, rigidity; and 12, negativism). The BFCRS-s5 included the four items from the BFCRS-s4 in addition to one more item (5, posturing/catalepsy).

Table 4 summarizes KANNER scale scores of the three visits. Some of the more distinguished items of BFCRS were identified and grouped into shorter versions for easier evaluation of PVS in future. The KANNER-s4 included four items (3, stupor; 5, staring; 10, rigidity; and 12, negativism) [24]. The KANNER-s6 included the four items from the KANNER-s4 in addition to two more items (2, immobility and 6, posturing).

In correlation, CRS-R score was significantly correlated with BFCRS, BFCRS-s4, BFCRS-s5, KANNER, KANNER-s4, and KANNER-s6 scores ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The significant correlations were also persistent in the second and third visits.

The items of CRS-R and shorter versions of BFCRS and KANNER scales are detailed side by side in Table 5.

Between PVS patients and controls, using Mann–Whitney U-test, significant differences were found in the scores of CRS-R, BFCRS, BFCRS-s4, BFCRS-s5, KANNER, KANNER-s4, and KANNER-s6 ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The same significant differences were persistent in the second and third visits.

Discussion

The most important finding is that BFCRS and KANNER scales had significant correlations with CRS-R. This could imply that catatonia rating scales could also be used in evaluating PVS patients. Upon closer examinations of scale components, all the three scales shared components such as consciousness levels and eye movements (Table 5), but BFCRS and KANNER scales have evaluations on rigidity and negativism, which CRS-R did not have. Evaluations of muscle tension, an important component of catatonia rating scales, might offer a more thorough assessment of PVS patients.

Table 1. Demographic data of the study participants

	Patients, *n* (%)
Gender	
Male	17 (56.7)
Female	13 (43.3)
Age (years), mean ± SD	50.69 ± 24.38
Causes of PVS	
Disease	18 (60.0)
Traffic accidents	7 (23.3)
Others	3 (10.0)
Accidents	1 (3.3)
Assault	1 (3.3)
Onset age of PVS (years), mean ± SD	46.03 ± 13.16
PVS duration (years), mean ± SD	8.92 ± 4.91

PVS, persistent vegetative state; SD, standard deviation

Table 2. Coma Recovery Scale-Revised scores of the three visits

Items	Mean ± SD		
	1st visit	2nd visit	3rd visit
1. Auditory	1.53 ± 1.66	1.43 ± 1.61	1.43 ± 1.61
2. Visual	2.23 ± 1.72	2.30 ± 1.77	2.30 ± 1.77
3. Motor	2.43 ± 2.03	2.60 ± 2.03	2.60 ± 2.03
4. Oromotor/verbal	0.80 ± 1.16	0.80 ± 1.16	0.80 ± 1.16
5. Communication	0.47 ± 0.82	0.57 ± 0.86	0.57 ± 0.86
6. Arousal	2.53 ± 0.68	2.60 ± 0.72	2.60 ± 0.72
Total score	10.00 ± 7.13	10.30 ± 7.21	10.30 ± 7.21

CRS-R, Coma Recovery Scale-Revised [8]; SD, standard deviation

As previously mentioned, CRS-R is the gold standard to distinguish MCS from PVS. But behavioral assessments are subjective and may differ significantly due to experiences and training time. There had been studies using electrophysiological signals or neuroimaging modalities to differentiate various disorders of consciousness. ^{18}F-fluorodeoxyglucose (FDG) position emission tomography (PET) and functional magnetic resonance imaging (fMRI) can evaluate brain metabolism and find hypometabolism during mental activation tasks in PVS patients, but FDG-PET shows better congruence with CRS-R scores and better predicted outcome than fMRI [25]. Using arterial spin labeling to compare cerebral blood flow (CBF) patterns, MCS patients have been found to have global decreased CBF and a selective reduction of CBF within the medial prefrontal and midfrontal cortices as well as gray matter [26]. Frontoparietal and parietal coherence of electroencephalography (EEG) can predict the improvement of CRS-R collected over 12 months [27]. Using PET scanning to investigate the various brain networks including default mode, frontoparietal, salience, auditory, sensorimotor, and visual networks, machine learning has been found to discriminate MCS from PVS with a high capacity (> 80%), and the PET findings correlated with CRS-R [28]. A 2015 meta-analysis of twenty clinical studies used CRS-R as the diagnostic gold standard to evaluate the sensitivity and specificity of various

Table 3. Bush-Francis Catatonia Rating Scale scores of the three visits

Items	Mean ± SD		
	1st visit	2nd visit	3rd visit
1. Excitement	0.10 ± 4.03	0.07 ± 0.25	0.07 ± 0.25
2. Immobility/stupor	2.07 ± 1.26	2.17 ± 1.26	2.17 ± 1.26
3. Mutism	2.27 ± 1.26	2.23 ± 1.25	2.23 ± 1.25
4. Staring	1.97 ± 1.43	1.93 ± 1.44	1.93 ± 1.44
5. Posturing/catalepsy	2.23 ± 1.28	2.17 ± 1.34	2.17 ± 1.34
6. Grimacing	0.23 ± 0.77	0.13 ± 0.57	0.13 ± 0.57
7. Echopraxia/echolalia	0.20 ± 0.61	0.07 ± 0.37	0.07 ± 0.37
8. Stereotype	0.43 ± 0.97	0.30 ± 0.84	0.30 ± 0.84
9. Mannerisms	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
10. Verbigeration	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
11. Rigidity	1.83 ± 1.21	1.73 ± 1.17	1.73 ± 1.17
12. Negativism	1.27 ± 1.23	1.07 ± 1.20	1.07 ± 1.20
13. Waxy flexibility	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
14. Withdrawal	2.60 ± 1.04	2.50 ± 1.14	2.50 ± 1.14
15. Impulsivity	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
16. Automatic obedience	0.27 ± 0.64	0.13 ± 0.51	0.13 ± 0.51
17. Mitgehen	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
18. Gegenhalten	0.20 ± 0.76	0.10 ± 0.55	0.10 ± 0.55
19. Ambitendency	0.30 ± 0.92	0.00 ± 0.00	0.00 ± 0.00
20. Grasp reflex	0.30 ± 0.92	0.20 ± 0.76	0.20 ± 0.76
21. Perseveration	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
22. Combativeness	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
23. Autonomic abnormality	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Total score	16.27 ± 6.34	14.08 ± 7.30	14.08 ± 7.30
BFCRS-s4	7.13 ± 4.50	6.90 ± 4.20	6.90 ± 4.20
BFCRS-s5	9.37 ± 5.48	9.07 ± 5.21	9.07 ± 5.21

BFCRS, Bush-Francis Catatonia Rating Scale [20-22]; SD, standard deviation

Table 4. KANNER scale scores[24] of the three visits

Items	Mean ± SD		
	1st visit	2nd visit	3rd visit
1. Excitement	0.07 ± 0.37	0.07 ± 0.37	0.07 ± 0.37
2. Immobility	5.67 ± 3.41	5.33 ± 3.61	5.33 ± 3.61
3. Stupor	4.93 ± 3.74	5.47 ± 3.60	5.47 ± 3.60
4. Mutism	6.20 ± 3.34	6.20 ± 3.34	6.20 ± 3.34
5. Staring	5.13 ± 3.85	5.13 ± 3.85	5.13 ± 3.85
6. Posturing	6.07 ± 3.30	5.73 ± 3.55	5.73 ± 3.55
7. Grimacing	0.53 ± 2.03	0.47 ± 1.80	0.47 ± 1.80
8. Stereotypy	0.53 ± 1.17	0.33 ± 0.92	0.33 ± 0.92
9. Mannerisms	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
10. Rigidity	4.67 ± 3.17	4.00 ± 3.20	4.00 ± 3.20
11. Flaccidity	0.33 ± 1.50	0.33 ± 1.50	0.33 ± 1.50
12. Negativism	3.00 ± 3.14	2.53 ± 3.06	2.53 ± 3.06
13. Refusal to eat	7.20 ± 2.44	6.67 ± 3.03	6.67 ± 3.03
14. Refusal to drink	7.20 ± 2.44	6.67 ± 3.03	6.67 ± 3.03
15. Impulsivity	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
16. Nudism	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
17. Incontinence (psychogenic)	8.00 ± 0.00	8.00 ± 0.00	8.00 ± 0.00
18. Combativeness	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
KANNER total	59.53 ± 23.63	56.93 ± 25.16	56.93 ± 25.16
KANNER-s4	17.73 ± 11.67	17.13 ± 11.38	17.13 ± 11.38
KANNER-s6	29.47 ± 17.43	28.20 ± 17.63	28.20 ± 17.63

KANNER scale scores. SD, standard deviation

diagnostic techniques and found that quantitative EEG (90% sensitivity and 80% specificity) is better than fMRI (44% sensitivity and 67% specificity) in detecting MCS [5]. Despite the advancement with those technological findings, most nursing homes do not have access to those advanced machines. Any clinical changes of PVS patients still rely on the careful behavioral observation over sufficient length of time by the clinical staff.

Aside from the similar symptoms, PVS and catatonia share a unique response to sedative drugs. In patients with brain damage due to strokes, trauma, and hypoxia, a recent review summarizing 23 clinical reports and 6 studies have demonstrated associations between subsedative doses of zolpidem and patients' recoveries, citing findings from imaging or electric studies of single-photon emission computed tomography, PET, EEG, magnetic resonance imaging, and magneto-encephalography [29]. Zolpidem acts on the gamma-aminobutyric acid $GABA_{1A}$ omega 1 subtype receptor, so its action through GABA receptors has been speculated to be the mechanism of action. But zopiclone, a GABA-ergic agonist on the omega 2 subtype, seemed to have no effect in zolpidem responders, in a case report [30], suggesting that zolpidem's receptor specificity might be related to its effect in awakening consciously disturbed patients.

A consistent stream of publications exist to view catatonia and zolpidem. Traditionally, speculated mechanisms of catatonia include low $GABA_A$ receptor binding, dopamine hypoactivity, and possibly glutamate (*N*-methyl-D-aspartate receptor) hyperactivity [31, 32]. The standard treatments of catatonia involved $GABA_A$ agonist benzodiazepines (BZDs) and electroconvulsive therapy (ECT) [22]. We have used a protocol combining intramuscular lorazepam and intravenous diazepam mostly and obtained great success in catatonia associated with schizophrenia [23, 33], mood disorder [34, 35], and, to some extent, organic causes [36]. The effect of zolpidem on improving catatonia was first reported by Mastain et al. in 1995 [37], and the team later verified that improvement of catatonia is associated with plasma concentration of zolpidem [38]. An open study was found that zolpidem is effective in five out of seven catatonic patients [39], along with many case reports since then [40-47]. Many of those patients have failed to respond or to tolerate the standard treatments of BZD and/or ECT, but have shown dramatic improvement after zolpidem prescription [37, 40-43]. Some of the patients responsive to zolpidem are also associated with organic causes [41, 44, 45]. A call exists to identify treatable catatonic patients from minimally responsive head injury survivors [48]. We suggest that PVS and catatonia share an underlying pathological mechanism and may share a similarity of treatment. As mentioned earlier, scores of catatonia rating scales can be used to predict treatment response [22]. Using catatonia scales on PVS patients may help identifying PVS patients responsive to sedative drugs.

Table 5. Side-by-side comparisons of key items from CRS-R [8], BFCRS [20-22], and KANNER[24] scales

CRS-R	BFCRS	KANNER
Auditory	2 - Immobility/stupor	3 - Stupor
4 - Consistent movement to command	0 = Absent	0 = Absent
3 - Reproducible movement to command	1 = Sits abnormally still, may interact briefly	2 = Inert, but may interact briefly
2 - Localization to sound	2 = Virtually no interaction with external world	4 = No reaction to any external stimuli
1 - Auditory startle	3 = Stuporous, nonreactive to painful stimuli	6 = No reaction to noxious stimuli 8 = No reaction to deep, painful stimuli
0 - None		
Visual	4 - Staring	5 - Staring
5 - Object recognition	0 = Absent	0 = Absent
4 - Object localization: reaching	1 = Poor eye contact, repeatedly gazes <20 seconds between shifting of attention; decreased blinking	2 = Poor eye contact, decreased blinking but will look at examiner
3 - Visual pursuit	2 = Gaze held longer than 20 seconds, occasionally shifts attention	4 = Gaze held, occasionally shifts attention to examiner
2 - Fixation	3 = Fixed gaze, non-reactive	6 = Fixed gaze; does not look at examiner; may look when requested
1 - Visual startle		8 = Fixed gaze/staring for>1 day
0 - None		
Motor	5 - Posturing/catalepsy	2 - Immobility/6 -posturing
6 - Functional object use	0 = Absent	0 = Absent
5 - Automatic motor response	1 = < 1 min	2 = Mild hypoactivity or bradykinesia
4 - Object manipulation	2 = > 1 min, < 15 min	4 = Bradykinesia, but is able to move on request
3 - Localization to noxious stimulation	3 = Bizarre posture, or mundane maintained more than 15 min	6 = Akinesia with few spontaneous movements but may be able to move on command
2 - Flexion withdrawal		8 = Akinesia with few spontaneous movements, lasting >1 day
1 - Abnormal posturing		0 = Absent
0 - None/flaccid		2 = Brief episodes of “freezing” in a position for usually <1 min
		4 = Longer episodes of more than one minute for <1 day
		6 = Bizarre posture, twisted or contorted body position <1 day
		8 = Any posture maintained for>1 day
Oromotor/verbal	2 - Immobility/stupor	3 - Stupor
3 - Intelligible verbalization		
2 - Vocalization/oral movement		
1 - Oral reflexive movement		
0 - None		
Communication	2 - Immobility/stupor	3 - Stupor
2 - Functional: Accurate		
1 - Nonfunctional: Intentional		
0 - None		
Arousal	2 - Immobility/stupor	3 - Stupor
3 - Attention		
2 - Eye opening w/o stimulation		
1 - Eye opening with stimulation		
0 - None		

BFCRS, Bush-Francis Catatonia Rating Scale [20-22]; CRS-R, Coma Recovery Scale-Revised [8]

Study limitations

The readers are warned against overinterpretation of our study results because this study has the following three limitations:

- The translated version of BFCRS and KANNER scales was not backtranslated into English to be reviewed by the original authors. Most professional terminologies were not translated at all due to lack of appropriate Chinese terms for them and remained in English, or in German, where the terms originated from. Given some of the items required advanced knowledge of the subject matter, we would advise the users to consult the original English text if the users felt that the translation was not clear. Interrater reliability, internal consistency, and validity were not yet done for the translated catatonia scales.
- The sample size in our study was rather small.
- This study did not include biomarkers from blood, cerebrospinal fluid, electrophysiological studies, or imaging studies. Their inclusion of those biomarkers could provide a more comprehensive overview of the updated status of PVS patients.

Summary

All of those scales are based solely on behaviors, instead of a direct measurement of consciousness. PVS and catatonia are

both heterogeneous mixtures of various diseases, associated with several neuropathological processes. Despite PVS has been studied rather extensively with anatomical and functional neuroimaging studies, more work is still needed to incorporate those findings with clinical observations [9]. In future, we hope to incorporate imaging modalities in the evaluation of those disorders of consciousness, be it PVS or catatonia.

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Conflicts of Interest

None.

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